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Adipose-Derived Molecules–Untouched Horizons in Alzheimer's Disease Biology

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The global incidence of Alzheimer's disease (AD) is on the rise with the increase in obesity and metabolic disease epidemic. Obesity is co-morbid with the increase in mass of adipose tissue, which secretes numerous molecules that are biologically important. Obesity and its associated conditions are perhaps involved in the causative pathway of AD. Immunologically important cytokines such as IL-1β, IL-10, and IL-18, which are released by adipose tissue, are also found to be associated with AD. Besides, the expression of IL-6, IFNγ, and TNF alpha are also associated with AD. Ang-I and Ang-II are found to mediate the progression of AD. Complement factors B, C4b, and H are differentially expressed in AD. Overall, several adipocyte-derived cytokines are found to be dysregulated in AD, and their role in AD remains to be studied. The induction of autophagy is a very promising strategy in the treatment of AD. A variety of adipose-derived molecules have been shown to modulate autophagy. However, very little literature is available on the role of adipose-derived molecules in inducing autophagy in microglial cells of AD. Understanding the role of adipose-derived molecules in the development of AD, especially in the induction of autophagy, would open up new avenues in devising strategies for the treatment of AD.

Keywords: adipose tissue, obesity, adipose-derived molecules, Alzheimer's disease, autophagy

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INTRODUCTION

Alzheimer's disease (AD) is one of the most prevalent neurodegenerative disorders. Individuals affected with AD show a decline in cognition and loss of self-dependency further leading to hospitalization and premature death. According to a recent WHO report, 60–70% of cases of dementia are contributed by AD. On the whole, it has been estimated that 5.2 million Americans of all ages have AD. Among this population, 5 million people are at the age of 65 or older (Alzheimer's Association, 2006). Further, one-third of people around the age of 85 have AD (32%) (Hebert et al., 2013). Several studies suggest that both overweight and obesity tend to increase the risk of AD (Gustafson et al., 2003; Kivipelto et al., 2005; Rosengren et al., 2005; Whitmer et al., 2005). Obesity, on the other hand, is a predisposing factor for vascular dysfunction (Zhang and Reisin, 2000). Furthermore, a strong association between dementia and adiposity has been stated by many researchers. Naderali et al. (2009) suggested that obesity-mediated defects in insulin and glucose

signaling may evoke AD (Naderali et al., 2009). It has also been observed that obesity-mediated progression of AD is likely to be more prevalent in men compared to women (Elias et al., 2003).

The brain is the master regulator of all the organ systems and functions through either direct or indirect modes. The indirect mode of communication between the brain and the organ systems involves the exchange of bioactive peptides that can cross the blood–brain barrier (BBB). Many of these bioactive peptides include a variety of cytokines and chemokines that are released from different organs and signal the brain. One of the major organs that produce a wide array of bioactive peptides is adipose tissue, and it is, therefore, now recognized as an endocrine organ (Trayhurn and Beattie, 2001; Kershaw and Flier, 2004). Adipose-derived molecules are the peptides that are specifically produced by adipose tissues. These peptides include hormones, enzymes, complement factors, immunomodulators, etc. An increase in adipose tissue mass or adiposity disrupts the homeostasis of these adipose-derived molecules. Expression levels of a variety of these molecules are directly proportional to adipose tissue mass (Benoit et al., 2004). Examples include leptin, adiponectin, apelin, etc (Azuma et al., 2003; de Courten et al., 2004). Adipose-derived molecules play a crucial role in the progression of AD (Warren et al., 2012). Thus the occurrence of AD may be linked to the magnitude of adiposity (Luchsinger and Gustafson, 2009). This review highlights the role of adipose-derived molecules in implicating AD that connects both obesity and AD. Furthermore, the possible roles of the molecules in inducing autophagy are discussed.

CYTOKINES

Adipose tissues [both white adipose tissue (WAT) and brown adipose tissue (BAT)] are well known to produce inflammatory cytokines, which rise with adiposity (Coppack, 2001; Fain, 2006). These cytokines play vital roles in the progression of AD (Rubio-Perez and Morillas-Ruiz, 2012).

Interleukins

Interleukins (IL) act as messengers and assist in communication between cells within and across the tissues. They regulate cell growth, differentiation, motility, the stimulation of immune responses, etc. Adipose tissues produce a wide variety of interleukins (Kern et al., 2001) including IL-1β, IL-4, IL-6, IL-8, IL-10, and IL-18. These interleukins have been known to correlate with AD.

Interleukin 1β (IL-1β)

Interleukin 1β is a cytokine involved in immune modulation. The hyperglycemic condition accelerates the synthesis of IL-1β in the adipose tissue of both humans and rodents via thioredoxin interacting protein (TXNIP) (Koenen et al., 2011). A comparison of the post-mortem brain of AD patients and the control group indicated an increased level of IL-1β in the AD patients, specifically at the frontal cortex and hippocampus. François et al. (2013) have demonstrated the relationship between autophagy and IL-1β. Autophagy induced IL-1β in microglia through degrading inflammasomes (François et al., 2013). These findings shed light on the involvement of IL-1β in AD.

Interleukin 4 (IL-4)

Interleukin 4 is a cytokine that is secreted by the adipose tissue (Ouchi et al., 2011). As an anti-inflammatory cytokine, IL-4 protects the brain from inflammation-induced damage. In amyloid precursor protein (APP)-transgenic mice, IL-4 enhances the degradation of amyloid beta (Aβ), thereby preventing the Aβ-induced cell death (Ouchi et al., 2011). In contrast, Chakrabarty et al. (2012) observed mIL-4 in the hippocampus favored amyloid deposition *in vivo* (Chakrabarty et al., 2012). Both studies revealed the association of IL-4 with AD. Besides, IL-4 is a well-known inducer of autophagy in B cells (Xia et al., 2018), which may also induce autophagy in brain cells.

Interleukin-10 (IL-10)

Interleukin-10 is also an anti-inflammatory cytokine that is produced by the adipose tissue. It is otherwise known as the human cytokine synthesis inhibitor factor (CSIF). IL-10 is mostly produced by visceral adipose tissue of obese subjects (Juge-Aubry et al., 2005). Human WAT explants also produce IL-10 when exposed to tumor necrosis factor alpha (TNF alpha) and lipopolysaccharide (LPS). In the microglial cell, IL-10 is capable of suppressing the monocyte chemoattractant protein-1 (MCP-1) production in concert with the exposure of Aβ peptide. Furthermore, it also modulates the immune process associated with AD development (Szczepanik et al., 2001). Despite this, there is no sufficient information available to conclude the exact mechanism of IL-10 in the development of AD. Conversely, the role of IL-10 in cardiac autophagy is established (Samanta and Dawn, 2016), though not in brain cells.

Interluekin-18 (IL-18)

White adipose tissue is one of the major sources of IL-18 (Wood et al., 2005). Sutinen et al. (2012) demonstrated that a high level of IL-18 increases Beta-secretase (beta-site APP cleaving enzyme-1) (BACE-1) (APP-cleaving enzyme) together with the γ-secretase complex in the brain (Sutinen et al., 2012). It also raises the level of Fe65, which regulates glycogen synthase kinase-3β (GSK-3β) by binding with the C-terminus of APP. Culture medium, when treated with IL-18, showed increased levels of soluble APP-β, thus exemplifying the importance of IL-18 in APP-β production. The elevated level of IL-18 in the brain for a prolonged period leads to AD (Bossù et al., 2010), possibly through increased Aβ. But the involvement of IL-18 in inducing autophagy remains elusive.

Tumor Necrosis Factor Alpha (TNF Alpha)

Adipose tissue produces TNF alpha, which plays key roles in the inflammatory pathway (Sewter et al., 1999; Hoareau et al., 2010). Many studies with rodent models demonstrated that overexpression of TNF alpha in adipose tissue promotes insulin resistance (Hotamisligil et al., 1993, 1995). TNF alpha acts as an initiator of inflammation in the brain (Feldmann and Maini, 2003) and regulates neuroinflammation. A post-mortem study localized TNF alpha within the amyloidogenic plaque of AD

patients' brain (Dickson, 1997). Later, TNF alpha was found to be increased in the cerebrospinal fluid (CSF) of AD patients (Tarkowski et al., 2003). Consequently, a clinical trial in AD patients using a TNF alpha inhibitor (Etanercept) showed that TNF alpha inhibition could be a promising approach to control AD (Tobinick et al., 2006). Furthermore, TNF alpha has been suggested to inhibit autophagy in microglia (Jin et al., 2018). This could be due to the induction of autophagy caused by the inhibition of TNF alpha.

Macrophage Migration Inhibitory Factor (MIF)

Adipose tissue secretes MIF (Skurk et al., 2005), which is an inflammatory cytokine of innate immunity. MIF is co-localized with Aβ-protein, promoting inflammation around the plaque areas, and is thus able to form amyloid-like fibrils. This notion validates its importance in neuroinflammation and plaque development (Oyama et al., 2000; Lashuel et al., 2005). Further, MIF is markedly increased in AD patients, indicating its importance in AD pathogenesis. MIF favors AD pathogenesis by accelerating the production of other cytokines (Popp et al., 2009; Bacher et al., 2010). An *in vitro* study using an MIF inhibitor in the neuroblastoma cell line revealed amelioration of the neurotoxic effect of MIF and Aβ protein production. Similar results were also observed with murine BV2 microglial cells (Bacher et al., 2010). This evidence sheds light on the potential of MIF inhibitors in developing treatment strategies for AD. However, the role of MIF is not studied in autophagy.

Leptin

The mature adipocytes secrete leptin that assists the brain in deciding the level of energy intake. Leptin thus regulates feeding behavior, energy expenditure, and other activities. Leptin transport across the BBB is facilitated by leptin receptors (Schulz et al., 2011), which are abundantly found in the hypothalamus, neocortex, cerebellum, and medulla. Moreover, leptin receptors are also found in cells that produce orexigenic and anorexigenic neuropeptides (Jequier, 2002). These neuropeptides are crucial to maintaining the energy intake. Leptin is now counted as a biomarker in predicting AD progression (Lieb et al., 2009). A recent investigation showed that leptin attenuates the hyper-phosphorylation of tau protein. Conversely, the hippocampal tissue and CSF of AD patients revealed a high level of leptin and leptin receptors (King et al., 2018). Leptin has been shown to induce autophagy in neuronal cells (Li et al., 2018), but this has not been demonstrated in relation to AD.

GROWTH FACTORS

Angiopoietins [Angiopoietin-1 (Ang-1) and Angiopoietin-2 (Ang-2)]

Angiopoietin-1 is involved in the remodeling of WAT during weight loss and gain; this process not only involves changes in adipocytes but is also associated with the distinct changes in the density of blood vessels and nerve fiber. Several adipokines are involved in this process. For instance, Tie proteins remodel the adipose tissue through vascular maturation (Dallabrida et al., 2003). Adipocyte-derived stem cells produce Ang-1 when supplemented with growth factors in the medium. The production of Ang-1 is time-dependent, and knockdown of Ang-1 negatively affects endothelial regenerative capabilities (Takahashi et al., 2013). This proves that angiogenesis is partially regulated by Ang-1. Therefore, understanding the role of Ang-1 in angiogenesis would help to delineate obesity and other related conditions. Furthermore, angiogenic activation of the brain cell endothelium favors the formation of β-amyloid, which is the hallmark of AD (Vagnucci and Li, 2003). The measurement of serum Ang-1 in AD patients and control revealed significantly increased Ang-1 in AD patients. Ang-1 level in serum is, therefore, suggested as a complementary technique together with mental status examination to diagnose AD (Schreitmüller et al., 2012). However, further studies are warranted to validate Ang-1 as a potential marker of AD, and its role in autophagy remains unstudied.

Ang-2 is also important in the vascularization of adipose tissue, which shows greater plasticity by expanding or reducing its size throughout the lifespan. Ang-2 regulates either vascular remodeling or regression, through positive or negative regulation. It is closely connected with obesity because leptin has a crucial role in inducing the expression of Ang-2, which is independent of other angiogenic factors [e.g., vascular endothelial cell growth factor (VEGF)] (Cohen et al., 2001). Tabata et al. (2009) reported the secretion of an angiopoietin-like protein-2 by adipocytes and considered it as a marker of adiposity (Tabata et al., 2009). Ang-2 promotes vascularization of subcutaneous WAT and improves metabolic homeostasis, and it is therefore has a promising role in mitigating high-fat diet-induced obesity (An et al., 2017). However, the function of Ang-2 is not yet established in AD and neither is autophagy.

Fibroblast Growth Factors (FGFs)

Fibroblast growth factors consist of 22 members and are secreted both by WAT and BAT. The FGFs produced by WAT are involved in a variety of functions including metabolism, and neural development (Itoh and Ohta, 2014). FGF-1 is significantly increased in WAT during obesity than FGF-2 (Mejhert et al., 2010). FGF-9 regulates the expansion of BAT under cold-induced conditions (Shamsi et al., 2018). FGFs have a potential therapeutic application against obesity, and understanding their molecular mechanism is thus pivotal (Nies et al., 2016). FGFs, on the other hand, are required for the development of various brain areas. For instance, the supplementation of FGFs increases neuronal survival in the midbrain, hippocampus, etc (Matsuda et al., 1990). The occurrence of FGFs is mostly associated with the plaques, and this was evidenced by the focal immunoreactivity of neuritic plaques (Stopa et al., 1990). The systemic administration of FGF in APP-23 transgenic mice resulted in decreased Aβ formation and tau synthesis (Katsouri et al., 2015). Overall, it is interesting to explore FGFs for their beneficial role in mitigating AD. FGF-2 has been reported to regulate autophagy in non-small-cell lung cancer cells (Yuan et al., 2017), which

leads to the speculation that it might induce autophagy in controlling AD.

Hepatocyte Growth Factor (HGF)

Hepatocyte growth factor is expressed as an angiogenic factor in adipose tissue. HGF expression is reduced during adipocytes differentiation and upregulated during hypoxia (Chu et al., 2009). In the human brain, HGF is localized in the astrocytes of white matter (Tsuboi et al., 2003), and its expression level varies in response to brain injury (Yamada et al., 1994). Therefore, its concentration is useful to assess the extent of damage in the white matter of AD patients (Laterra et al., 1997). It remains to be further elucidated whether HGF could be used as a biomarker for AD. HGF and MET together induce autophagy in certain cancer cells (Huang, 2018). However, the role of HGF in controlling autophagy in brain cells is not established.

Insulin-Like Growth Factor-1 (IGF-1)

Insulin-like growth factor-1 is responsible for the increase in tissue mass through the regulation of growth hormones. In adipose tissue, the differentiation of pre-adipocytes to adipocytes is favored by the growth factors. Particularly, the newly differentiated adipocytes are highly sensitive to IGF-1 (Zezulak and Green, 1986). The IGF-1 level is altered in AD patients' brain, suggesting the effect of disrupted signaling of IGF-1 in AD. Besides, IGF-1 polymorphism rs972936 is associated with the high prevalence of AD (Vargas et al., 2011). Furthermore, IGF-1-mediated signals are implicated in tau phosphorylation, the cleavage of APP, transport of Aβ, memory formation, etc (Freude et al., 2009). IGF-1 prevents autophagy in human colorectal carcinoma cells (Wang and Gu, 2018), but the role of IGF-1 in the regulation of autophagy remains to be elucidated.

Nerve Growth Factor (NGF)

Nerve growth factor is an emerging neurotrophin in adipose tissue biology. It is expressed in both WAT and BAT of rodents that were fed with a high-fat diet. Furthermore, both neurotrophins were found to have roles in the pathogenesis of other metabolic diseases, including cardiovascular diseases (Sornelli et al., 2009). In adipocytes, NGF is involved in energy homeostasis by regulating glucose and lipid metabolism (Chaldakov et al., 2003). Furthermore, NGF also plays a crucial role in neural disorders. In particular, the activity of NGF is elevated in the frontal and occipital cortex of AD patients. Measurement of the quantity of NGF is used as a diagnostic criterion for AD (Crutcher et al., 1993). Though NGF has been shown to activate autophagy in Schwann cells (Li et al., 2020), its role in regulating autophagy in brain cells need to be established.

Tissue Factor (TF)

Tissue factor genes are expressed in the adipose tissue of obese rodents (Samad et al., 1998) and atherosclerotic plaque of humans (Pfeiffer and Schatz, 1995). TF is a cell-surface receptor that activates factor VII and initiates the coagulation cascade in the cardiovascular system (Edgington et al., 1991). TF is expressed in the brain parenchyma, neurons, astrocytes, and in the cortex. However, the immunoreactivity of TF was prominent in senile plaques (Faulk et al., 1990). TF also activates the coagulation factor in the brain by forming a complex with factor VII via the extrinsic pathway (Fleck et al., 1990; McComb et al., 1991). Further insight into TF would help to develop treatment/diagnostic strategies for AD. However, the role of TF in autophagy is not studied.

Transforming Growth Factor Beta (TGF-β)

Transforming growth factor beta is a multi-functional growth factor and plays a crucial role in the determination and differentiation of mesenchymal progenitors in the adipogenic pathway (Fujimoto et al., 2003; Sato et al., 2009). Specifically, TGF-β inhibits adipogenesis through the smad3-dependent pathway (Choy and Derynck, 2003; Tsurutani et al., 2011). TGF-β1 is a candidate gene for AD, and its overexpression induces the deposition of the Aβ peptide (Mattson et al., 1997). Besides, TGF-β1 is involved in cellular responses following brain injury, and its level is found to be elevated in AD patients (Gómez-Pinilla and Cotman, 1993). Furthermore, overexpression of TGF-β1 triggers Aβ accumulation in senile plaques of AD patients (Luedecking et al., 2000). TGF-β is a potent inducer of autophagy in other cells, but its role in AD remains elusive. Altogether, this evidence emphasizes the importance of TGF-β and helps understanding the downstream signaling pathways of TGF-β in AD to strategize further therapeutic intervention.

Vascular Endothelial Cell Growth Factor (VEGF)

Vascular endothelial cell growth factor helps in the expansion and lifelong growth of adipose tissues (Cao, 2007; Lijnen, 2007). Concomitant neovascularization parallel to the expansion of adipocytes is required for the efficient delivery of oxygen and nutrients. Adipose tissues release a variety of angiogenic growth factors, including VEGF, FGFs, etc., for neovascularization (Cao, 2007). Angiogenic suppression is one of the promising therapeutic approaches for the effective treatment of obesity and diabetes. Angiogenic inhibitors have been shown to possess promising efficacy in individuals with metabolic syndrome (Rupnick et al., 2002; Cao, 2010). It is well known that hypoxia leads to obesity due to inadequate angiogenesis, which is perhaps caused by the impaired VEGF signaling in the adipose tissue. However, the role of VEGF in obesity is unclear (Sung et al., 2013). Hypoxia also results in AD due to pathological alteration of the vasculature, which is one of the key features of AD, leading to the accumulation of atherosclerotic plaques and Aβ in arterial blood vessels of AD patients. However, the role of Aβ in vascularization is poorly understood. The levels of Aβs 40 and 42 in brain arterioles were found to be elevated in AD patients and transgenic AD mouse model. VEGF inhibits Aβ-induced endothelial apoptosis *in vitro*. In line with the above finding, neuron-specific expression of VEGF in transgenic mice

restored memory in rodent model of AD (Religa et al., 2013). Evidence has suggested that VEGF expression is increased in response to autophagy induction (Yao et al., 2020). The exact relationship between VEGF and autophagy in AD remains to be elucidated. However, the above findings suggest that improvement of vascular functions would be a novel approach for the treatment of AD.

IMMUNOMODULATORY PROTEINS

Monocyte Chemotactic Protein-1 (MCP -1)

Monocyte chemotactic protein-1 belongs to the chemokine family. MCP-1 is involved in the remodeling and expansion of adipose tissue during the early stages of obesity (Low et al., 2001). Therefore, the disruption of MCP-1 expression is considered to be important in the alteration of the function and metabolism of adipose tissue, especially during the transition between lean and obese states (Sartipy and Loskutoff, 2003). Besides, MCP-1 recruits monocytes, thereby initiating and maintaining the inflammatory reactions in the adipose tissue (Sartipy and Loskutoff, 2003). MCP-1 also influences glucose and lipid metabolism (Loskutoff and Samad, 1998). In the CNS, MCP-1 is produced by astrocytes (Hurwitz et al., 1995) and microglia (Ishizuka et al., 1997). Sokolova et al. (2009) identified MCP-1 as the major predictor of AD, and they found consistent upregulation of MCP-1 in AD brain tissue. They further localized MCP-1 in neurons, astrocytes, and within plaques through immunohistochemistry (Sokolova et al., 2009). Yet, the involvement of MCP-1 in autophagy needs to be investigated further.

C-Reactive Protein (CRP)

In adipose tissue, pro-inflammatory cytokines, such as IL-6 (Hotamisligil et al., 1995) and TNF alpha (Heinrich et al., 1990), stimulate the secretion of CRP (Warren et al., 1987). In particular, CRP levels are found to be elevated in visceral adipose tissue (Saijo et al., 2004). In diagnostics, CRP is used as a marker of inflammation (Stefanska et al., 2011). Inflammation, on the other hand, is crucial in cognitive decline, AD, and vascular dementia. Positively, a plethora of studies have linked AD with CRP levels. Furthermore, CRP was also found in both neurofibrillary tangles and senile plaques of AD patients (Engelhart et al., 2004). O'Bryant et al. (2013) found a decreased level of CRP among AD patients and suggested the rise in CRP is dependent on the progression of AD (O'Bryant et al., 2013). Another study, however, found no significant association between plasma CRP at the baseline and subsequent cognitive decline. Therefore, it was concluded that reduced levels of plasma CRP can be used as a biomarker to diagnose AD (Yarchoan et al., 2013). Though the data from the literature is contradicting, it needs to be further investigated. In the autophagic perspective, CRP is found to have a negative correlation with autophagy in kidney injury in mice (Bian et al., 2017). However, the role of CRP in regulating neuronal autophagy is unclear and needs to be explored.

Serum Amyloid A (SAA) Proteins

Serum amyloid A proteins are mediators of metabolism and inflammation, and they are therefore correlated with the metabolic syndromes (Lin et al., 2001; Yang et al., 2006). Hitherto, four functional isoforms of SAA (SAA 1–4) have been identified in mice (Uhlar and Whitehead, 1999), among which SAA3 is predominantly expressed in the adipose tissue (Meek and Benditt, 1986; Reigstad et al., 2009). Scheja et al. (2008) found SAA3 upregulation in the adipose tissue of high-fat-fed mice and suggested SAA3 as a mediator of chronic inflammation and insulin resistance (Scheja et al., 2008). SAA3 is also found on the myelin sheath and underlying axonal membrane of cortical projection neurons, where large quantities of cholesterol are present. This leads to amyloidosis in the brain that eventually causes chronic inflammation and promotes AD (Chung et al., 2000). Furthermore, the systemic inflammation was suggested to increase the SAA proteins and found to enhance the amyloid deposition in the brain (Guo et al., 2002). SAA proteins, however, were never found to be associated with neuronal autophagy.

CHEMOKINES

Chemerin

Chemerin is a chemoattractant protein and adipokine (Wittamer et al., 2003), secreted by the adipose tissue (Ernst and Sinal, 2010), which appears to promote adipocyte differentiation (Jialal et al., 2013). Several studies have shown the increased chemerin expression during adipogenesis in 3T3 L1 adipocytes (Bozaoglu et al., 2007; Goralski et al., 2007). In contrast, Sell et al. (2009) reported that chemerin mediates a negative crosstalk between adipose tissue and skeletal muscle, thereby contributing to the negative relationship between obesity and insulin sensitivity (Sell et al., 2009). Chemerin also serves as a ligand for CMKLR1 (chemokine-like receptor 1) (Kulig et al., 2011). Peng et al. (2015) reported a higher mRNA expression of CMKLR1 in the brain of AD patients and mice in response to systemic administration of LPS (Peng et al., 2015). In transgenic mice (AβPP/PS1), CMKLR1 and Aβ42 are co-localized in the hippocampus and cortex. There was a specific interaction between Aβ42 and CMKLR1 in rat basophilic leukemia (RBL) cells, which suggest CMKLR1 as a receptor for Aβ42. Furthermore, Aβ42 stimulates CMKLR1-RBL cells and primary glial cells to internalize the Aβ42-CMKLR1 complex, which helps in the clearance of Aβ42 (Kulig et al., 2011). Very recently, chemerin was reported to induce autophagy in bovine mammary epithelial cells (Hu et al., 2019). Therefore, it is reasonable to speculate that it might induce autophagy in microglial cells also, which needs to be explored.

Regulated Upon Activation, Normally T Cell Expressed and Secreted (RANTES)

Regulated upon activation, normally T cell expressed and secreted, otherwise known as chemokine ligand 5 (CCL5), is a pro-inflammatory chemokine strongly involved in inflammation (Fischer et al., 2001). Wu et al. (2007) observed an increase

in RANTES in WAT of obese mice and humans. In morbidly obese cases, RANTES expression was higher in visceral adipose tissue compared to subcutaneous adipose tissue (Wu et al., 2007). However, physical exercise was suggested to overcome the deleterious effects of RANTES-associated obesity (Baturcam et al., 2014). RANTES induces neuroinflammation and promotes the onset of neurodegenerative diseases, such as multiple sclerosis, AD, Parkinson's disease (PD), and HIV-associated dementia (Galimberti et al., 2006). Kester et al. (2012) reported decreased expression of RANTES mRNA in the blood of AD patients (Kester et al., 2012). Tripathy et al. (2010) revealed RANTES upregulation in cerebral microcirculation of AD patients. They further confirmed that the treatment of neurons *in vitro* with RANTES offered a neuroprotective effect. Therefore, they suggested using RANTES to develop a novel therapeutic strategy for AD (Tripathy et al., 2010). Even though RANTES was proven to be involved in AD, its role in autophagy has not been established so far.

PROTEINS AFFECTING THE FIBRINOLYTIC SYSTEM

Plasminogen Activator Inhibitor 1 (PAI-1)

Plasminogen activator inhibitor 1 is, in part, secreted by the adipose tissue (Alessi et al., 2007). PAI-1 is increased in obese humans and found to be decreased during weight loss. It is also associated with type-2 diabetes as a potential circulating marker. However, its role in obesity is not fully revealed (Alessi et al., 2007). In the AD mice model, the level of PAI-1 was increased (Kutz et al., 2012). Melchor et al. (2003) reported that the tissue plasminogen activator (tPA)-plasmin system plays a vital role in the degradation of Aβ *in vivo*. In AD patients, the chronic elevation of Aβ peptide in the brain correlates with the increased level of PAI-1 and inhibition of tPA–plasmin system. The tPA-plasminogen proteolytic cascade increases Aβ degradation and prevents Aβ-induced neurodegeneration (Melchor et al., 2003). This indicates that PAI-1 inhibits the plasmin activity and results in increased accumulation of Aβ. Positively, PAI-1 inhibitors were also suggested to use for therapeutic approaches against AD (Skrzypczak-Jankun and Jankun, 2010; Kutz et al., 2012). Conversely, the function of PAI-1 is not established in neuronal autophagy.

COMPLEMENT AND COMPLEMENT-RELATED PROTEINS

Complement Factor B (CFB)

Complements are part of innate immunity and play crucial roles in assisting the antibodies and phagocytic cells to eliminate pathogens. It was observed that adipose tissue explants of obese patients were able to produce complement factors B, D, and C3 (Fain et al., 2004). CFB when overexpressed in the 3T3-L1 cell line, the genes associated with adipocytes differentiation/maturation were also enhanced. This proves the efficacy of CFB in adipocyte differentiation (Matsunaga et al., 2018). Interestingly, a study by Manral et al. (2012) compared the CSF samples of AD patients and control and revealed the differential expression of CFB. This advocates CFB as a marker for AD (Manral et al., 2012). A very recent meta-analysis study showed that the concentration of CFB was lowered in AD (Krance et al., 2019). However, the evidence is lacking about CFB in inducing autophagy.

Complement Factor H (CFH)

The expression of CFH was significantly increased in the subcutaneous fat of humans. Furthermore, the expression was also highly correlated with insulin resistance (Moreno-Navarrete et al., 2010). In a study by Thambisetty et al. (2008), the plasma CFH level was increased up to 13-fold in AD patients compared to control patients (Thambisetty et al., 2008). The CFH was also found to be accumulated in the amyloid plaque. Toledo et al. (2014), however, indicated that CFH is not a suitable biomarker for AD (Toledo et al., 2014). The current understanding of the role of CFH in autophagy is limited and needs to be established.

PROTEINS IN METABOLIC PROCESS

Adiponectin

Adiponectin is one of the cytokines produced by adipose tissue. It is involved in many physiological processes, such as insulin sensitivity, glucose homeostasis, and fatty acid catabolism (Dzielińska et al., 2003; Ouchi et al., 2003). Adiponectin levels are inversely proportional to the adipose tissue mass, and they are therefore found to be at low concentrations during obesity. The role of adiponectin in cognition and brain activity remains controversial. For instance, Une et al. (2011) showed that elevated adiponectin levels were associated with AD (Une et al., 2011). In contrast, van Himbergen et al. (2012), in a population-based study, showed an elevated level of adiponectin in dementia-free individuals (van Himbergen et al., 2012). On the other hand, Gu et al. (2010) found no significant association between adiponectin levels and the risk of cognitive decline and dementia (Gu et al., 2010). A similar observation was made by Bigalke et al. (2011). This view was further supported by other researchers as well. Teixeira et al. (2013) inferred that there is no correlation between adiponectin levels and mild cognitive impairment, and AD (Teixeira et al., 2013). Adiponectin has been proven to induce autophagy in skeletal muscle and reduce insulin sensitivity (Liu et al., 2015). However, the role of adiponectin in the modulation of neuronal autophagy is still unclear and needs to be explored.

Cholesteryl Ester Transfer Protein (CETP)

Adipose tissue majorly contributes to the secretion of CETP, which, in turn, helps adipocytes in the accumulation of cholesteryl ester from the HDL of a dietary source (Radeau et al., 1998). CETP concentration is found to be elevated during

hyperlipoproteinemic states. This implies the enhanced delivery of lipoproteins to adipose tissue and increased CETP gene expression in adipocytes (Radeau et al., 1995). The brain, in part, also synthesizes CETP, which might play an important role in the transport and redistribution of cholesterol within the brain, possibly by enhancing the neuronal uptake of HDL particles. Furthermore, it has also been proven that cholesterol positively regulates the production of Aβ (Rodríguez et al., 2006). Cholesterol, on the other hand, was also reported to impair Aβ degradation, eventually culminating its role in autophagy (Barbero-Camps et al., 2018). Sanders et al. (2010) found that single nucleotide polymorphism (SNP) at CETP codon 405 homozygosity is associated with slower memory decline and a lower incidence of dementia and AD risk (Sanders et al., 2010). Therefore, it is reasonable to speculate CETP as a causative agent of AD. However, the role of CETP in autophagy is not established.

Lipoprotein Lipase (LPL)

Lipoprotein lipase plays a crucial role in the physiology of adipocytes because it majorly contributes to the production of fatty acids. In general, lipoprotein particles transported out of the vasculature system contribute to a significant source of fatty acids for adipocyte storage (Mead et al., 2002). Apart from adipose and muscle, LPL is also secreted by the brain. In mouse primary astrocytes, LPL binds to Aβ and promotes cell-surface association and uptake of Aβ (Nishitsuji et al., 2011). LPL is thus a novel Aβ-binding protein that promotes cellular uptake and degradation of Aβ. LPL is also co-localized with senile plaques in the brains of AD patients, and if there are any mutations they are associated with the severity of pathophysiological features of AD (Gonzales and Orlando, 2007). The role of LPL in autophagy has not been reported.

Retinol Binding Protein 4 (RBP4)

In adipocytes, systemic glucose metabolism is regulated by the release of serum RBP4 (Yang et al., 2005). Therefore, RBP4 overexpression causes insulin resistance, while the reduced expression ameliorates insulin resistance. Furthermore, elevated levels of RBP4 were associated with type 2 diabetes. Altogether, adipocytes utilize RBP4 to regulate whole-body insulin sensitivity. The presence of cellular retinol-binding protein 1 (CRBP1) and cellular retinoic acid-binding protein 1 (CRABP1) was confirmed in the dendritic layers and dentate gyrus (Shudo et al., 2009). Retinoid signaling is pivotal in the brain and is suggested to have a physiological role in hypothalamus, amygdala, hippocampus, etc. This underscores the importance of retinoid signaling and RBP4 in AD (Lane and Bailey, 2005). To date, however, there was no evidence available on RBP4 in the regulation of autophagy.

Resistin

Resistin is an adipokine, which hostile insulin action. Resistin is upregulated with genetic forms of obesity and downregulated with anti-diabetic drugs (Letra et al., 2014). In postmenopausal women, increased resistin mRNA expression causes insulin resistance and culminates in obesity-related disorders (Sadashiv et al., 2012). Lu et al. (2013) attributed neuroprotective effects to resistin due to its efficacy in acting against Aβ deposition. Resistin inhibits AD, perhaps by decreasing the level of reactive oxygen species, improving the mitochondrial function, and preventing apoptosis (Lu et al., 2013). Resistin was recently suggested as a potential biomarker to diagnose AD (Yu et al., 2018). In the SH-SY5Y human neuroblastoma cell line, resistin inhibits autophagy through the repression of autophagic markers. In wild-type mice, resistin treatment was found to inhibit the mRNA expression of autophagy markers. This suggests resistin as a potential inhibitor of autophagy (Miao et al., 2018).

ENZYMES FOR STEROID METABOLISM

11β-Hydroxysteroid Dehydrogenase Type 1 (11β-HSD1)

11β-HSD1 generates active glucocorticoids (cortisol and corticosterone) that are strong inhibitors of angiogenesis. 11β-HSD1 supports the increased expression of angiogenic factors such as VEGF, TGF-β, and HGF, which are directly involved in the augmentation of adipose tissue. Thus, it is prudent to consider the role of 11β-HSD1 in adipose tissue dysfunction during obesity and angiogenesis (Lee et al., 2013). Age-related cognition was found to be declined upon chronic exposure to glucocorticoids, and this is inhibited by the 11β-HSD1 inhibitor (UE2316). Treatment with UE2316 consequently decreased the number of β-amyloid plaques and improved the memory in the AD mice model (Sooy et al., 2015). Furthermore, selective inhibitors of 11β-HSD1 also improved the memory and ameliorated the condition of AD in aged rodents (Mohler et al., 2011). Therefore, inhibition of 11β-HSD1 would be a novel strategy for the treatment of age-related cognitive disorders. Interestingly, another potent inhibitor of 11β-HSD1, RL-118, improved autophagy markers such as Beclin1, light chain 3B (LC3B), AMP-activated protein kinase alpha (AMPK α), and mammalian target of rapamycin (mTOR), which signified the role of 11β-HSD1 in autophagy. Additionally, RL-118 was proven to prevent neuroinflammation and cognitive decline associated with AD (Puigoriol-Illamola et al., 2018). 11β-HSD1 is thus a key player associated with adipose tissue, AD, and autophagy. Therefore, we suggest it as a potential target to manage the complications.

17β-Hydroxysteroid Dehydrogenase (17β-HSD)

Adipose tissues from rats and humans express 17β-HSD, which is involved in the peripheral synthesis of androgens and estrogens (Martel et al., 1992). It was also reported that 17β-HSD binds with the β-amyloid peptide (He et al., 1999). The high levels of 17β-HSD abolished the steroid hormone homeostasis in synapses and eventually lead to the loss of synapses in the hippocampus of the AD mouse model (He et al., 1999). The role of 17β-HSD has never been explored in autophagy.

Cytochrome P450 Enzymes

Cytochrome P450 is induced in the WAT of rats (Ellero et al., 2010). The brain also secretes low levels of cytochrome P450 in various isoforms. These enzymes are likely to be involved in neurosteroid synthesis, the metabolism of drugs, and the protection of the brain from toxins (Nicholson and Renton, 1999). Cytochrome P450 46A1 (CYP46A1) helps in the clearance of cholesterol from the brain. Increased CYP46A1 expression in mice improves cognition and decreases the manifestations of AD (Mast et al., 2014). CYP46A1 could, therefore, be exploited for its beneficial role in AD. However, the role of cytochrome p450 has not been studied in autophagy.

CONCLUSION AND FUTURE DIRECTION

Recent evidences have pointed out that obesity is a predisposing factor for the development of AD and there is a strong association between dementia and adiposity. The current review advocates the possible correlation between the expressions of biomolecules secreted by adipose tissue with dysregulation in neurons thereby leading to progression toward AD. Obesity-mediated signaling may evoke AD by secreting a variety of signaling molecules, which includes cytokines, growth factors, immunomodulatory protein, complement and complement-related proteins, steroidogenic enzymes, etc. The precise mechanism that promotes AD through factors secreted by adipose tissue, however, remains elusive. It is well established that autophagy prevents the development of AD. Surprisingly, the roles of a number of adipose-derived molecules in autophagy, especially in microglial cells, have not been studied in detail, and study into this area might thus provide vital clues.

AUTHOR CONTRIBUTIONS

PP, SAr, DS, and SAc conceived the idea and wrote the manuscript. SAc edited the manuscript. PP, DS, and SAr developed the idea and edited the manuscript to the final form.

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