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Understanding chronic inflammation: couplings between cytokines, ROS, NO, Ca_i^{2+}, HIF-1α, Nrf2 and autophagy

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Chronic inflammation is an important component of many diseases, including autoimmune diseases, intracellular infections, dysbiosis and degenerative diseases. An important element of this state is the mainly positive feedback between inflammatory cytokines, reactive oxygen species (ROS), nitric oxide (NO), increased intracellular calcium, hypoxia-inducible factor 1-alpha (HIF-1α) stabilisation and mitochondrial oxidative stress, which, under normal conditions, enhance the response against pathogens. Autophagy and the nuclear factor erythroid 2-related factor 2 (Nrf2)-mediated antioxidant response are mainly negatively coupled with the above-mentioned elements to maintain the defence response at a level appropriate to the severity of the infection. The current review is the first attempt to build a multidimensional model of cellular self-regulation of chronic inflammation. It describes the feedbacks involved in the inflammatory response and explains the possible pathways by which inflammation becomes chronic. The multiplicity of positive feedbacks suggests that symptomatic treatment of chronic inflammation should focus on inhibiting multiple positive feedbacks to effectively suppress all dysregulated elements including inflammation, oxidative stress, calcium stress, mito-stress and other metabolic disturbances.

KEYWORDS

cytokines, inflammation, NF-κB, iNOS, nitric oxide, autophagy, HIF-1α, calcium flux

1 Introduction

Chronic inflammation is a major medical problem that poses enormous diagnostic and therapeutic challenges worldwide. Despite major advances in recent years, available therapies are often unsatisfactory. Understanding the molecular changes that occur under this condition is essential for the development of effective, comprehensive therapeutic approaches. The immune system is a highly complex self-regulatory system

characterised by numerous self-regulatory couplings that adapt the strength and type of response to the nature of the pathogen. The current work extends this analysis to include other elements of cellular self-regulation that are in predominantly positive feedback with inflammatory mediators and with each other, thereby helping to drive the inflammatory response. These elements are oxidative stress, represented by the activity of NADPH oxidases (NOXs), inducible nitric oxide synthase (iNOS) and mitochondrial reactive oxygen species (mito-ROS) (electron leakage from the cytochrome chain), calcium stress (an increase in intracellular calcium concentration and endoplasmic reticulum stress) and hypoxia-inducible factor 1-alpha (HIF-1α), induced under both anaerobic and aerobic conditions. As these elements are mainly in positive feedback with each other, they are referred to in the current work as the Positive Coupling System (PCS).

The intensity of the inflammation must be high enough to fight the infection but not to the point of self-destruction. The regulatory factors are mainly the transcription factors nuclear factor erythroid 2-related factor 2 (Nrf2)/FOXO, which promote antioxidation and autophagy. The following sections will mainly discuss the negative feedbacks between them and the PCS elements.

HIF-1α is a double-faced factor because it is involved in driving up the inflammatory spiral and also has a protective effect on the mitochondria by protecting them from free radical damage. Nitric oxide (NO) produced by iNOS can also activate and inhibit the inflammatory spiral, depending on the metabolic context.

Increasing knowledge about the mutual feedbacks between the mentioned elements of self-regulation allows us to build generalised models of their common interactions. The construction of generalised models is becoming a new challenge at the current level of knowledge and, in the opinion of the authors, will represent a new direction in the development of molecular biology.

The details of the common relationships between the analysed elements are presented in the following sections of the paper. The first part of the paper discusses the basic signalling pathways involved in the transmission of information between analysed elements. The second part discusses the mainly positive feedbacks between inflammation, reactive oxygen species (ROS), NO, Ca_i^{2+} and HIF-1α. The third part discusses the controlling role of autophagy and Nrf2/FOXO and their inhibitory effects on the mentioned positively coupled elements.

1.1 Chronic inflammation

Chronic inflammation is usually generated in one of four cases: 1) the chronic presence of an intracellular pathogen in the cell (1–6), 2) an autoimmune response induced by immune cells against their own tissues in the absence of the pathogen, 3) pathological gut microbiota inducing the chronic inflammation (7) and 4) another metabolic condition or disease in which the initiating factor is another disturbance coupled with inflammation, e.g. oxidative stress, impaired autophagy and calcium stress, which may occur in the course of certain diseases such as atherosclerosis, neurodegenerative diseases and intoxication (8).

In chronic inflammation, an equilibrium develops between a destructive factor (e.g. an intracellular pathogen) and repair factors that are unable to restore the cell or tissue to a healthy state. To understand the problem of chronic inflammation, it is necessary to know the detailed molecular regulatory mechanisms that control this process, both at the local level, i.e. short self-regulatory loops (e.g. stimulation of calcium efflux from the cell when its intracellular concentration increases), and at the global level, i.e. interactions between functionally distant elements such as HIF-1α, Ca_i^{2+}, O_2^-/H_2O_2, NO, Nrf2 and autophagy. Such interactions are just the subject of the current work.

When analysing the many feedbacks between the many regulatory elements of the cell, it is often difficult to identify the initiating factor, the so-called first domino, that sets off the cascade of molecular perturbations. Identifying such a factor is very important for restoring balance in the cell, but it may not be enough if the system has drifted far from a healthy state. The underlying cause is different in the four types of chronic inflammation mentioned above. In chronic intracellular infections, it is most often the pathogen itself (1–6). In degenerative diseases such as Alzheimer's or Parkinson's, there are abnormal proteins (β-amyloid and tau) that disrupt many metabolic pathways (9). In autoimmune diseases without specific foreign initiating proteins, the question of the initiating factor is more complex. It may be abnormal autoantibodies that react with surface proteins and induce a variety of abnormal intracellular responses (10). In the case of intestinal microbiota dysbiosis, the cause of chronic inflammation is the intestinal pathogens that induce low-level inflammation in the intestinal mucosa, which then spreads to the whole organism (11).

An analysis of the literature shows that in intracellular pathogens and degenerative diseases, the common denominator of molecular pathology is blocked autophagy, which prevents the removal of abnormal proteins and sets in motion the inflammatory-oxidative spiral. Autophagy will therefore be an important point of analysis in the current work. Another important issue of great complexity is the process of resolution of inflammation, which requires specific and individual review, especially in the context of the feedbacks presented, because the entry into a chronic state may also depend on the inability of the regulatory system to activate the resolution process despite the fact that the initiating pathogen has been removed.

2 Kinase pathways and inflammation

Current work focuses on feedback analysis between cytokines, ROS, NO, Ca_i^{2+}, HIF-1α, Nrf2 and autophagy. Signalling pathways such as mitogen-activated protein kinases (MAPKs) [p38, c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinases 1 and 2 (ERK1/2)], PI3K/Akt, Janus kinase/signal transducer and activator of transcription (JAK/STAT), AMP-activated protein kinase (AMPK) and cAMP/protein kinase A (PKA) are strongly involved in the communication between these elements. These signalling pathways play numerous roles in cellular self-regulation

and are already relatively well-understood mechanisms of intracellular communication. These pathways are involved in the transduction of many signals, including those between the elements analysed. Let us summarise the information on these pathways with a focus on inflammation. The second key point is the role of the subsequent pathways in the regulation of autophagy because it seems to be a common feature of very different types of chronic inflammation. If it is impaired, the accumulation of cellular debris and pathogens maintains inflammation, and there is no way to bypass this mechanism of inflammatory induction. A summary of these relationships is shown in Figure 1.

2.1 P38 MAPK

The p38 MAPK signalling pathway is one of the key regulators of cellular responses to a variety of stimuli, including environmental stresses and inflammatory signals. It is mainly activated by stress factors [oxidative stress, hypoxia, ultraviolet (UV) or ionising radiation, and osmotic disturbances] (12), inflammatory factors [e.g. TNF-α (13, 14), IL-1β (15, 16) and transforming growth factor beta (TGF-β) (17, 18)], pathogens [bacterial lipopolysaccharides (LPS) from bacteria (19) and activating Toll-like receptors (TLRs)] and surface receptor interactions (integrin and Vascular Endothelial Growth Factor receptors in the endothelium) (20). Inhibitors of the p38 MAPK pathway include natural regulatory mechanisms such as MAPK phosphatases (MKPs) and proteins that block kinase interactions with their substrates (12). The activation of the p38 MAPK pathway leads to several biological effects, the most important of which are the activation of genes encoding cytokines such as IL-6, IL-8 or TNF-α (21–23), and the induction of cyclooxygenase-2 (COX-2) expression (24, 25), which increases prostaglandin production. The p38 MAPK pathway also plays a key role in apoptosis by activating proapoptotic proteins in

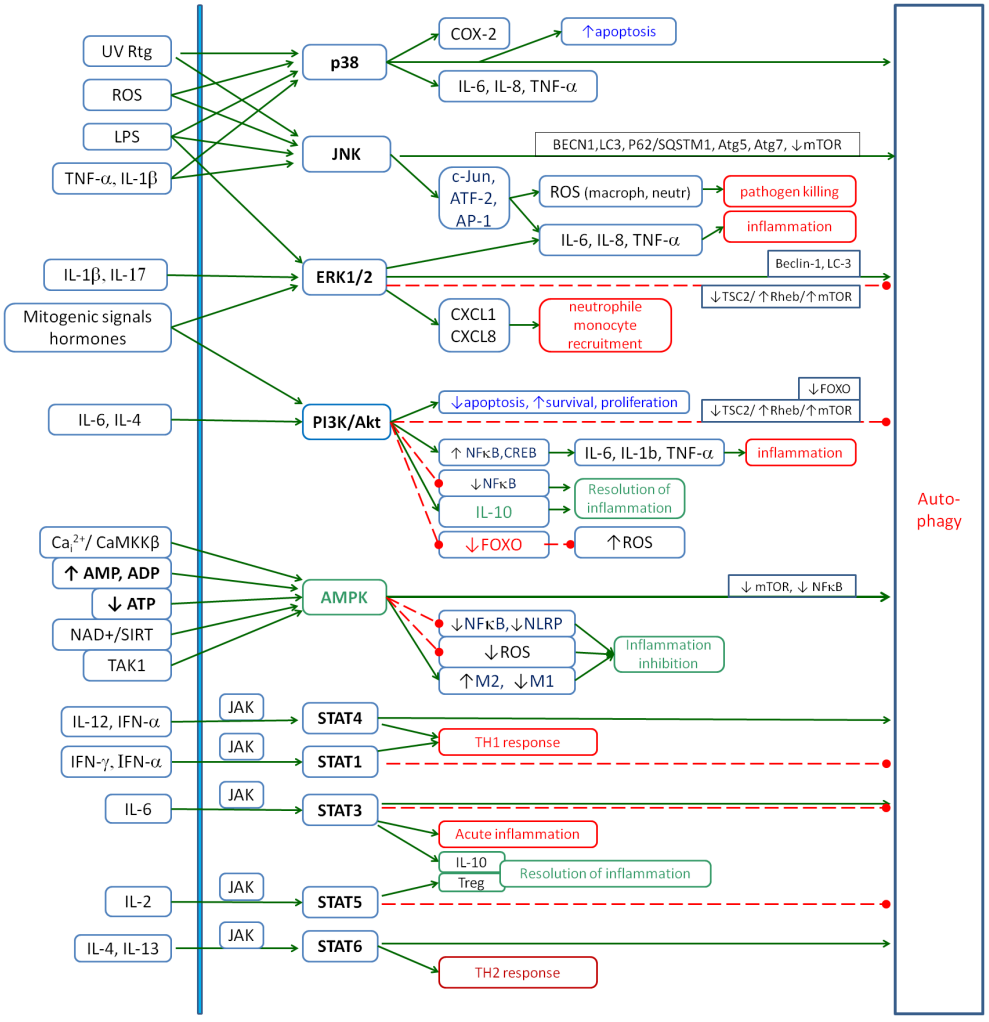

FIGURE 1
The role of the main signalling pathways involved in the inflammatory response: p38, JNK, ERK1/2, PI3K/Akt, AMPK and JAK/STAT. The figure shows the main factors that activate these pathways and their main inflammatory effects. Special attention is given to their influence on autophagy as one of the key processes involved in chronic inflammation. Solid arrows, activation; red dashed lines with •, inhibition. JNK, c-Jun N-terminal kinase; ERK1/2, extracellular signal-regulated kinases 1 and 2; AMPK, AMP-activated protein kinase; JAK, Janus kinase; STAT, signal transducer and activator of transcription.

response to cellular stress (26, 27). In addition, p38 MAPK regulates the cell cycle by arresting it in the G1 or G2/M phase in response to DNA damage (28). In the tumour microenvironment, this pathway promotes angiogenesis through VEGF stimulation and promotes tumour cell invasion and survival (29). It is thus a central regulator of the cellular response to environmental and inflammatory stimuli. Its precise regulation is crucial for maintaining cellular homeostasis, and dysregulation of this pathway can lead to inflammatory, cancer and neurodegenerative diseases. p38 MAPK is also involved in activating the autophagy process (30).

2.2 ERK1/2

The ERK1/2 signalling pathway plays a key role in the regulation of a variety of biological processes including cell proliferation, differentiation, survival and migration. The activation of the ERK1/2 pathway is associated with responses to mitogenic signals such as growth factors, as well as hormonal stimuli and changes in the extracellular environment. It also plays an important role in the regulation of inflammatory processes, controlling the expression of genes associated with the immune response and the production of cytokines and chemokines (31). Its activation occurs in response to inflammatory stimuli such as pro-inflammatory cytokines (e.g. IL-17A and IL-1β) (16, 32), bacterial LPS (33), growth factors (e.g. VEGF and EGF) (34) and interactions with TLRs and chemokine receptors (31). Receptor tyrosine kinases (RTKs) or G protein-coupled receptors (GPCRs) play a key role in these processes by transducing the signal through the activation of the kinase cascade, leading to the phosphorylation and activation of ERK1/2 by MEK1/2 kinase (31).

The activation of the ERK1/2 pathway promotes the synthesis of pro-inflammatory cytokines, such as IL-6, IL-8, TNF-α and IL-1β, and chemokines, such as CXCL1 and CXCL8, which are responsible for the recruitment of neutrophils and monocytes to the site of inflammation (31, 35–37). The ERK1/2 pathway also promotes phagocytosis (38) and plays a role in stimulating angiogenesis by regulating VEGF expression, which improves blood supply to the inflamed area (39, 40). Excessive or uncontrolled activation of the ERK1/2 pathway leads to chronic inflammatory conditions such as rheumatoid arthritis (41), psoriasis (41) and Crohn's disease (42), where it can cause abnormal activation of T and B lymphocytes, leading to autoimmunity.

The ERK1/2 signalling pathway is a promising therapeutic target. MEK1/2 inhibitors, such as trametinib, have been used to treat diseases associated with the over-activation of this pathway, including certain cancers (43). In the context of inflammation, ERK1/2 inhibitors reduce the production of pro-inflammatory cytokines and chemokines (31, 44, 45).

This signalling pathway affects autophagy in different ways, depending on the context and the details of the interaction. Under conditions of cellular stress and nutrient deprivation, ERK1/2 promotes autophagy by activating the Beclin-1 protein, but this effect is thought to be at least partly downstream of PI3K/Akt inhibition (46, 47). In contrast, under favourable conditions of cellular growth and proliferation, ERK1/2 can inhibit autophagy by activating mTOR through the TSC2/Rheb/mTORC1 pathway, which is particularly prevalent in cancer (48) and is thought to be also important in neurodegeneration (49).

2.3 JNK

The JNK signalling pathway plays an important role in the regulation of inflammatory responses, acting as a mediator of stress signalling, cytokine production and immune cell activity. This pathway is activated by a variety of stimuli, including pro-inflammatory cytokines such as TNF-α and IL-1β (50), ROS (51), LPS and environmental stressors such as UV radiation and osmotic stress (52). Activation occurs via upstream kinases such as MAP kinase kinase 4/7 (MKK4/7), which phosphorylates and activates JNK. JNK, in turn, translocates to the nucleus to regulate the activity of transcription factors such as c-Jun, ATF-2 and AP-1, thereby driving the expression of inflammatory genes.

In the context of inflammation, the JNK pathway is one of the key regulators of cytokine production. By activating the transcription factor AP-1, JNK enhances the expression of pro-inflammatory mediators such as IL-6, IL-8, and TNF-α and chemokines that attract immune cells to the site of inflammation (53–55). JNK also influences processes such as apoptosis and proliferation (56). In macrophages and neutrophils, JNK promotes the production of ROS, which contributes to the destruction of pathogens but can also lead to tissue damage if uncontrolled (57). JNK also plays a role in the resolution of inflammation by promoting apoptosis in damaged or dysfunctional cells, thereby limiting excessive inflammation and maintaining tissue homeostasis (58), and by promoting autophagy, which reduces debris-mediated inflammation (58, 59).

Chronic activation of JNK has been implicated in autoimmune diseases such as rheumatoid arthritis (60), where it contributes to the sustained production of pro-inflammatory cytokines and tissue damage. In metabolic diseases such as obesity and type 2 diabetes, JNK activation in adipose tissue and the liver is associated with insulin resistance and systemic inflammation (61). In addition, in cancer, JNK can promote tumour progression by supporting an inflammatory microenvironment that promotes angiogenesis, invasion and metastasis (62, 63). Targeting the JNK pathway has emerged as a potential therapeutic strategy for inflammatory and autoimmune diseases (52).

2.4 PI3K/Akt

The PI3K/Akt signalling pathway plays a role in balancing pro- and anti-inflammatory processes. It is activated in response to a variety of extracellular stimuli, including cytokines, growth factors and pathogen-associated molecular patterns (PAMPs). In the context of inflammation, the PI3K/Akt pathway promotes the survival and activation of macrophages, neutrophils and

lymphocytes (64, 65). By activating transcription factors such as NF-κB and cAMP response element-binding protein (CREB), Akt facilitates the production of pro-inflammatory cytokines such as IL-6, IL-1β and TNF-α, which amplifies the inflammatory response (66–70). In addition, Akt promotes the production of chemokines that attract immune cells to the site of inflammation (71).

At the same time, the PI3K/Akt pathway is important for preventing excessive or chronic inflammation by supporting the production of anti-inflammatory IL-10 and other regulatory cytokines (72–74). Akt also negatively regulates inflammation through its inhibitory interactions with downstream molecules such as GSK-3β (glycogen synthase kinase-3β, activator of NF-κB) (75, 76). Akt plays a role in the resolution phase of inflammation by promoting the survival and phagocytic activity of macrophages during the clearance of apoptotic cells and debris, a process known as efferocytosis.The hyperactivation of this pathway can contribute to chronic inflammation under conditions such as rheumatoid arthritis, inflammatory bowel disease and asthma, where it drives sustained immune cell activation and cytokine production (77, 78). Conversely, insufficient PI3K/Akt signalling can impair anti-inflammatory mechanisms and promote uncontrolled inflammation, as seen in certain autoimmune diseases (79). In addition to inflammatory diseases, excessive PI3K/Akt signalling has been implicated in cancer, where it supports an inflammatory tumour microenvironment that promotes angiogenesis, immune evasion and metastasis (80). In metabolic disorders such as obesity and type 2 diabetes, chronic inhibition of the PI3K/Akt pathway in adipose tissue and other organs is associated with insulin resistance and low-grade systemic inflammation (81, 82). In the context of autophagy, PI3K/Akt inhibits it mainly through the TSC2/Rheb/mTORC1 pathway (48, 83). However, inhibition of FOXO by Akt in some cell types leads to inhibition of autophagy, inhibition of antioxidant enzyme production and inhibition of apoptosis, which promotes chronic inflammation (84, 85). In conclusion, the influence of this pathway on inflammation is complex, non-linear, and concentration- and metabolic context-dependent and requires further in-depth analysis.

2.5 JAK/STAT

The JAK/STAT signalling pathway plays an important role in inflammation, mediating the effects of cytokines and growth factors that regulate immune responses, cell survival, proliferation and differentiation (86, 87). This pathway is activated by the binding of cytokines, such as interferons (IFNs), interleukins (ILs) and tumour necrosis factor (TNF), to their respective receptors on the cell surface. Upon ligand binding, receptor-associated JAKs are activated by autophosphorylation, creating docking sites for STAT proteins. STAT proteins are then phosphorylated, dimerised and translocated to the nucleus, where they regulate the expression of genes involved in inflammatory and immune responses. The JAK/STAT signalling pathway is central to the regulation of both acute and chronic inflammation. Different STAT proteins are activated by different cytokines. STAT1 is activated by the interferons IFN-α and IFN-γ. It drives the Th1 response important for intracellular pathogen defence and regulates the expression of genes involved in antiviral immunity and macrophage activation (88). STAT3 is activated by IL-6 and promotes the transcription of genes (including through interactions with NF-κB) that sustain the inflammatory process, including acute-phase proteins and chemokines such as CXCL1 and CCL2, which recruit immune cells to sites of inflammation (89, 90). This pathway also promotes cancer progression by activating pro-cancer inflammation. However, STAT3 also drives the production of IL-10 to enter the resolution phase of inflammation. STAT4 is activated by IL-12 and IFN-α and drives the differentiation of Th1 cells, which produce IFN-γ and enhance the pro-inflammatory response (91). STAT5 supports the expansion of regulatory T cells (Tregs) in response to IL-2, contributing to the resolution of inflammation and maintenance of immune tolerance (92). STAT6 is activated by IL-4 and IL-13 and promotes the differentiation of Th2 cells, which are involved in anti-parasite immunity and allergic inflammation (93). The effects of individual JAK/STAT pathways on autophagy vary, depending on the type of pathway and also the metabolic context. A predominantly activating effect is observed for the STAT4 and STAT6 pathways, whereas a predominantly inhibitory effect is observed for the STAT1 and STAT5 pathways. The STAT3 pathway is the most dependent on the metabolic context.

Dysregulation of the JAK/STAT pathway is implicated in many inflammatory and autoimmune diseases. Sustained activation of STAT3 has been implicated in diseases such as rheumatoid arthritis, inflammatory bowel disease and psoriasis, where it drives the sustained production of inflammatory cytokines and tissue damage (94, 95). Inflammatory signals mediated by STAT3 and STAT5 can promote tumourigenesis by supporting angiogenesis, immune evasion and tumour cell survival (96).

2.6 AMPK

AMPK is one of the most important pro-regenerative and anti-inflammatory pathways in metabolic self-regulation. It is activated by liver kinase B1 (LKB1) in response to metabolic stress, hypoxia or exercise when cellular ATP levels decrease. AMP or ADP levels increase its activity. A high NAD^+/NADH ratio also induces this kinase via SIRT1, which deacetylates LKB1 and facilitates its phosphorylation (97). Conversely, AMPK increases the NAD^+/NADH ratio by several mechanisms, thus closing the positive loop that drives cell regeneration (98, 99). It is noteworthy that calcium/calmodulin-dependent protein kinase kinase β (CaMKKβ) can activate AMPK through LKB1 in response to increased cellular Ca^{2+} levels, and this effect is independent of the AMP-to-ATP ratio (100, 101). The next activator of AMPK is the TAK1 protein (TGF-β-activated kinase 1), which activates AMPK in response to inflammation and stress signals (102). The main role of AMPK is to activate the catabolic and inhibit the anabolic processes. AMPK exerts potent anti-inflammatory effects primarily by inhibiting pro-

inflammatory pathways. It suppresses NF-κB signalling, a key regulator of inflammatory cytokines, by phosphorylating and inhibiting IκB kinase (IKK) (103). In addition, AMPK inhibits the activation of the NLRP3 inflammasome, a multi-protein complex responsible for the production of IL-1β (104). It also improves mitochondrial function and reduces levels of ROS (105). Together, these actions collectively reduce inflammation at the molecular level.

Another role of AMPK in inflammation is its ability to promote the anti-inflammatory M2 macrophage phenotype over the pro-inflammatory M1 phenotype (97, 101). M2 macrophages produce cytokines such as IL-10 and TGF-β, which facilitate tissue repair and resolution of inflammation. AMPK by promoting autophagy via mTOR inhibition helps maintain cellular homeostasis and resolve inflammatory signals (106, 107).

Reduced AMPK activity is associated with chronic inflammatory conditions such as obesity, type 2 diabetes, atherosclerosis and non-alcoholic fatty liver disease (NAFLD) where low AMPK activity exacerbates NF-κB signalling, cytokine production and immune cell infiltration (108, 109). Dysregulated AMPK signalling has also been implicated in autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus, where it contributes to prolonged pro-inflammatory responses (110, 111). Chronic inflammation driven by low AMPK activity can also create a tumour-promoting environment in cancer (112, 113), while in neuroinflammatory diseases such as Alzheimer's and Parkinson's, dysregulated AMPK signalling contributes to neuronal damage and degeneration (114, 115).

2.7 cAMP/PKA

Similar to AMPK, the cAMP/PKA pathway has mainly anti-inflammatory and antioxidant properties. The anti-inflammatory mechanism is that the CREB–CREB-binding protein (CBP) complex formed by CREB phosphorylation by PKA can lead to the dissociation of the NF-κB–CBP complex, which blocks the action of NF-κB (116). PKA also inhibits activation of the pro-inflammatory ERK, AKT, STAT3 and NF-κB pathways through phosphorylation and inhibition of the TNFR1 receptor (117), so downregulation of PKA activity increases the strength of the coupling between inflammation and oxidative stress. The other inflammation-resolving pathway is via EPAC1/2 activation, which also inhibits NF-κB and GSK-3β (117). During the inflammatory phase, cAMP levels are reduced by an increase in the activity of PDE4 (which catalyses the breakdown of cAMP to AMP), which contributes to an increase in the severity of inflammation (118).

The cAMP/PKA pathway is a central messenger in the pro-resolving signalling pathways and is induced by, or induces, the production of other pro-resolving mediators as inflammation resolves (117, 118). For this reason, it is also an activator of the maturation of phagosomes, the main mechanism for removing extracellular debris after infection (119). The anti-inflammatory effect of cAMP is also mediated by the reduction of oxidative stress through an increase in the activity of sirtuin 3, which activates the production of antioxidant enzymes (120).

Adequate levels of cAMP are also essential for proper mitochondrial function. PKA phosphorylates complex I, leading to an increase in its activity and a decrease in electron leakage from this complex (121). However, the phosphorylation of complex IV by PKA leads to effective control of ATP production by properly functioning inhibition of ATP production under conditions of high ATP levels, whereas the dephosphorylation of complex IV leads to uncontrolled inhibition of this complex and a subsequent increase in electron leakage (122). Next, the phosphorylation of complex V by PKA stabilises the oligomers of this complex, improving ATP synthesis, whereas the lack of phosphorylation leads to the instability of the enzyme structure, lower ATP levels and inhibition of complex V by AIF1, shifting metabolism towards aerobic glycolysis (123, 124).

The effect of cAMP/PKA on autophagy is complex and depends on the metabolic context (125). On the one hand, autophagy is inhibited by the phosphorylation of Atg1/ULK1, a key initiator of autophagy (126), which limits the formation of autophagosomes; on the other hand, autophagy can be activated indirectly by activating EPAC and AMPK, further inhibiting mTOR, and by inhibiting NF-κB (117), which is an inhibitor of autophagy.

2.8 Pathway balance in chronic inflammations

The balance between the activity of the discussed pathways is one of the important elements regulating inflammation and preventing it from becoming chronic. The dominant current view of the development of chronic inflammation focuses on determining the role of individual pro- and anti-inflammatory pathway activities, which is, of course, an important aspect of the analysis. However, the present article focuses on the couplings between cytokines, ROS, NO, Cai^{2+}, Nrf2 and autophagy. From the point of view of autophagy, some of the pathways discussed are stimulatory, some are inhibitory, and the action of others depends on the metabolic context. Thus, an imbalance in the ratio of these pathways towards excessive inhibition of autophagy may be one of the important causes of the transition of the system to chronic inflammation. According to the authors, future research on chronic inflammation should focus not only on determining the qualitative change in the activity of individual pathways but also on quantitatively comparing their activity and the overall effect on the elements analysed with a particular focus on autophagy.

3 Positive feedbacks regulating the inflammation

In the following subsections, the common relationships between the elements discussed, which drive inflammation mainly through the use of positive feedbacks, will be discussed step by step. From the point of view of control theory, positive feedback allows the equilibrium of the controlled system to move far from the initial state. However, it is a dangerous phenomenon for the controlled

system because, if uncontrolled, it leads to the destruction of the system (the values of the positively coupled elements increase to infinity or the destruction of the system). For this reason, control mechanisms must be in place to prevent an uncontrolled and inappropriate increase in the controlled elements. In cellular metabolism, these are mainly the Nrf2/FOXO transcription factors and autophagy. Even small perturbations of such control mechanisms can lead to the formation of a new equilibrium state in which the concentrations and/or activities of the regulated elements are too high, which should be taken into account when analysing the relationships and planning future experiments and therapeutic strategies.

3.1 The positive coupling between the inflammation and ROS

The positive feedback between inflammatory cytokines and NOX-mediated ROS appears to be the main axis of the intracellular and extracellular response to various pathogens. The relationship is bidirectional, and many reciprocal relationships between ROS and various cytokines and interleukins have been described in different tissues and research conditions. On the one hand, NOXs are activated by several cytokines, and on the other hand, ROS generated by NOXs activate multiple immunological activators such as IL-6 and TNF-α (127).

3.1.1 Role of NADPH oxidases

There are three main sources of ROS in the cell. The first one is the electron leakage from the cytochrome chain in the mitochondria (mito-ROS and mito-stress) (128), the second is the activity of NOXs (129), and the third is endoplasmic reticulum stress, where H_2O_2 is produced during protein folding as sulphur bonds are formed between cysteines. Other enzymes that produce ROS are xanthine oxidase, cytochrome P450, lipoxygenase and cyclooxygenase [103]. Externally, ROS are mainly produced by sources such as ionising radiation, UV light, xenobiotics and environmental pollutants [56].

The NADPH oxidase family is a group of seven enzymes (NOX1–5 and DUOX1–2) that produce O_2^- and H_2O_2 to kill microorganisms and also perform various signalling functions. Different types are found in different tissues and parts of the cell and are regulated differently to perform different functions (129, 130). The immune response to pathogens consists largely of the production of H_2O_2 and O_2^- by NOXs. The production of these molecules must increase to high levels during infection but must not exceed the limit of cell self-destruction. In healthy people, their activity should be limited to prevent the production of free radicals. In acute and chronic diseases, they are active to varying degrees (131–142).

3.1.2 NOX → inflammation

ROS produced by NOXs are involved in the activation of inflammation by activating pro-inflammatory transcription factors, such as the nuclear factor of activated T cells (NFAT), NF-κB and AP-1. Figure 2 shows the major cytokines being involved in the inflammatory response upon the activation of these transcription factors. NF-κB is the major ROS-dependent transcription factor, which is responsible for cytokine and chemokine gene expression (143). It is subject to numerous regulations by several factors involved in the regulation of inflammation, such as NO, HIF-1α, Nrf2 and kinase pathways: p38, JNK, ERK1/2, AMPK and PI3K/Akt. It is also involved in multiple regulatory couplings. NFAT is the transcription factor that is mainly activated by increased intracellular calcium and the calcineurin pathway (144), but ROS are also mentioned as an activator of NFAT (145). AP-1 is the transcription factor that can be activated by various cell stress conditions, including ROS (146).

One of the ways that pathogens activate inflammation is through Nod-like receptors (NLRs), a family of intracellular sensors of microbial or danger-associated molecular patterns. Nod-like receptor X-1 (NLRX-1) is capable of activating NF-κB and inflammation, and ROS mediate this activation (147, 148). Overexpression of NLRX-1 can induce ROS production to levels similar to those induced by TNF-α, a well-characterised activator of ROS. In another study, ROS mediated the IL-6 secretion upon advanced glycation end products (AGE) or LPS induction, which was dependent on ROS-induced NF-κB activation (149). A similar mechanism of IL-6 production was presented in abdominal aortic aneurysm inflammation that was stimulated by angiotensin II-activated NOX-derived ROS production (150). In another study, cadmium-induced IL-6 production in trophoblast cells through ROS-dependent activation of ERK1/2 (151).

There is also ample evidence that ROS regulate the expression of many pro-inflammatory genes. For example, NOX-dependent ROS have been shown to induce the expression of transforming growth factor beta 1 (TGF-β1), angiotensin II, MCP-1 and plasminogen activator inhibitor-1 (152).

3.1.3 Inflammation → NOX

Priming of NOXs occurs in response to a variety of cytokines such as TNF-α (153–155), IL-1β (156), IL-6 (157), IL-4 (158), IFN-γ (159), IL-8 (160), IL-12 (161), IL-15 (162), IL-17 (163), IL-23 (164) and TGF-β (165–169). There are several pathways that are used by cytokines to activate NOXs. The first one is Rac, which is the component protein of the NOX complex that is critical for the activation of NOX1 and NOX2. It is involved in many signals that increase NOX activation (129, 170). It is thought to act downstream of ROS production induced by cytokines such as TNF-α or interleukin-1β (171). TNF-α is also able to stimulate the membrane translocation of 47(phox) to activate NOX (143). Other cytokines involved in Rac-induced NOX activation are GM-CSF, TGF-β, PDGF and VEGF (172–176). AngII also activates NOX by Rac1 (170), which closes the positive loop between AngII and NOX.

Other signalling pathways used by cytokines to activate NOX are p38 MAPK, PI3K/Akt and protein kinase C (PKC). The PI3K pathway is used by IL-4 to activate NOX1 and NOX5L (177). IL-4 induced an intracellular calcium flux *via* the insulin receptor substrate (IRS)–PI3K–phospholipase Cγ (PLC-γ) pathway, which

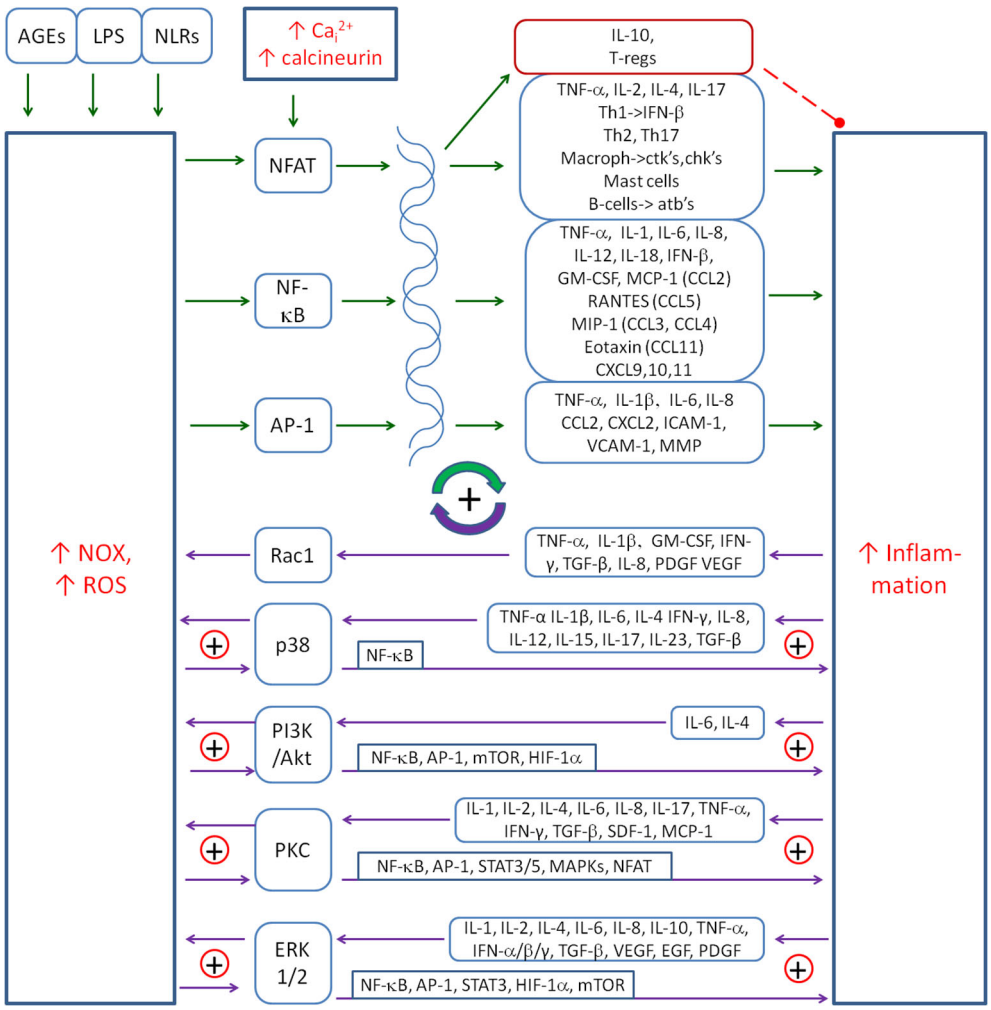

FIGURE 2
The main positive coupling between the inflammation and NOX-derived ROS that drive and amplify the inflammatory response. The main factors involved in this coupling are the transcription factors (NF-κB, AP-1 and NFAT), signalling pathways (p38, PI3K/Akt and ERK1/2) and the protein kinase C (PKC). Solid arrows, activation; red dashed line with •, inhibition; ⊕, the positive coupling between elements. NOX, NADPH oxidase; ROS, reactive oxygen species; NFAT, nuclear factor of activated T cells.

in turn induced PKC-dependent activation of NOX5. ROS in turn promoted IL-4 receptor activation through the oxidative inactivation of protein tyrosine phosphatase 1B (PTP1B), which physically associates with and deactivates the IL-4 receptor (158), closing a small positive loop between IL-4 and NOX5.

Many cytokines can activate the p38 pathway and thereby activate NOX (178). The most important are as follows: TNF-α (13), IL-1β (179, 180), IL-6 (181, 182), TGF-β (183), IL-34, IL-17 and GM-CSF. NOX can be activated by the p38 MAPK pathway, but p38 can also be activated by NOX-derived ROS, e.g. as a result of TNF-α (184), which closes the small positive loop between p38 and NOX. p38 MAPK can also activate inflammation by activating the pro-inflammatory NF-κB (185), which creates another positive feedback loop between p38 and inflammation. The whole forms a system of mainly positive feedback loops between cytokines, p38 and NOX. The details of the common couplings between NOX-derived ROS and the inflammatory cytokines are shown in Figure 2.

ERK1/2 is another mediator between ROS and inflammation. It activates transcription factors such as NF-κB (186), Elk-1 (186), AP-1 (31), Egr-1 (187), STAT3 (188) and HIF-1α (189), which induce the transcription of cytokines and/or NOXs, thereby further amplifying the inflammation–NOX coupling (190). In addition, ERK1/2 inhibits FOXO, which contributes to the reduction of the antioxidant response (191).

3.2 Nitric oxide and its couplings

3.2.1 Role of iNOS

NO produced by iNOS has several functions in the cell, particularly in the context of the immune and inflammatory response. Its activity is important in the destruction of pathogens. NO and its derivatives damage key structures of pathogens, such as cell membranes, proteins, nucleic acids and enzymes, leading to

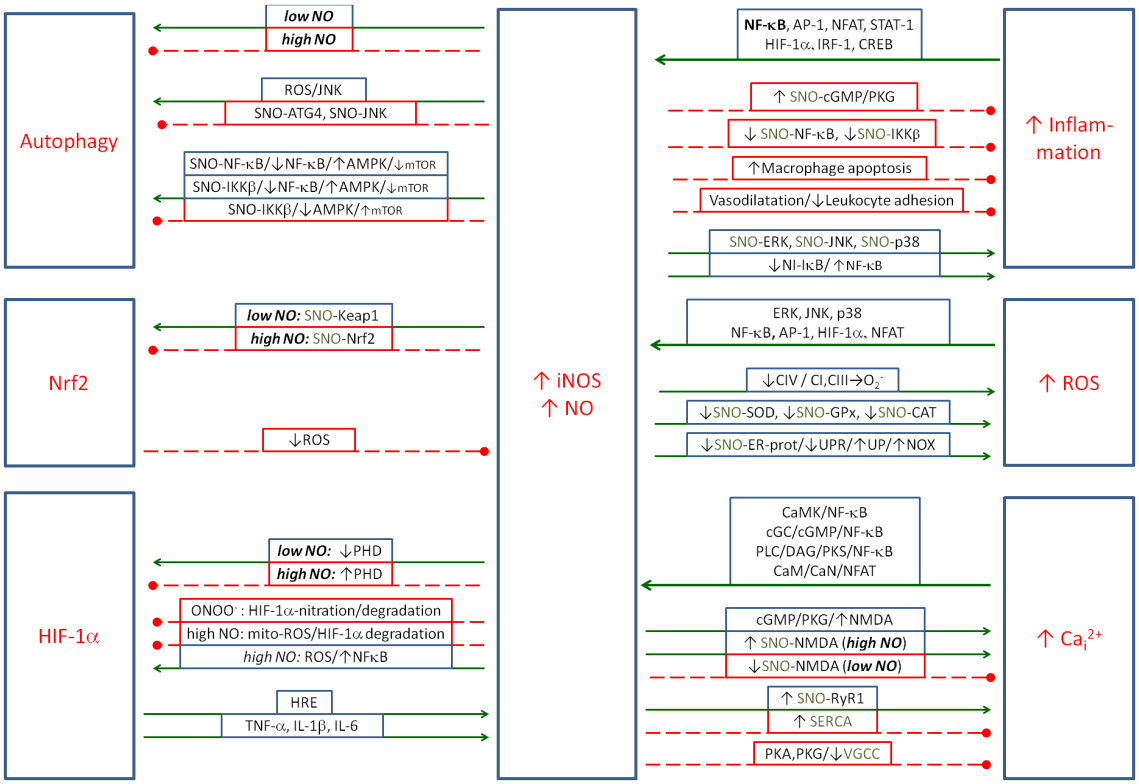

FIGURE 3
The metabolic couplings between the nitric oxide produced by iNOS and the elements of Positive Coupling System (inflammation/ROS/NO/HIF-1α/Ca_i^{2+}) and with regulatory elements: Nrf2 and autophagy. NO is the double-faced element, as in some cases it amplifies, and in some cases, it controls the inflammatory spiral. Solid arrows, activation; red dashed lines with •, inhibition. iNOS, inducible nitric oxide synthase; ROS, reactive oxygen species; NO, nitric oxide; HIF-1α, hypoxia-inducible factor 1-alpha.

their death (192). At the high concentrations reached during iNOS activity, NO can cause nitrosative stress and damage to cells and tissues, including cytotoxic effects on host cells. Reactive nitrogen species (e.g. peroxynitrite and $ONOO^-$), formed when NO reacts with O_2^-, have potent oxidative effects and can damage lipids, proteins and DNA, contributing to chronic inflammation and tissue damage (192). It also acts on the mitochondria, contributing to increased free radical production and mitochondrial stress, which reduces energy production, lowers mitochondrial potential and promotes apoptosis (193). Although NO produced by iNOS does not play a major role in the regulation of vascular tone (this is mainly the responsibility of endothelial Nitric Oxide Synthase (eNOS)), its excess can indirectly affect blood vessels (194). High levels of NO can cause vasodilation, which contributes to increased blood flow at sites of inflammation, thereby increasing the access of immune cells to the infected or damaged area (194).

Unlike oxygen radicals, which are removed by anti-free radical enzymes, e.g. SOD, catalase and glutathione peroxidase, there are no specialised pathways to remove NO from the cell. The main pathway for its removal from the cell is diffusion, as NO readily crosses lipid membranes. In the bloodstream (195), NO reacts rapidly with the haemoglobin, which binds NO, converting it to nitrate (NO_3^-) (196). However, the peroxynitrite is neutralised by catalase (197), peroxiredoxin-3 (Prx-3) (198) or glutathione (199).

3.2.2 Couplings between NO and inflammation

NO is coupled mainly negatively with inflammation; however, some positive couplings have also been described (see Figure 3). Pro-inflammatory cytokines activate NO production, while NO inhibits the inflammatory process by several mechanisms. This action appears to be related to the strong oxidative effects of NO and $ONOO^-$, which force the precise regulation of NO induction in the presence of intracellular pathogens.

Pro-inflammatory cytokines (such as IL-1, IL-6, IFN-γ and TNF-α) and pro-inflammatory transcription factor NF-κB play a key role in the induction of iNOS. The main mediating pathway is NF-κB, which leads to the transcription of the iNOS gene and an increase in NO production (200). The NF-κB pathway is crucial because it acts as the major transcription factor that activates iNOS expression in response to cytokine stimulation. Other pathways that also contribute to some extent to the activation of iNOS transcription are the AP-1 (activator protein-1) (201), NFAT (202), signal transducer and activator of transcription 1 (STAT-) (203), HIF-1α (204) and interferon regulatory factor 1 (IRF-1) (205). In the case of the cAMP/PKA/CREB pathway, CREB increases the expression of iNOS (206), but the increase in cAMP reduces the increased expression of iNOS and other inflammatory markers such as TNFα, IL-1β, IL-6, NF-κB, MMP-2 and MMP-9 in H9c2 cardiac cells, probably through different intermediate

mechanisms (207). The above transcription factors cooperate in the induction of iNOS, and their cooperation allows the fine-tuning of iNOS expression levels to specific physiological conditions, such as inflammation, oxidative stress or hypoxia.

Conversely, NO is known to have mainly anti-inflammatory properties. NO acts mainly through cyclic GMP (cGMP) (208) and also directly through protein modifications (*S*-nitrosylation) (209), affecting the function of enzymes and regulatory proteins. cGMP activates protein kinase G (PKG), which leads to vascular smooth muscle relaxation, resulting in lower blood pressure (210). cGMP also inhibits platelet aggregation, which has an anticoagulant effect (211). cGMP also activates signalling pathways, such as PKG, which may have anti-inflammatory effects. PKG can inhibit leukocyte adhesion and activation, reduce the production of pro-inflammatory cytokines and decrease the reactivity of immune cells (212, 213). This effect is partly related to the inhibition of NF-κB by cGMP (214). NO can also inhibit NF-κB through *S*-nitrosylation of its p65 subunit, which blocks its ability to bind to DNA (215). NO can also nitrosylate and inhibit IKK-β (NF-κB activator) (215, 216). Conversely, nitrosylation of I-κB leads to NF-κB activation (217).

Another mechanism of NO's anti-inflammatory action is the induction of apoptosis in activated macrophages and other immune cells under certain conditions, leading to a reduction in the inflammatory response. This mechanism prevents chronic inflammation by removing over-activated cells (218, 219). Another mechanism by which NO inhibits the inflammatory response is through its vasodilatory effect on vascular smooth muscle, which reduces leukocyte adhesion to the endothelium. Reduced leukocyte adhesion reduces the influx of inflammatory cells to the site of inflammation, thereby limiting the development of the inflammatory response (220, 221). Conversely, NO can activate inflammation by activating MAPK kinases (ERK, JNK and p38) through the induction of oxidative stress (e.g. through the production of reactive nitrogen species such as peroxynitrite) (222). The activation of MAPK kinases promotes the inflammatory response by affecting the expression of pro-inflammatory cytokines.

3.2.3 NO + O_2^- → $ONOO^-$

The coupling between iNOS and NOX is mainly functional (223). NO and O_2^- produced by these two enzymes generate the dangerous radical $ONOO^-$, which greatly enhances the destructive effect of both radicals. In the experiment with primary co-cultures of rat cerebellar granule neurons and glia, the increase of NO or O_2^- alone produced a benign toxic effect, but the co-activation of both enzymes produced a strong effect of neuronal death (223). The pro-surviving effect of NMDA (N-Methyl-D-Aspartate Receptor) inhibitor observed in this study suggests an important role of Ca_i^{2+} in this process.

3.2.4 NO → ROS

NO can enhance the production of oxygen free radicals in several ways. In the mitochondria, NO inhibits complex IV (cytochrome *c* oxidase) in the respiratory chain by competing with oxygen for the active site of this enzyme. Inhibition of complex IV leads to electron accumulation in the mitochondria, which increases electron leakage and O_2^- generation by complexes I and III (224). Next, NO and its derivatives can nitrosylate key antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx) and catalase, reducing their activities and leading to the accumulation of ROS in cells (225). It can also nitrosylate certain proteins in the endoplasmic reticulum, leading to the accumulation of misfolded proteins, endoplasmic reticulum (ER) stress and subsequent NOX activation (226).

3.2.5 ROS → iNOS

Conversely, ROS also activate iNOS in several ways. The main mechanism is through the activation of key transcription factors such as NF-κB, AP-1 and STAT1, which are essential for iNOS gene transcription (203, 227). ROS activate IKK, which phosphorylates IκB inhibitor, leading to NF-κB activation. ROS also activate MAPK kinases (ERK, JNK and p38), which phosphorylate and activate Jun and Fos proteins, which form the AP-1 complex. AP-1 binds to the iNOS promoter and promotes its expression. ROS can also enhance STAT1 activation by cytokines (e.g. IFN-γ), promoting its binding to the iNOS promoter (228). Pathways leading to the activation of the above-mentioned transcription factors are mainly MAPKs: p38, JNK and ERK1/2, which phosphorylate, among others, NF-κB and AP-1, promoting the transcription of pro-inflammatory cytokines, but also iNOS. Another indirect ROS mechanism is the activation of iNOS by an increase in Ca_i^{2+}.

3.2.6 NO → Ca_i^{2+}

NO can modulate Ca_i^{2+} levels by a variety of indirect mechanisms, and the final result depends on the physiological context. NO can nitrosylate RyR1 calcium channels, which increases its channel activity at lower O_2 tension and increases Ca_i^{2+} levels (229). This mechanism may contribute to the ER stress. To compensate for this, NO activates the sarco/endoplasmic reticulum Ca^{2+}-ATPase (SERCA) calcium pump, which increases Ca^{2+} uptake into the ER (230).

NO also nitrosylates NMDA channels, inhibiting Ca^{2+} influx into the cell in physiological concentrations but increasing it in high concentrations (229, 231). NMDA receptor activation and Ca_i^{2+} increase can also occur via the NO/cGMP/PKG pathway (232). Another way in which NO increases Ca_i^{2+} is through the activation of transient receptor potential (TRP) channels by nitrosylation, which can increase Ca^{2+} influx into the cell (233). Conversely, NO can directly or indirectly inhibit voltage-gated calcium channels (VGCCs), thereby reducing Ca^{2+} influx into the cell through PKG and PKA signalling (234). It is generally accepted that excess NO and associated changes in Ca^{2+} concentration can lead to excitotoxicity in neurons, which is associated with neurodegenerative diseases (e.g. Alzheimer's and Parkinson's) (235), and that dysregulation of NO-Ca^{2+} signalling is implicated in inflammation and tissue damage (236).

3.2.7 Ca_i^{2+} → iNOS

Ca_i^{2+} is a known activator of neuronal Nitric Oxide Synthase (nNOS) and eNOS but does not directly activate iNOS. However,

Ca_i^{2+} induces iNOS indirectly mainly through NFAT and NF-κB. High Ca_i^{2+} activates the calmodulin/calcineurin/NFAT signalling pathway, which contributes to the transcription of iNOS (237). NF-κB is also the transcription factor, which is postulated to mediate the iNOS activation by Ca_i^{2+} (238). Ca^{2+} ions can activate NF-κB via the calmodulin/calcineurin/CaMK (239, 240), soluble guanylyl cyclase (sGC)/cGMP (241) and PLC/diacylglycerol (DAG)/PKC pathways (242). Another pathway is the activation of ROS production in the mitochondria by mitochondrial Ca^{2+}, which further leads to NF-κB activation.

3.2.8 NO → autophagy

Nitric oxide plays a critical role in the regulation of autophagy, exerting both activating and inhibitory effects depending on its concentration, cellular context and signalling pathways involved. At physiological levels, NO generally promotes autophagy, helping to remove damaged organelles and maintain cellular homeostasis. However, under pathological conditions such as chronic inflammation or oxidative stress, excessive NO acts as an inhibitor, exacerbating cellular damage.

NO activates autophagy primarily through the AMPK–mTOR pathway (243). In response to metabolic stress, NO can induce energy stress by increasing the AMP-to-ATP ratio, which activates AMPK. Activated AMPK inhibits mTOR, a key suppressor of autophagy, thereby initiating the autophagosomal process via the activation of the ULK1 complex. In addition, NO can increase the production of ROS, which activate pathways such as JNK, further enhancing autophagy in response to oxidative stress.

Conversely, NO can inhibit autophagy under certain conditions, particularly when present in excess. One important mechanism is the *S*-nitrosylation of key autophagosomal proteins such as ATG4, which impairs their function and blocks the elongation of the autophagosomal membrane (244). Another pathway is the nitrosylation and deactivation of JNK1, which is an important autophagy activator (see Figure 1) (245). NO also nitrosylates (inhibits) IKKβ, which reduces AMPK phosphorylation (activation). This leads to the activation of mTORC1 and inhibition of autophagy. *S*-Nitrosylation of IKKβ is thought to be a negative feedback mechanism during inflammation to prevent excessive activation of NF-κB, thereby protecting tissues from chronic inflammation or damage (215, 216). NO can also activate sGC, leading to increased levels of cGMP and potential mTOR activation, thereby suppressing autophagy (246, 247).

Another pathway of NO activity is via TSC1/2 (tuberous sclerosis complex), a known inhibitor of mTOR and activator of autophagy. IKKβ, Akt and ERK1/2 inhibit this complex, and AMPK activates it, contributing to the regulation of autophagy (245). Finally, in the case of chronic inflammation, the chronic NF-κB activation is a factor that inhibits AMPK and activates mTOR, thereby contributing to autophagy inhibition, which seems to be an important element of the overall autophagy inhibition in chronic information observed under several conditions. The dual role of NO in autophagy highlights its dependence on the metabolic context. Excess of NO and over-nitrosylation seems to be an important element driving the entry of inflammation into a chronic state when the summary effect on autophagy is the inhibitory one.

3.2.9 NO and $ONOO^-$ → Nrf2

Nrf2 is the central antioxidant transcription factor, which is responsible for inhibiting excessive oxidative stress and inflammation. Its coupling with iNOS/NO is NO concentration dependent. Nrf2 is regulated by Kelch-like ECH-associated protein 1 (Keap1). It contains many reactive cysteine residues (e.g. Cys151, Cys273 and Cys288) that are susceptible to *S*-nitrosylation, leading to a reduction in its ability to bind Nrf2 (248). This leads to Nrf2 release and translocation to the nucleus. In addition, 8-nitro-cGMP-dependent *S*-guanylation of Keap1 leads to Nrf2 activation, with the concomitant expression of the targeted antioxidant enzymes that play a role in signalling under oxidative stress conditions (249, 250).

At low concentrations, NO activates Nrf2 by nitrosylating Keap1 (248). The other pathway of Nrf2 activation is the activation of PKC-α by NO in kidney cells (251) or PKC-ε (252), which phosphorylate Nrf2 and have the same effect (253). Among the PKC isoforms, PKC-δ plays a predominant role in phosphorylating Nrf2, particularly at serine 40, promoting its dissociation from Keap1 (254). $ONOO^-$ at physiological concentrations also has the ability to activate Nrf2 (255–257). The intermediate pathway for this effect may be PI3K/Akt (258).

$ONOO^-$, as a dangerous radical, is also known for its destructive effects on the activities of various enzymes. In contrast to the activation of Nrf2 by NO and $ONOO^-$, inhibitory effects of $ONOO^-$ on Nrf2-induced enzymes have been demonstrated, e.g. HO-1 (259), catalase (260), Mn-SOD (261), peroxiredoxin II E (262), glutathione peroxidase (263) and thioredoxin reductase (263). It can therefore be concluded that exceeding a certain level of $ONOO^-$ concentration in the cell leads to a breakdown of the antioxidant barrier, which is probably a part of the molecular pathology in various diseases.

3.2.10 NO → mitochondria

NO is a reversible inhibitor of mitochondrial complex IV. This inhibition, although readily reversible, can have profound consequences for the cell (264). Inhibition of the cytochrome chain at the level of complex IV can lead to the production of superoxide due to the electron leakage from complexes I and III, which in turn leads to the production of $ONOO^-$. $ONOO^-$ is the irreversible inhibitor of complex IV, which enhances the regulatory effect of NO (197). $ONOO^-$ can also irreversibly damage many of the mitochondrial enzymes including aconitase, NADH/co-Q reductase, quinol/cytochrome *c* reductase, succinate dehydrogenase and the ATP synthetase (265, 266). The resulting collapse of the mitochondrial membrane potential can open the mitochondrial permeability transition pores (mPTPs), release the cytochrome *c* into the cytoplasm and trigger apoptotic cell death.

3.2.11 NO—summary

The effect of nitric oxide is both activating and inhibitory in all the relationships discussed. It exhibits outstanding non-linear

properties, contributing predominantly to the maintenance of homeostasis at low physiological concentrations and leading to metabolic collapse at high concentrations. This implies the need for a detailed in-depth analysis of the role of NO depending on the metabolic context and, above all, NO concentration.

3.3 Calcium stress

Ca_i^{2+} is associated with inflammation and oxidative stress through a number of couplings and is also involved in enhancing the immune response. Figure 4 shows the detailed relationships between intracellular and endoplasmic calcium, ROS and HIF-1α. The main influence of Ca_i^{2+} is through its positive loop with the NOX-mediated ROS.

Calcium is an important intracellular messenger molecule that is significantly involved in antimicrobial defence. Normal resting Ca_i^{2+} levels in the cytoplasm of most cells are typically very low, ranging from approximately 50 to 100 nM (267). Calcium ions are the second messengers that cause the activation of multiple downstream proteins. The pumping of calcium ions out of the cell requires a large amount of energy, as the divalent ions must be pumped out against a high electrical (approximately −70 to −90 mV) and high concentration gradient (on the order of 1,000-fold) (268). The pumping out of one Ca_i^{2+} ion requires one molecule of ATP so that the reduction of energy production in the mitochondria, e.g. by HIF-1α-mediated PDH inhibition, can lead to a further increase of Ca_i^{2+} in the cytoplasm and mitochondria (269, 270). However, Ca_i^{2+} ions contribute to the opening of mPTPs, leading to a decrease in the mitochondrial membrane potential Ψ_m (271), which worsens the conditions for energy production and facilitates apoptosis.

3.3.1 ER stress and Ca^{2+}

The increase in cytoplasmic Ca_i^{2+} is the main form of calcium stress, but the second important type of calcium stress is associated with the ER. The two are interrelated, as increases in Ca_i^{2+} are often associated with decreases or increases in Ca_{ER}^{2+}. The ER is a major store of Ca^{2+} and typically maintains a much higher concentration than the cytosol. The Ca_{ER}^{2+} levels are typically in the range of 300 to 800 μM (272, 273), which is essential for proper protein folding and serves as a reservoir that can release Ca^{2+} when needed for signalling purposes. Many of the chaperones and enzymes involved in protein folding in the ER, such as calnexin and calreticulin, require adequate Ca_{ER}^{2+} for their structural stability and functional activity (274). During ER stress, calcium homeostasis is often disrupted (275–277). The ER can release Ca^{2+} into the cytosol, leading to an increase in cytosolic Ca^{2+} concentration. This release can activate various signalling pathways, including those that lead to cellular responses such as apoptosis or autophagy if the stress is severe or prolonged. Conversely, prolonged ER stress can lead to depleted ER calcium levels, which can affect protein folding and other ER functions, leading to the accumulation of misfolded proteins (277–280).

Oxidative protein folding refers to the process by which proteins acquire their proper structure through the formation of disulfide bonds between cysteine residues in the proteins. This reaction is mediated by a number of protein disulfide isomerases and oxidoreductases such as ER oxidoreductin 1 (Ero1) and protein disulfide isomerase (PDI) (281, 282). Changes in Ca_{ER}^{2+} levels can affect the activity of Ero1 and PDI, which in turn alters the production of H_2O_2, a by-product of disulfide bond formation. At low Ca^{2+} concentrations in the ER, Ero1 activity is reduced, which reduces H_2O_2 production. This results in reduced oxidative stress in the ER but may also affect protein folding. At high concentrations of

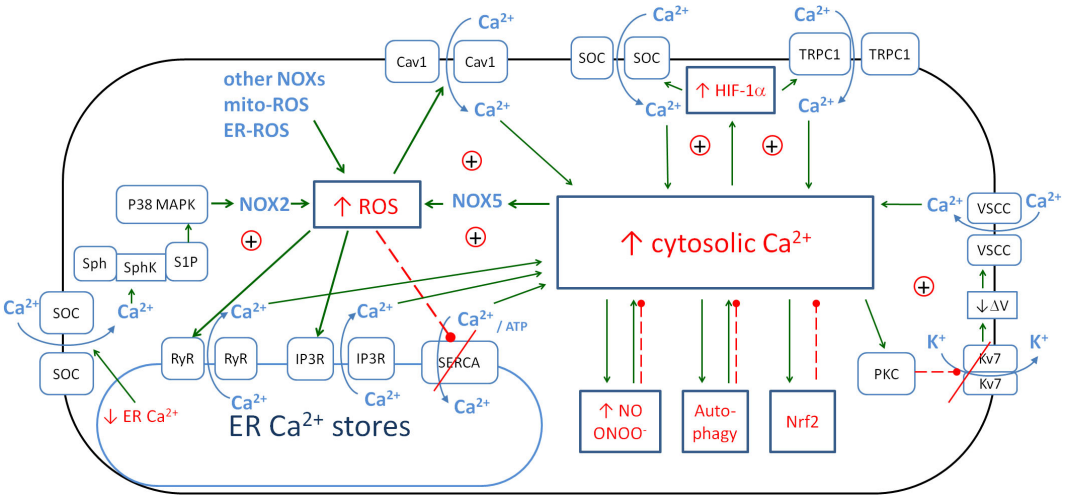

FIGURE 4
The metabolic links between cytosolic Ca^{2+}, endoplasmic Ca^{2+}, ROS and HIF-1α create the positive couplings that enhance the anti-pathogen response. The details of the couplings with iNOS/NO are in Figure 3, with autophagy, and Nrf2 in Figure 6. Solid arrows, activation; red dashed lines with •, inhibition; ⊕, positive coupling between elements; red line crossing out, inhibition of the channel. ROS, reactive oxygen species; HIF-1α, hypoxia-inducible factor 1-alpha; iNOS, inducible nitric oxide synthase; NO, nitric oxide; Nrf2, nuclear factor erythroid 2-related factor 2.

Ca^{2+} in the ER, Ero1 activity increases, which increases H_2O_2 production (283). The ER contains specific glutathione peroxidases, such as GPx7 and GPx8, which are critical for reducing peroxide levels (284, 285). These enzymes use glutathione (GSH) as a substrate to convert H_2O_2 to water, directly neutralising it. Peroxiredoxins, such as Prx-4, are another group of ER-localised antioxidants that help reduce peroxides (286, 287).

Inefficient removal of H_2O_2 in the ER leads to oxidative stress, which can damage the calcium pumps (such as SERCA). This impairs its ability to pump Ca^{2+} into the ER, resulting in reduced ER calcium levels. A decrease in ER calcium due to oxidative stress impairs the activity of the calcium-dependent enzymes, leading to the accumulation of misfolded proteins in the ER, which initiates an unfolded protein response (UPR). However, prolonged oxidative stress and impaired calcium levels can compromise the effectiveness of these responses, leading to chronic ER stress and a vicious cycle of low Ca_{ER}^{2+} and high H_2O_2.

Chronic ER stress has been implicated in a variety of diseases, reflecting its fundamental role in cell function and survival. It has been implicated in neurodegenerative diseases [Alzheimer's (276), Parkinson's and Huntington's (279)], diabetes (both type 1 and 2), cardiovascular disease (atherosclerosis and heart failure) (274), cancer, obesity, inflammatory bowel disease and liver disease (275). In summary, there is a similarity between the ER and mitochondria in that both organelles produce ROS as a by-product and have the mechanisms to reduce the functionally relevant oxidative stress.

3.3.2 Ca_i^{2+} ↔ NOX

One of the major pathways for Ca_i^{2+} elevation is oxidative stress and the regulation of Ca_i^{2+} signalling by NOX enzymes (288). Three pathways for ROS-induced Ca_i^{2+} elevation have been described. The first is the Ca^{2+} influx via the opening of voltage-gated L-type Ca^{2+} channels (Cav1) (289, 290). The second pathway is Ca^{2+} release from intracellular stores (291, 292), for example, via the ryanodine receptor (RyR) family, which have reactive cysteine residues that are highly sensitive to oxidation by ROS (293). ROS also act on another type of Ca^{2+} release channel, namely, the inositol 1,4,5-trisphosphate receptor (IP3R) family (294, 295). Finally, ROS can modulate the activity of Ca-ATPase pumps (SERCA) that remove Ca_i^{2+} from the cytoplasm (292, 296, 297) in a bimodal manner. The mechanism of ROS-dependent Ca_i^{2+} pump activation involves the mechanisms of ROS-dependent *S*-glutathiolation of protein cysteines mediated by the interaction of glutathione and peroxynitrite (296). This activation of the Ca^{2+} pump by *S*-glutathiolation occurs at low ROS concentrations. Increased oxidative stress leads to the irreversible oxidation of thiols and thus to enzyme inhibition (292). In this way, the negative regulatory coupling becomes the positive one contributing to the increase in oxidative stress and inflammation. The restoration of the negative regulatory coupling may be an important part of the treatment of many pathological conditions.

The increase in intracellular calcium concentration is induced by NOX-derived ROS, but the opposite regulation also takes place. An increase in cellular calcium levels is associated with many metabolic effects. One of these is the activation of NADPH oxidases (129, 298, 299). The details of the stimulatory effect of calcium ions on the activity of individual NOX enzymes have been described in reviews (129, 300, 301). In brief, the activating effect of calcium ions on NOX can be direct and indirect. The direct effect is described in relation to NOX5. The expression of NOX5 is restricted to a few tissues, although it is found in human vascular smooth muscle cells (VSMCs), endothelial cells and whole vessels—important tissues in the development of COVID-19 pathology. Calcium induces the binding of the N-terminal domain of NOX5 to its dehydrogenase domain, thereby relieving autoinhibition. In microvascular endothelial cells, NOX5 expression is also increased by endothelin-1 and AngII and mediates the activation of ERK1/2 (302). Another association of NOX5 with endothelial cells was shown by Guzik et al. (303). They showed that NOX5 expression is higher in human coronary arteries with coronary artery disease than in those without the disease. This increased NOX5 expression was accompanied by a sevenfold increase in activity.

In the case of NOX2, the role of Ca_i^{2+} is indirect. In non-excitable cells, Ca^{2+} influx is essentially mediated by store-operated calcium entry (SOCE), a complex mechanism in which the depletion of intracellular Ca^{2+} stores from the ER leads to Ca^{2+} entry through Ca^{2+} store-operated calcium channels (SOCs) at the plasma membrane. Extracellular Ca^{2+} entry is known to be involved in NOX2 activation. Schenten et al. (304) showed that sphingosine kinase (SphK)-regulated NOX2 activation depends on the depletion of intracellular Ca^{2+} stores. Their results define a pathway leading to NOX2 activation, in which store depletion-dependent SphK activation induces p38 MAPK-mediated S100A8/A9 translocation. S100A8/A9, also known as calprotectin, functions as a damage-associated molecular pattern (DAMP) that activates various signalling pathways, including those involving NOX2 as a defence mechanism against pathogens (304). However, its role in inflammation and oxidative stress is more complex, as some anti-inflammatory properties have also been described (305).

The important pathway for Ca_i^{2+} elevation is the activation of phospholipase C (PLC), which leads to Ca_i^{2+} elevation and further stimulation of PKC. PKC can be activated by increases in intracellular calcium, but it can also contribute to increases in Ca_i^{2+} levels. Haick et al. (306) showed that PKC activation leads to the suppression of Kv7 (family of voltage-gated potassium channels) currents, membrane depolarisation and Ca^{2+} influx through L-type voltage-sensitive calcium channels (VSCCs) (306). Thus, a positive loop between the PKC activity and Ca_i^{2+} concentration can be observed, which is switched on by PLC activation. Several mechanisms can activate PLC. GPCRs can activate PLC-β, and RTKs can activate PLC-γ. High concentrations of calcium ions can activate the PLC-δ isoform. PLC can also be indirectly activated by ROS and $ONOO^-$.

3.3.3 Inflammation → Ca_i^{2+}

The binding of cytokines to receptors activates signalling pathways, such as the MAPK, PLC pathways or NF-κB, which can influence the increase in intracellular calcium ion concentration through various pathways. The activation of PLC leads to the

breakdown of phosphatidylinositol-4,5-bisphosphate (PIP2) into inositol-1,4,5-triphosphate (IP3) and DAG. IP3 binds to IP3 receptors in the ER, causing the release of Ca^{2+} ions from the ER into the cytoplasm (307). In turn, DAG activates transient receptor potential canonical (TRPC) channels, leading to an influx of Ca^{2+} ions from the extracellular space (308). Cytokines can also activate SOCE channels for Ca^{2+} to facilitate the influx of ions from the outside after the depletion of calcium stores in the ER (309).

3.3.4 Ca_i^{2+} → inflammation

Calcium ions induce inflammation mainly by increasing the production of free radicals, which activate the inflammatory cascades described above. However, there are several pathways that activate inflammation without the mediation of ROS. Increased Ca_i^{2+} concentration is a signal that activates the NLRP3 inflammasome, which catalyses the conversion of pro-IL-1β to active IL-1β (310). The activation of the inflammasome further increases cytokine release and enhances Ca_i^{2+} mobilisation, creating a positive feedback loop between inflammation and Ca_i^{2+}. Ca_i^{2+} also enhances the transcription of pro-inflammatory genes through the activation of factors such as NF-κB (311), which then increases the activity of iNOS, leading to NO production.

3.3.5 Ca^{2+} → autophagy

Ca_i^{2+} is an important regulator of autophagy. Under normal conditions, Ca_i^{2+} activates the autophagy in healthy cells mainly by activating calcium/calmodulin-dependent kinase kinases (CaMKKs), in particular CaMKKβ (312–315). This kinase activates AMPK (316), which in turn inhibits mTOR, a key negative regulator of autophagy. In addition, calcineurin activated by high intracellular Ca^{2+} levels can dephosphorylate transcription factor EB (TFEB), a master regulator of lysosomal biogenesis and autophagy genes (317–319). Dephosphorylated TFEB translocates to the nucleus and enhances the transcription of autophagy-related genes, thereby promoting autophagy.

ER stress is one of the important conditions that increase Ca_i^{2+} concentration by its release from Ca^{2+} stores and initiates the above-mentioned pathways (320). However, autophagy can be activated by the inter-organelle transfer of Ca^{2+} from the ER to the mitochondria via the mitochondria-associated membrane (MAM) (321). Key proteins located at the MAM include the IP3Rs on the ER side and the voltage-dependent anion channels (VDACs) on the mitochondrial outer membrane, which are connected by the chaperone protein glucose-regulated protein 75 (GRP75) (322). Ca^{2+} is released from the ER via IP3Rs into the MAM space and is then rapidly taken up by the mitochondria via VDACs and the mitochondrial Ca^{2+} uniporter (MCU). This Ca^{2+} transfer is essential for the activation of mitochondrial enzymes involved in energy production, such as those in the Krebs cycle. The transfer of Ca^{2+} from the ER to the mitochondria can affect mitochondrial dynamics and promote mitochondrial fission, which is often associated with the initiation of autophagy (323).

However, autophagy can modify Ca_i^{2+} levels in a bimodal manner. Autophagy can increase Ca_i^{2+} levels by depleting intracellular Ca^{2+} stores such as the ER or by affecting the membranes of lysosomes where Ca^{2+} channels are located (324). The depletion of these stores may lead to a transient increase in cytosolic Ca^{2+}, which may produce feedback to promote further autophagic activity. Conversely, although autophagy can be stimulated by Ca^{2+}, the process itself tends to balance Ca^{2+} levels within the cell. Excessive autophagy can lead to the excessive depletion of Ca^{2+} stores, lowering intracellular Ca^{2+} levels to a point where autophagic activity is reduced, thus preventing cellular damage from excessive autophagy (325).

In conclusion, intracellular calcium is mainly positively associated with inflammation and oxidative stress, but some described negative couplings at physiological concentrations act as regulators of excessive Ca_i^{2+} increase.

3.4 Activation of HIF-1α pathway

The next important player in the inflammatory response is HIF-1α. Figure 5 shows the detailed relationships between this factor and inflammation, ROS, NO, Ca_i^{2+} and mitochondria. Under normal conditions, HIF-1α levels increase during the hypoxia state. In this case, it has a protective function against the overproduction of free radicals in the mitochondria during hypoxia or hypoxia/reperfusion by reducing pyruvate entry into the mitochondria and NADH "pressure" on the cytochrome chain, thereby reducing mito-stress (128). Its protective effect has been demonstrated, for example, in myocardial infarction, where it activates the anaerobic glycolysis enzyme 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 2 (PFK-2/FBPase-2) and supports anaerobic ATP production (326). In another study, HIF-1α-deficient mice showed greater intestinal barrier disruption and a more severe course of colitis (327).

HIF-1α is degraded by HIF prolyl hydroxylase domains (PHDs), and inhibition of PHDs results in the stabilisation of HIF-1α. However, Factor Inhibiting HIF (FIH) is an oxygen-dependent enzyme that causes the hydroxylation of HIF-1α, which in turn inhibits the interaction of the HIF-1α subunit with CBP/p300 (HIF-1α co-activator) (328–330). This interaction is required for the transcription of HIF-dependent genes. Therefore, FIH provides a mechanism for reducing the transcriptional activity of the HIFs in normoxia.

HIF-1α can be stabilised by the inhibitory effect of succinate (SC) on the HIF prolyl hydroxylases (331–335). Increased levels of Krebs cycle molecules in the cytoplasm such as oxaloacetate, fumarate, malate and succinate may be the effect of pyruvate dehydrogenase (PDH) inhibition. Thus, a possible positive feedback loop may be observed in which HIF-1α inhibits PDH, inhibited PDH increases the concentration of succinate, and increased succinate stabilises HIF-1α.

3.4.1 NOX/ROS → HIF-1α

ROS generated by NOXs are important activators and stabilisers of HIF-1α. They inactivate PHDs, leading to an increase in the stability of the HIF-1α protein. ROS also activate PKA and mTOR, which phosphorylate HIF-1α, increasing its

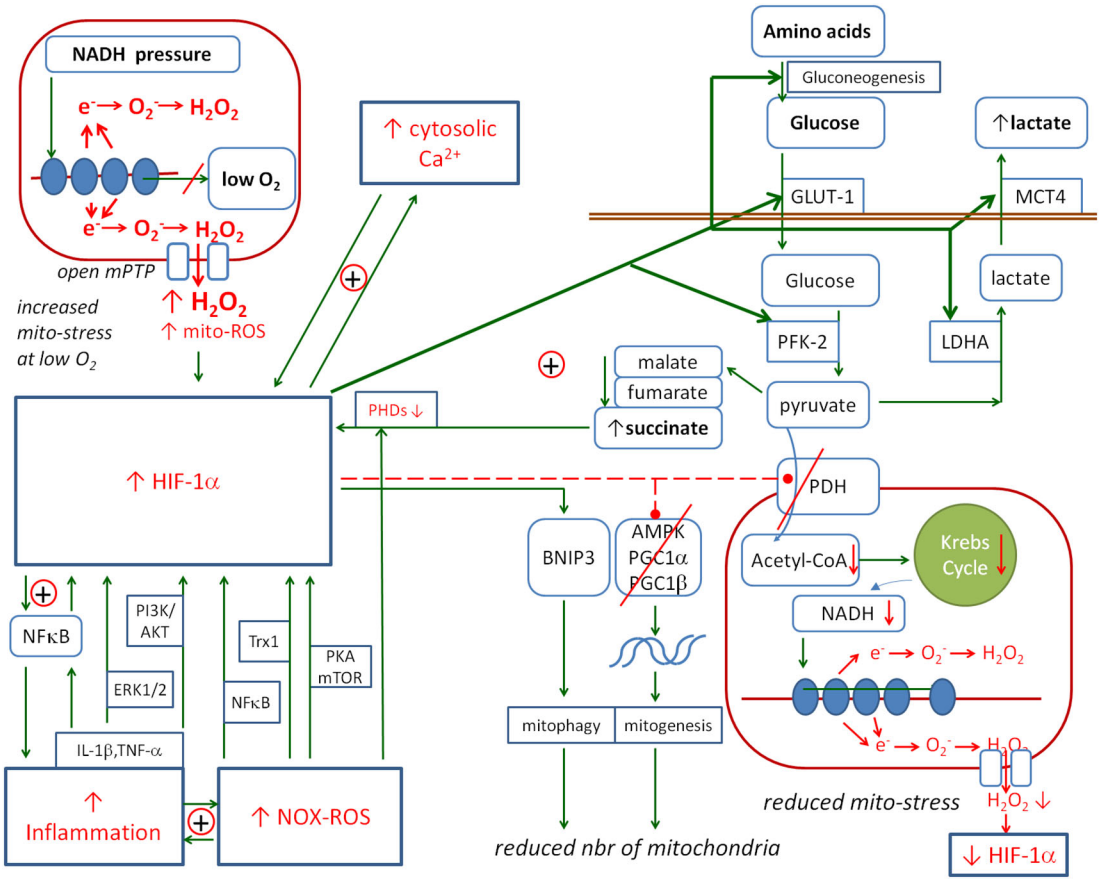

FIGURE 5
The metabolic links between HIF-1α and mitochondria. HIF-1α is activated by inflammation, ROS and Ca_i^{2+}. Its activation promotes the pathways that prevent mitochondrial ROS production: HIF-1α activates the anaerobic glycolysis and reduces the number of mitochondria. The positive loop between HIF-1α and succinate enhances the protective effect on mitochondria. Solid arrows, activation; red dashed lines with •, inhibition; ⊕, positive coupling between elements; red line crossing out, inhibition of the channel or pathway. HIF-1α, hypoxia-inducible factor 1-alpha; ROS, reactive oxygen species.

stability and leading to its accumulation in the cell (336, 337). ROS also upregulate the expression of thioredoxin 1 (Trx1), which increases the transcriptional activity of HIF-1α (338). However, ROS-mediated HIF-1α induction also occurs at the transcriptional level, and it is dependent on NF-κB—a major transcription factor for inflammatory cytokines (336). Finally, ROS generated by exogenous H_2O_2 or by a NOX4 transcriptionally induce HIF-1α via the NF-κB binding site in the HIF-1α promoter (339).

3.4.2 HIF-1α → NOX

The reverse relationship, i.e. the activation of NOX by HIF-1α under certain conditions, has also been reported, albeit in small numbers. André-Lévigne et al. (340) reported that HIF-1α activates the transcription of NOX4 in the context of wound repair activation. In another article, Diebold et al. reported that the transcription of NOX2 is activated by HIF-1α in the context of the urotensin-II-activated angiogenesis (341, 342).

3.4.3 HIF-1α ↔ NF-κB-positive coupling

HIF-1α activates the inflammation mainly through NF-κB (343), which is crucial for inducing the production of pro-inflammatory cytokines, e.g. TNF-α and IL-6. Conversely, NF-κB has been shown to contribute to increased *Hif1a* mRNA transcription under hypoxic conditions (344, 345). BelAiba et al. (344) showed that the expression of the NF-κB p50 and p65 subunits increased HIF-1α mRNA levels, while blocking NF-κB with the NF-κB inhibitor attenuated the induction of HIF-1α mRNA by hypoxia. Reporter gene assays revealed the presence of an NF-κB site in the HIF-1α promoter, and mutation of this site abolished HIF-1α induction by hypoxia. Gel shift analysis and chromatin immunoprecipitation confirmed the binding of the p50 and p65 subunits of NF-κB to the HIF-1α promoter under hypoxia. In another study, Frede showed that LPS increased HIF-1α mRNA expression through the activation of an NF-κB site in the promoter of the HIF-1α gene, and hypoxia post-translationally stabilised HIF-1α protein (345).

3.4.4 Cytokines → HIF-1α

The previous subsection discussed the coupling between HIF-1α and the pro-inflammatory NF-κB. The direct effect of cytokines on HIF-1α has also been observed. Malkov et al. (346) discussed the influence of two cytokines, TNF-α and IL-1β, on HIF-1α. Both can activate HIF-1α via both the NF-κB and PI3K/Akt pathways (347–349). The activation of these pathways results in increased HIF-1α protein synthesis and stabilisation under normoxic conditions. TNF-α stimulation leads to the activation of NF-κB, which can bind to the HIF-1α promoter and enhance HIF-1α transcription. The PI3K/Akt pathway stabilises HIF-1α through the post-translational modification and inhibits its degradation. This pathway is used by both TNF-α and IL-1β. In addition, IL-1β uses the ERK1/2 pathway to increase HIF-1α activity (350–352). In another paper, Zhang et al. (353) showed that the synthesis of HIF-1α was upregulated by IL-1β in hepatocellular carcinoma cells via cyclooxygenase-2. Their findings revealed a HIF-1α/IL-1β signalling loop between cancer cells and tumour-associated macrophages in a hypoxic microenvironment, leading to epithelial–mesenchymal transition and cancer cell metastasis.

The above observations close a positive loop coupling between HIF-1α and inflammation that contributes to the amplification of inflammation, especially in the case of hypoxia, which is an important element of the local environment in viral or bacterial infections (354).

3.4.5 Ca_i^{2+} ↔ HIF-1α

HIF-1α is the master regulator of hypoxic transcriptional responses and controls the transcription of several calcium modulators, which can lead to the remodelling of the calcium signalling. Translational regulation of HIF-1α is estimated to account for up to 50% of the increased HIF-1α protein levels under hypoxia, and this process is promoted by calcium signalling (355, 356). The interplay between Ca_i^{2+} and HIF-1α and their positive feedback in cancer cells has been reviewed by Azimi (357). The Ca_i^{2+} modulatory proteins being involved in the direct positive feedback with HIF-1α are the transient receptor potential C1 calcium channel (TRPC1) and stroma interaction molecule-1 (STIM1; Ca_{ER}^{2+} sensor). HIF-1α activates their transcription. Conversely, TRPC1 regulates the translation of HIF-1α (358), and STIM1 promotes HIF-1α transcription and accumulation (359). In addition to TRPC1 and STIM1, other proteins that have been described to increase the activity of HIF-1α include TRPC5, TRPC6, TRPM8 and TRPM2. TRPC5 regulates the HIF-1α expression and its nuclear translocation in breast cancer cells (360), TRPC6 controls the hydroxylation and stability of HIF-1α in glioma (361), TRPM8 promotes HIF-1α levels by suppressing RAK1-mediated HIF-1α ubiquitination in prostate cancer (362), and TRPM2 increases HIF-1α levels by increasing transcription and decreasing degradation in neuroblastoma (363). However, Vestra et al. showed that HIF-1α expression in LPS-stimulated THP-1 macrophages could be blocked by the CaMKII (calcium/calmodulin-dependent protein kinase II) inhibitor KN93, suggesting a role for this complex in HIF-1α activation (364). Summing up, the interplay between HIF-1α and Ca_i^{2+} is described mainly in cancer conditions. Further research is required to explain if similar relations take place in the case of chronic inflammation.

3.4.6 HIF-1α vs. mitochondria

The mitochondria are the ATP factories and the elements of the cell that are extremely sensitive to oxygen deprivation, so various metabolic disorders in the mitochondria trigger the activation of HIF-1α to activate protective mechanisms against the effects of these disorders. The main detrimental element associated with energy production is the production of free radicals due to electron leakage from the cytochrome chain, known as mito-stress. In contrast to the positive coupling of HIF-1α with cytokines, NOX and Ca_i^{2+}, the coupling with mito-stress is mainly negative. The mechanisms linking mitochondrial metabolism to HIF-1α are compensatory, preventing mitochondrial damage or facilitating mitochondrial survival under stress conditions. The mechanisms observed are aimed at reducing the flow of electrons through the cytochrome chain in order to reduce their leakage under conditions of oxygen deprivation. The positive feedback between HIF-1α and succinate/fumarate acts as the amplifier of this inhibitory relationship. Succinate and fumarate contribute to the stabilisation of HIF-1α through their inhibitory effect on PHD, while the activation of HIF-1α leads to an increase in their concentration in the mitochondria by blocking PDH, activating glycolysis (GLL), gluconeogenesis (GNG) and the glucose transporter GLUT-1, all of which contribute to an increase in succinate in the cell.

3.4.7 HIF-1α → mitochondria

There are several ways in which HIF-1α affects mitochondrial activity. The general effect is to inhibit their work. HIF-1α inhibits the pyruvate dehydrogenase complex, thereby reducing the entry of pyruvate into the mitochondria and reducing NADH production. At the same time, it positively regulates lactate dehydrogenase A (LDHA) expression and promotes the conversion of pyruvate to lactate (365) and further removal of lactate from the cell by upregulating the monocarboxylate transporter 4 (MCT4) (366). HIF-1α also reduces the number of mitochondria by inhibiting the PPAR co-activator-1 (PGC-1) family members PGC-1α and PGC-1β (peroxisome proliferator-activated receptor gamma co-activator 1-alpha/beta), which are the essential transcription factors for mitochondrial biogenesis (367). Lu et al. (368) showed that in an *in vitro* mouse genioglossus myoblast model, HIF-1α inhibited AMPK (a low-energy sensor that activates ATP production) under hypoxic conditions, which inhibited mitochondrial biogenesis, decreased the PGC-1α levels and increased apoptosis.

In addition, the population of the mitochondria is reduced by the activation of mitophagy. The known HIF-1α target gene is Bcl-2/adenovirus E1B 19 kDa-interacting protein 3 (BNIP3), which is involved in autophagy and is able to reduce the mitochondrial population (369). This mechanism requires the HIF-1-dependent expression of BNIP3 and the constitutive expression of Beclin-1 and Atg5. The effect of this reduction is also to decrease mito-ROS

production (370). HIF-1α activation also causes mitochondrial fission in human models of pulmonary arterial hypertension, which is supported by the phosphorylation of dynamin-related protein 1 (DRP1), and this process may also be associated with the ability to reduce the mitochondrial population (371).

3.4.8 Mitochondria → HIF-1α

The main factor activating HIF-1α from the mitochondria is mito-ROS. Brandes et al. presented the detailed locations in cytochromes where the electron leakage takes place (128, 269). The system of cytochromes and electron leakage can be modelled by a pipe with holes in which the NADH concentration represents the input pressure, the O_2 concentration represents the suction force, and the holes in the pipe represent the sites of electron leakage from cytochromes. They showed that the leakage does not depend on the flow rate but on the "pressure" of electrons inside the cytochromes. Both increased input pressure (NADH concentration) and increased output pressure (low O_2 concentration) increase electron leakage approximately according to the laws of fluid flow through the tube (128, 269). Thus, blocking both complex I and complex II in different ways resulted in a decrease in OXPHOS activity, a decrease in electron leakage from complex III, an increase in oxygen concentration and a decrease in ROS production, thereby affecting the reduction of HIF-1α activity (372, 373). However, Chandel et al. (374) confirmed that hypoxia increased mitochondrial ROS generation at complex III, leading to the accumulation of HIF-1α protein, demonstrating that mitochondrial-derived ROS are both necessary and sufficient to initiate HIF-1α stabilisation during hypoxia.

The other HIF-1α stabilising factors are, as mentioned above, succinate and fumarate. Downregulation of succinate dehydrogenase (SDH) and fumarate hydratase (FH) activities, which are common hallmarks of cancers, results in the accumulation of succinate, inhibition of PHD activity and induction of HIF-1α (375).

To summarise the role of HIF-1α in generating a response to intracellular pathogens, on the one hand, it has a protective effect on the mitochondria, protecting them from the oxidative stress accompanying the inflammatory response; on the other hand, it participates in the response to pathogens by contributing to the enhancement of the positive feedback between inflammation, ROS and Ca_i^{2+}. Excessive excitation of HIF-1α during such a response can lead to excessive mitochondrial deactivation, resulting in a deficiency of the energy to remove pathogens and free radicals and pump Ca_i^{2+} out of the cytoplasm.

3.4.9 HIF-1α → NO

HIF-1α is one of the activators of iNOS gene transcription leading to increased NO production (376, 377). At physiological concentrations, this is likely to contribute to the enhanced cytoprotective effect of HIF-1α. Another metabolic element linking HIF-1α to NO is fumarate. It has been postulated in the context of hypertension that when fumarate accumulates in the cell, which may occur when HIF-1α is expressed, there is a reduced availability of L-arginine necessary for NOS action, which is formed during the breakdown of argininosuccinate into fumarate and L-arginine, leading to a reduction in NO production (378, 379).

3.5 Autophagy

An important element of the antiviral defence is the proper functioning of the autophagy system, which is involved in the clearance of pathogen proteins from the cell. The growing interest in autophagy is related to the observation that many intracellular pathogens chronically induce autophagy blockade, thereby preventing their complete clearance from the cell (1–6). Three subcategories of autophagy have been defined—chaperone-mediated autophagy, microautophagy, and macroautophagy—collectively referred to as autophagy (380). The autophagic cascade occurs constitutively at a basal level in various cells and is initiated under stress conditions, such as endoplasmic reticulum stress (ERS), growth factor deprivation, nutrient deprivation, mitochondrial damage and inflammation. Autophagy is also coupled to oxidative stress and inflammation, and the couplings are context-dependent, positive to drive or negative to control the level of antimicrobial metabolic excitation. Figure 6 shows a summary of the couplings between autophagy and the PCS.

3.5.1 Autophagy ↔ inflammation

Inflammatory cytokines are also involved in the autophagy processes. One of the main functions of autophagy is to eliminate intracellular pathogens, so autophagy must work in concert with the immune system. The interaction between autophagy and inflammation is very complex, and both positive and negative couplings can be observed. Almost all cytokines are coupled to autophagy in different ways. The most important pathways linking inflammation and autophagy are shown in Figure 6. The most important cytokines in this process are IFN-γ, TNF-α, IL-1, IL-2, IL-4, IL-6, IL-10 and IL-17 (381–385). In the majority of cases, autophagy activation dominates over inhibition. The main pathways involved in the activation are MAPK—ERK1/2 (386, 387), JNK (388) and p38 (22, 389–392)—which in different ways promote the transcription of key autophagy genes and the production of autophagy proteins including the Atg family, Beclin1, microtubule-associated protein 1 light chain 3 (LC3), DRAM1, TSC1/2 and GBP1/IRGM.

The other signalling pathways involved in autophagy inhibition are JAK1/2-STAT1 (385), PI3K/Akt and NF-κB (390–392). mTOR is the key negative regulator of autophagy, and its inhibition is an important target of several autophagy pathways. The major inhibitors of mTOR are AMPK (106, 107), TSC1/2 (245) and JNK (58, 59). The PI3K/AKT and ERK1/2 signalling pathways activate mTOR (48). The inhibitory effect on autophagy is also observed in the case of the transcription factor NF-κB, and two pathways of this activity are described. It activates mTOR and Bcl-2/BCL-xL proteins, both of which are inhibitors of autophagy (393–396).

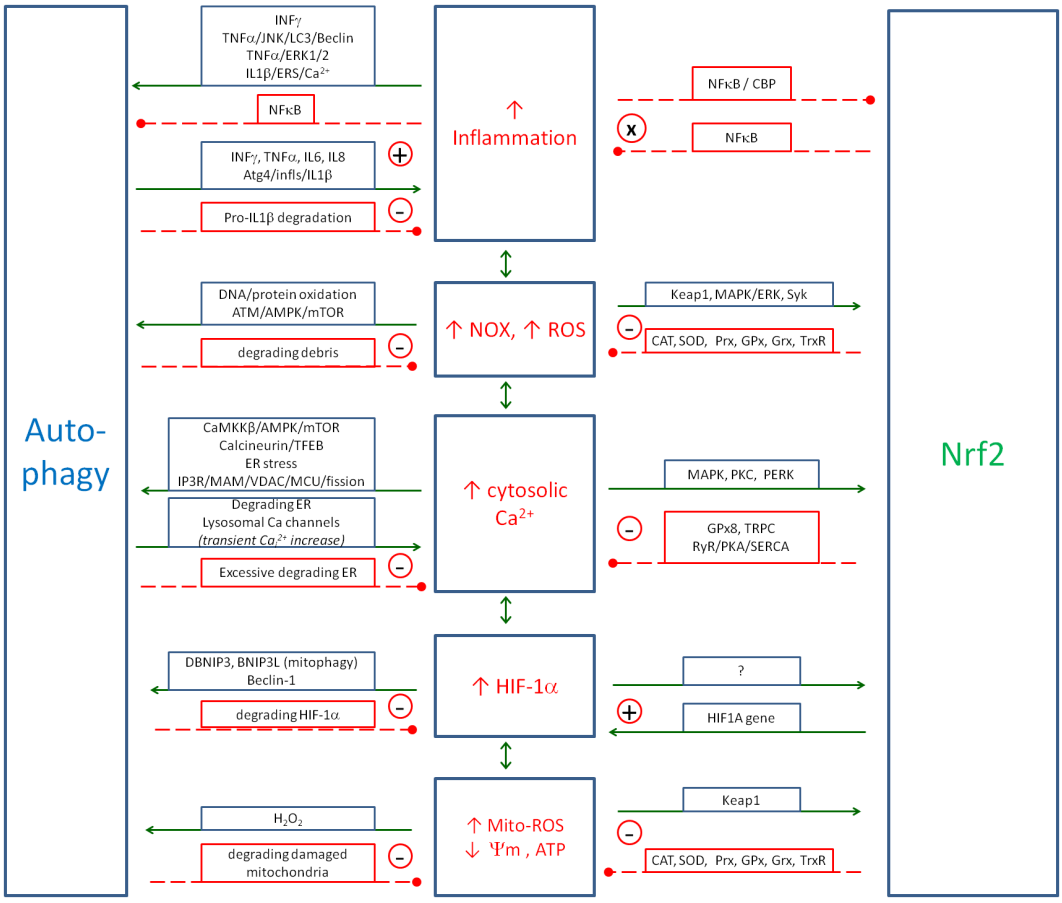

FIGURE 6
Regulatory role of autophagy and Nrf2 on the Positive Coupling System (PCS; inflammation/ROS/NO/HIF-1α/Ca_i^{2+}). The figure shows the metabolic pathways by which Nrf2 and autophagy control and inhibit the self-excitation of PCS. In two cases, however, the relationship is positive. NF-κB and Nrf2 (marked with **x**) inhibit each other, and such a double inhibitory coupling serves as a switch between the inflammatory and antioxidant states—activation of one inhibits the other and vice versa. In the case of HIF-1α and Nrf2, the coupling is not quite positive. Nrf2 activates HIF-1α to support the mitochondrial protection provided by HIF-1α. In addition, inhibition of one element also inhibits the other and vice versa, which seems to support the termination of the antiviral response. In the case of the relationship between inflammation and autophagy, both positive and negative couplings are observed. The positive ones seem to enhance the antiviral response in the early phase of infection. The couplings with iNOS/NO are shown in Figure 3. Solid arrows, activation; red dashed lines with •, inhibition; ⊕, positive coupling; ⊖, negative coupling; ⊗, double-negative coupling. Nrf2, nuclear factor erythroid 2-related factor 2; ROS, reactive oxygen species; NO, nitric oxide; HIF-1α, hypoxia-inducible factor 1-alpha; iNOS, inducible nitric oxide synthase.

3.5.2 p38 ↔ NF-κB coupling

The p38 MAPK and NF-κB are the elements of inflammatory regulation associated with autophagy that interact with each other in a positive loop coupling (397–399). Understanding this coupling appears to be important for understanding the development of the chronic state in some autoimmune diseases (400–404), as well as the severe course of COVID-19.

The p38 MAPK kinase can be activated by stress signals such as cytokines, UV irradiation, heat shock and osmotic shock (22, 389). Once activated, p38 can phosphorylate a number of substrates including transcription factors such as NF-κB (405), which then modulate gene expression in response to stress. NF-κB is typically activated by pro-inflammatory cytokines (such as TNF-α and IL-1), bacterial or viral infections, and other stressors. Its activation leads to the translocation of NF-κB from the cytoplasm to the nucleus, where it influences the expression of genes involved in immune response, cell survival and proliferation. p38 can enhance NF-κB activation by phosphorylating NF-κB itself or its inhibitory protein IκB (inhibitor of kappa B). The phosphorylation of IκB typically leads to its degradation, freeing NF-κB to enter the nucleus and activate transcription. Conversely, components regulated or produced by NF-κB, such as TNF-α, IL-1β, IL-6, IFN-γ, GM-CSF and IL-17, can activate the p38 MAPK pathway (390–392), creating a feedback loop that amplifies the response to stress.

In the context of autophagy, NF-κB generally acts as an inhibitor (393, 394). When activated, NF-κB can suppress the expression of several autophagy-related genes, thereby inhibiting the autophagic process (394–396). It also activates mTORc1, Bcl-2 and Bcl-xL, which are known autophagy inhibitors. The inhibitory effect of NF-κB on autophagy is thought to be a mechanism that favours cell survival and inflammation. However, p38 has been shown to promote autophagy (406, 407). This involves the phosphorylation of several downstream targets that can initiate the autophagic process.

As p38 and NF-κB are positively coupled, both are increased in the inflammatory state, and the overall effect depends on the cellular context. This bidirectional activity of p38/NF-κB coupling on autophagy may be one of the metabolic pathways leading to chronic persistence when autophagy inhibition prevails over stimulation, as autophagy inhibition and NF-κB overactivity are the hallmarks of the chronic infectious or autoimmune state (404, 408, 409). It should be noted that to inhibit autophagy, it is sufficient to inhibit one element of the entire complex pathway of its activation. In contrast, to increase autophagy activity, none of the regulatory elements must be blocked. Only under these conditions can the stimulation of the pathway have a stimulatory effect.

When analysing the impact of autophagy on the inflammatory process, two main effects can be discussed. The first is the reduction of cellular debris that typically activates PCS elements. This cleaning of the cell is important for the return to a healthy state but does not reflect the direct inhibition of the PCS elements. The second effect is the direct activation or inhibition of inflammation by autophagy molecules or by the autophagy process. Autophagy can facilitate the production and release of pro-inflammatory cytokines (410–413). For example, it supports the processing and maturation of IL-1β by delivering cytokine precursors to inflammasomes (414). However, autophagy can reduce inflammation by degrading pro-inflammatory cytokines and the components of inflammasomes that are responsible for their activation. This process helps to control excessive inflammatory responses and maintain cellular homeostasis (415). Multiple connections complicate the analysis; the final effect is context-dependent and requires further research.

3.5.3 Autophagy ↔ oxidative stress

One of the major autophagy regulators is oxidative stress. The relationship between the two is complex. The main link is negative coupling, where ROS mainly activate autophagy but autophagy reduces the tendency to generate ROS. The accumulation of oxidative stress causes oxidation and damage to cellular components, including proteins, DNA and lipids, which turn on the autophagic process (416). Mitochondrial ROS, produced primarily in the mitochondrial electron transport chain, play a critical role in signalling pathways that activate autophagy (417). ROS production increases under stress conditions, such as nutrient deprivation leading to the activation of autophagic processes (418, 419). H_2O_2 is relatively stable compared to other ROS and can diffuse between cellular compartments, acting as a signalling molecule to modify proteins involved in autophagosome formation. For example, H_2O_2 can oxidise the cysteine residue on Atg4, promoting the lipidation of LC3, a critical step in autophagosome maturation (418). ROS can also activate the ataxia-telangiectasia mutated (ATM) kinase, which then triggers downstream signalling to AMPK (420–422). The activation of AMPK results in the promotion of autophagic processes to maintain cellular homeostasis (423, 424). ROS levels are also associated with reduced energy production, which in turn activates signalling pathways such as the aforementioned AMPK and inhibits the mammalian target of rapamycin (mTOR), a key negative regulator of autophagy (425, 426).

However, autophagy functions to reduce oxidative stress by degrading damaged mitochondria and other cellular debris that would otherwise contribute to increased ROS production (427–429). This protective role is critical in preventing the accumulation of oxidative damage, thereby maintaining cellular integrity and function. Impairment of autophagy increases the oxidative stress (430). Furthermore, antioxidant molecules moderately or completely suppress autophagic execution (431).

In summary, the relationship between ROS and autophagy is not linear but is characterised by a complex feedback mechanism in which ROS induce autophagy, and autophagy can modulate ROS levels. This feedback is essential for adaptation to environmental and metabolic stresses.

3.5.4 Autophagy ↔ HIF-1α

Both autophagy and HIF-1α are essential for cellular survival and homeostasis under hypoxic conditions and are linked by multiple regulatory mechanisms. In general, there is a negative coupling between them. HIF-1α activates autophagy (432, 433), and autophagy reduces the HIF-1α activity by degrading this molecule (434).

HIF-1α can induce the expression of several genes involved in autophagy. For example, HIF-1α has been shown to upregulate BNIP3 and BNIP3-like (BNIP3L), which are involved in mitophagy, the selective autophagy of the mitochondria. By promoting the removal of dysfunctional mitochondria, these proteins help to maintain cellular energy production and reduce ROS levels under hypoxia (435). HIF-1α can also directly enhance autophagy by interacting with the autophagy-related protein Beclin-1 and promoting the formation of autophagosomes. This helps the cell conserve resources and maintain energy production during periods of oxygen deprivation (436).

3.5.5 Autophagy couplings—summary

Looking at Figure 6, essentially all of the PCS elements have autophagy-activating activity, and autophagy essentially inhibits all PCS elements. This creates a generalised negative feedback that allows the inflammation and other PCS elements to be silenced, as the amount of pathogen in the cell decreases, and the cell can gradually return to normal function.

There is some complexity in the interactions between autophagy and inflammation, where, especially in the early stages of infection, positive feedback can be observed to enhance inflammation through autophagy. These relationships require more detailed studies, as the overall effect of autophagy on inflammation may be activating or inhibiting at different stages of infection. However, it should be noted that the direct inhibitory effect of autophagy is only observed against inflammation and not against other PCS elements. Therefore, it seems that autophagy cannot be identified as an element that directly controls and inhibits the amplitudes of the PCS spiral.

A separate topic related to the coupling between autophagy and PCS is the issue of chronic infection. Numerous publications have indicated that pathogens with the ability to enter a chronic state

within the cell have the ability to block autophagy (1–6, 437–440). By removing damaged organelles and intracellular pathogens, autophagy prevents the accumulation of microbial antigens that can trigger inflammatory pathways. This cleaning process is critical for preventing chronic inflammation and has been implicated in diseases such as atherosclerosis and autoimmune disorders (441, 442). When autophagy is blocked, the cell is unable to completely remove the pathogen, leading to continued low levels of activation of the PCS system, but not enough to stimulate autophagy to remove the pathogen completely (443). A dynamic equilibrium is then created between the presence of a small amount of the pathogen in the cell, and non-lethal activation of the PCS system is then produced, which manifests in the patient with symptoms of chronic fatigue associated with mitochondrial uncoupling and possibly mild inflammatory symptoms such as pain, redness, swelling or exudation, depending on the location of the pathogen (444–449). However, more research is needed to determine how much of the chronic inflammation of different organs is related to the presence of chronic pathogens and/or impaired autophagy.

3.6 Regulatory role of NRf2

The positive couplings that drive the immune response against the pathogens must be controlled by a number of negative regulators to prevent the response from going beyond the level of self-destruction. One of the key negative regulators that directly control the PCS spiral is the transcription factor Nrf2.

3.6.1 Nrf2 ↔ oxidative stress

Nrf2 is the major nuclear transcription receptor that activates the production of several proteins involved in detoxification and oxidative stress reduction. Oxidative stress induces an antioxidant response as a compensatory mechanism through the activation of the Nrf2 signalling pathway. At low levels of ROS, Nrf2 is associated with the Keap1, which targets Nrf2 for proteasomal degradation. At high levels of ROS, Nrf2 dissociates from Keap1 and translocates to the nucleus, where it binds to the antioxidant response elements (AREs) of target gene promoters (450). The proteins produced include catalase (CAT), SOD, peroxiredoxin (Prx), thioredoxin (Trx), GPx, glutaredoxin (Grx), metallothioneins (MTs), glutathione reductase (GSR), Trx reductase (TrxR) and sulfiredoxin (Srx). Many of the antioxidant enzymes/proteins regulated by Nrf2 are localised to specific compartments within the cell to control redox signalling in the local environment. Nrf2 also regulates the expression of several oxidant signalling proteins, thereby affecting programmed cellular functions. Some regulators, such as p62 and DJ-1, activate Nrf2 and can be triggered by oxidants via Nrf2, forming a positive feedback loop with Nrf2 to increase its activity (451).

3.6.2 Nrf2 ↔ inflammation

Nrf2 is the main factor that reduces the level of ROS in the cell, but it has also been described to reduce the effects of inflammation. The relationship between Nrf2 and inflammation is complex. In particular, there is a double-negative coupling between Nrf2 and NF-κB, which needs to be explained in detail (452). Nrf2 negatively regulates the NF-κB pathway through several mechanisms. First, Nrf2 inhibits oxidative stress-mediated NF-κB activation by reducing the intracellular ROS levels (453). In addition, Nrf2 prevents proteasomal degradation of IκBα and inhibits nuclear translocation of NF-κB (454, 455).

A direct effect of Nrf2 on inflammation has also been observed. According to a study by Jiang et al. (456), Nrf2 mediates anti-inflammatory signalling in macrophages, which plays a critical role in preventing liver ischaemia/reperfusion injury by blocking the transcription of pro-inflammatory cytokines. In another study, Nrf2 suppressed the inflammatory response of macrophages by blocking the transcription of pro-inflammatory cytokines, which was independent of ROS levels (457). This study identifies Nrf2 as a negative upstream regulator of cytokine production and provides a molecular basis for an Nrf2-mediated anti-inflammatory approach (458).

The inverse relationship is also negative. NF-κB decreases free CBP, which is a transcriptional co-activator of Nrf2. This inhibitory effect of NF-κB occurs by competing with the CH1-KIX domain of CBP while also promoting the phosphorylation of p65 at Ser276, which in turn prevents CBP from binding to Nrf2 (458, 459). This results in double-negative coupling between Nrf2 and NF-κB, which is actually a type of positive coupling between them. On the one hand, high Nrf2 activity reduces NF-κB activity, and reduced NF-κB activity contributes to increased Nrf2 activity. Conversely, high NF-κB activity reduces Nrf2 activity, and reduced Nrf2 activity further contributes to increased NF-κB activity. This mechanism helps to stabilise the cell in a state of inflammation and fight against some pathology (high NF-κB/low Nrf2) or in a state of health (low NF-κB/high Nrf2). It is important to note that such a regulatory mechanism is an unstable point of self-regulation, and even a small stimulus can tip the balance towards hyperinflammation or recovery. Therefore, targeting the activation of Nrf2 and the inhibition of NF-κB may be a promising therapeutic target against various types of chronic inflammation.

3.6.3 Nrf2 ↔ calcium stress

Calcium plays an important role in several cellular signalling pathways, but its relationship with Nrf2 is indirect rather than direct. Calcium can activate various signalling pathways, such as MAPK pathways, which can modulate Nrf2 activity (460, 461). In particular, certain MAPKs such as ERK1/2 and p38 can phosphorylate Nrf2, increasing its stability and nuclear accumulation. The other pathway is PKC, a family of enzymes that are activated by calcium and DAG. Activated PKC can phosphorylate Nrf2 or its regulatory proteins, thereby affecting Nrf2 activation and the subsequent antioxidant response (462, 463).

The Nrf2 plays a critical role in cellular defence mechanisms against oxidative stress by regulating the expression of several antioxidant and cytoprotective genes. Its influence extends to maintaining intracellular calcium levels and modulating ER stress responses. The main effect of Nrf2 on ER stress is to increase the expression of glutathione peroxidase GPx8, a critical enzyme

involved in protein folding and ER homeostasis (464). On the other hand, ER stress activates Nrf2 through a PERK-dependent mechanism (465), as PERK is known to directly phosphorylate Nrf2 and induce its dissociation from Keap1 without the involvement of ROS. Nrf2 is also able to reduce intracellular calcium by suppressing the redox-sensitive TRPC channels, thereby inhibiting calcium influx in renal podocytes (466). Another study showed that Nrf2 plays a protective role in the process of oxidative stress-induced Ca_i^{2+} increase in skeletal muscle and that Nrf2 inhibition increased RyR and PKA protein expression in C2C12 cells, improved sarcoplasmic reticulum calcium release function, decreased SERCA protein expression and reduced sarcoplasmic reticulum calcium recovery, all of which contributed to the increase in Ca_i^{2+} (467). In conclusion, Nrf2 and Ca_i^{2+} work in the classical negative coupling, where Ca_i^{2+} induces Nrf2 and Nrf2 reduces the calcium stress.

3.6.4 Nrf2 ↔ HIF-1α

The interplay between Nrf2 and HIF-1α is poorly studied. Available publications have suggested a significant synergistic relationship between these factors. The general link between Nrf2 and HIF-1α is through the action of ROS, which induces both these transcription factors (468). Two signalling pathways have been postulated to transduce ROS signals into Nrf2 and HIF-1α activation. Jang et al. showed that the ROS-sensitive spleen tyrosine kinase (Syk) is able to activate both transcription factors in B cells (469). In another study, Wang showed that a similar effect can be observed via the ROS-activated ERK1/2 pathway (470). Lacher et al. (471) showed that the gene for HIF-1α transcription is one of the non-canonical targets of Nrf2 and that Nrf2 activates HIF-1α transcription. This study found that Nrf2 activity is associated with high HIF-1α gene expression in several cellular contexts. In addition, Wang et al. (470) observed that inhibition of Nrf2 reduced HIF-1α activity, which is consistent with Lacher's findings. They also observed that inhibition of HIF-1α reduced Nrf2 activity. A similar effect of Nrf2 inhibition by HIF-1α inhibitors was observed by Jang (469), but it is not clear whether these effects were direct or indirect, e.g. by reducing Ca_i^{2+} levels.

This type of coupling qualifies it as a positive one. However, it is necessary to distinguish between positive coupling, in which two elements are mutually stimulated, and coupling, in which inhibition of one element also causes inhibition of the other and vice versa. In this case, there is no mutual excitation leading to the self-destruction of the system. According to previous studies, the excitatory effect is only observed in one direction (Nrf2 → HIF-1α), so the self-activation loop is not closed. Thus, the reciprocal coupling is more related to the mutual silencing of the two factors.

The whole relationship can be interpreted as a synergistic protective effect of both factors under oxidative stress, where Nrf2 activates the production of antioxidant enzymes and HIF-1α reduces the production of free radicals by the mitochondria. From this point of view, HIF-1α appears to be an ambivalent element. On the one hand, it is involved in the enhancement of the PCS spiral, and on the other hand, it helps stabilise it. The sum of its effects depends very much on the metabolic context.

4 Summary

A growing number of studies describing the relationships between individual signalling pathways and other pieces of the molecular puzzle are making it possible to construct increasingly complex graphs of interactions to understand the workings of the cell as a whole. The paper presents a fairly universal mechanism of interactions between seven key elements of self-regulation that form the cell's self-regulatory mechanism in response to various intracellular pathogens and other stressors. A literature review of all the mutual interactions between the seven elements of cellular homeostasis has been analysed, from which a picture emerges of the mutual excitation of the five elements mainly to enhance the response against pathogens and the controlling effect of autophagy, Nrf2 and partially HIF-1α and NO as elements to prevent excessive escalation of this response. To the authors' knowledge, this is the first such comprehensive analysis of the regulatory interactions. Particular attention should be paid to the Nrf2/HO-1 axis and autophagy. It should be noted that even a slight weakening of the control of these positive feedbacks can result in the new equilibrium state of the system being far beyond the adaptive capacity of the cell. However, at least in the theory, even a small improvement in the control of such mechanisms can significantly shift the equilibrium of regulated elements towards the correct and adequate level for fighting the pathogen. However, it must be remembered that as long as the pathogen is present in the cells, the balance can be shifted towards chronic inflammation, chronic oxidative, nitrosative and calcium stress.

The other general conclusion can be drawn about the strategy for treating chronic inflammation. The multiplicity of reciprocal positive couplings suggests that a one-drug strategy may be doomed to failure. Reducing only one of the five elements involved in the reciprocal positive couplings would not reduce the others, as they remain in the positive loops and continue to drive the system into pathology and chronic inflammation. According to the authors' opinion, at least three to four upregulated elements should be downregulated simultaneously to achieve the final effect of reducing all the coupled components. The optimal way is to use drugs or herbs that regulate all the elements presented. In this case, an additive or even hyper-additive effect would be expected from the co-application of drugs acting on different dysregulated elements of the overall regulation. Special attention should be paid to herbs, as they usually have a well-defined low toxicity, and there is increasing evidence that many of them influence the elements of metabolism discussed above (472–489).

It is important to note that the relationships presented between the coupled elements are relatively universal and can probably be applied to many diseases in medicine, including acute and chronic infections, and autoimmune and degenerative diseases. However, individual diseases and the tissues involved are likely to differ in the strength of the mutual feedback and the molecular details.

Chronic intracellular infections remain a significant medical problem. Examples of such pathogens include Lyme disease, *Bartonella*, chlamydia, *Mycoplasma*, tuberculosis and viruses such as SARS-CoV-2, Epstein–Barr virus (EBV), herpes group,

Coxsackie group, Ebola virus, Zika virus, enteroviruses and measles virus (490–500). SARS-CoV-2 is reported to be chronic, and it is postulated to be one of the causes of the long COVID syndrome (501–510). EBV and cytomegalovirus are also capable of causing chronic inflammation and coagulopathies, including disseminated intravascular coagulation (DIC) (511–513). Current therapies against these pathogens are long and often of limited efficacy. New drugs are constantly being sought to cure cells of chronic pathogens. Understanding the molecular relationships can greatly accelerate the identification of therapeutic strategies. In particular, many studies have indicated that intracellular pathogens block autophagy as a common component of impaired intracellular metabolism in their chronic state (1–6).

Autoimmune and degenerative diseases are different from chronic infectious diseases. In the case of intracellular infections, many pathogen proteins disrupt many physiological regulatory couplings, which seem to require multiple drug therapies in order to regulate the disrupted couplings and clear pathogens from the cell. In the case of autoimmune or degenerative diseases, the number of initial perturbed elements is likely to be limited, and the problem of the optimal therapy is to find the metabolic element that is the first domino to fall, further triggering all other dysregulations.

4.1 Limitations of the article

The article outlines the many feedbacks involved in the self-regulation of the inflammatory process, but it has some limitations. The main limitation is that the many molecular interactions described were derived from a large number of experiments based on different cell lines. Further research is needed to determine whether the described interactions are universal or only occur in selected cell types. In particular, cells of the immune system may be subject to significantly different regulatory mechanisms in relation to their function than host cells attacked by pathogens or autoantibodies.

Another limitation is that only a subset of molecular elements was analysed (seven core elements and seven kinase signalling pathways). The analysed transcription factors activate the production of a large number of different proteins, which may also affect the analysed feedback in different ways. Thus, the described feedback system should be treated more as a framework for extending the model, incorporating more elements into it and analysing their effects on elements of the current model. Knowledge within the currently analysed elements is also constantly evolving. In particular, the cytokine system is extremely complex in its operation and knowledge of its effects on other elements of the regulatory system evolves.

Another limitation is that, for some relationships, there are a number of studies indicating opposite effects of one element on another through different pathways, making it difficult or impossible to determine the exact relationship. The opposing pathways of interaction may depend on the concentration/activity of the element, or they may be part of a more complex regulation that allows the activity to be better adapted to the metabolic context. This requires more detailed studies that may significantly modify the current model, in particular metabolic contexts.

4.2 Challenges for future research

The present article represents an important turning point in the development of molecular biology because, to the best of the authors' knowledge, it is the first attempt to build a multidimensional model of cellular self-regulation according to the rules of control theory. In such systems where many elements are mutually coupled, a change in one element causes a change in all the others, and a new equilibrium state is reached. There are important conclusions to be drawn from this article, which are different for molecular biologists and physicians. Molecular biologists focus on the correctness of the relationships between elements, while physicians focus on finding the causes of disease.

From the molecular biologist's point of view, it is necessary to develop the regulatory model to be analysed. The first conclusion is the need to carefully validate whether the influence of one factor on another is direct, forming an elementary edge in the graph of interrelationships, or indirect, i.e. through other elements in the graph of interrelationships.

The second tip for future experiments is the need to simultaneously examine the influence of a specific factor on many regulatory parameters of the model, preferably all of them. For example, when studying the effect of a particular drug, it is recommended to examine changes in cytokine levels; NOX and iNOS activities; NF-κB, HIF-1α and Nrf2 activities; Ca_i^{2+} levels, autophagy activation, signalling pathways activity, etc. This will give a more holistic picture of the effect on metabolism.

Next, in the future research perspective, it is necessary to undertake a study to describe each edge of the graph of interrelationships between elements by means of appropriate differential equations. The exemplary ordinary differential equation-based dynamic model describing the response of Nrf2, Keap1, Srxn1 and GSH to oxidative stress was described by Hiemstra et al. (514). This work provides a future perspective for molecular biology. Once the equations for each interaction are mathematically described, it will be possible to create a generalised system of differential equations describing the behaviour of the system, as well as to model the behaviour of the system under the action of deregulatory stimuli (e.g. viral proteins) and/or drugs. This will allow the mathematical optimisation of therapies for various diseases.

In order to build mathematical models, it is necessary to study the variability of concentrations and activities of individual system components in the time domain to observe the magnitude and dynamics of changes in activity under the influence of a specific stimulus. In order to fit equations to time courses, it is necessary to have at least several measurements of parameters at different times after the stimulus. In view of the above, it is necessary in the future to collaborate with computer scientists specialising in the analysis of the self-regulation of multidimensional systems in order to build mathematical models of metabolic self-regulation. This distant goal

must be kept in mind when designing experiments so that the data obtained can be of value in building such future mathematical models.

From the perspective of a scientist looking for a cure for a particular disease, building a multidimensional molecular model of the disease will facilitate the search for a cure. The challenge for molecular biology in this case is to build a qualitative and then a mathematical regulatory model of the diseases. The number of diseases in which perturbations in cytokines, calcium stress, mitochondrial stress, reticuloendoplasmic stress, autophagy, HIF-1α or Nrf2 are observed is very large and includes autoimmune diseases (515–517), neurodegenerative diseases (518–520), cardiovascular disease (521–523), type 2 diabetes (524, 525), hypertension (526), obesity (527), metabolic syndrome (528), non-alcoholic steatohepatitis (529–531), chronic obstructive pulmonary disease (532–534), depression (535–537) and schizophrenia (538–540). Particular attention should be paid to sepsis, a metabolic state in which inflammation and oxidative stress are particularly high and directly life-threatening (541). Thus, the above model has a very wide range of potential applications in medicine because, as presented, all these elements are coupled. However, it is important to bear in mind that the current model is likely to be only a part of the larger individual disease models that will be developed in the future.

In a system with many feedback loops, it is often not easy to identify the first domino that triggers a cascade of changes in the cell leading to the development of the disease. The study of parameter variability in the time domain will make it possible to determine the sequence of changes and thus potentially identify the initiating factor. However, the study of the effect of a given drug on all elements of self-regulation will make it possible, at the level of cellular experiments, to better determine whether a given drug has a chance of being effective in treating/curing a specific disease. In the case of diseases with chronic inflammation, it may be necessary to look for combinations of drugs that effectively balance all the dysregulated elements of self-regulation at the same time, as it is generally unlikely that a single drug will balance all the metabolic disorders. This is generally possible if it balances the first element of the metabolic cascade.

A comprehensive understanding of the intricate network of cellular self-regulation not only deepens our knowledge of disease mechanisms but also paves the way for more targeted and effective therapeutic strategies, marking a crucial step towards precision medicine.

Author contributions

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