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PERSPECTIVE
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From Plant Survival Under Severe Stress to Anti-Viral Human Defense – A Perspective That Calls for Common Efforts

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Reprogramming of primary virus-infected cells is the critical step that turns viral attacks harmful to humans by initiating super-spreading at cell, organism and population levels. To develop early anti-viral therapies and proactive administration, it is important to understand the very first steps of this process. Plant somatic embryogenesis (SE) is the earliest and most studied model for *de novo* programming upon severe stress that, in contrast to virus attacks, promotes individual cell and organism survival. We argued that transcript level profiles of target genes established from *in vitro* SE induction as reference compared to virus-induced profiles can identify differential virus traits that link to harmful reprogramming. To validate this hypothesis, we selected a standard set of genes named 'ReprogVirus'. This approach was recently applied and published. It resulted in identifying 'CoV-MAC-TED', a complex trait that is promising to support combating SARS-CoV-2-induced cell reprogramming in primary infected nose and mouth cells. In this perspective, we aim to explain the rationale of our scientific approach. We are highlighting relevant

background knowledge on SE, emphasize the role of alternative oxidase in plant reprogramming and resilience as a learning tool for designing human virus-defense strategies and, present the list of selected genes. As an outlook, we announce wider data collection in a 'ReprogVirus Platform' to support anti-viral strategy design through common efforts.

Keywords: viral diseases, early cell reprogramming, ReprogVirus, somatic embryogenesis, alternative oxidase (AOX), aerobic fermentation, stress tolerance, SARS-CoV-2

BACKGROUND

Effective immunologic protection contributes to resilient behavior of higher organisms. It is essentially based on the diversity of innate and adaptive cell responses and cell memory tools (1–4). Immunologic responses are energy consuming and require efficient metabolic reprogramming. However, metabolic reorganization is only recently recognized as an integrated part of immunology (5–8). It is increasingly understood that plants and animals have similar responses and cell memory mechanisms to manage immunology (1, 3). These insights enable science to profit from experimental systems across organisms and to apply a higher degree of abstraction for gaining relevant knowledge on early reprogramming events that link to overall resilience.

Somatic Embryogenesis (SE) – An Experimental Tool to Identify Markers for Early Reprogramming and Resilience

In plants, SE can be induced *in vitro* as a model for a resilient response upon severe stress of highly variable origins (9–18). SE induction depends essentially on the death of neighboring cells [(19); see also in (17)] and is defined as asexual regeneration of plants from single or few somatic cells, which can subsequently develop into an embryo in a similar process as it is known for zygotic embryogenesis in seeds [see reviews in (20)]. The discovery of SE in plants in 1958 revolutionized cell biology and stem cell research (9, 10). For the first time, it was revealed that totipotency could be acquired from differentiated somatic cells as it had been predicted by Haberlandt in 1902 (21, 22). SE is routinely used in plant biotechnology to massively propagate selected genotypes from individual plants. It can be utilized to help plants growing-out of virus threats, when propagation is induced from healthy parts of an infected plant (23). SE induction can be seen as an example of environment-inducible, molecular-physiological plasticity, a trait that is *per se* important marker for understanding resilient performance (17, 24–26).

It is common knowledge that energy-consuming reprogramming in eukaryotes is complex, individual- and context-dependent and integrates hormonal, epigenetic and metabolic actions regulated through a wide network of cell signaling factors, second messengers and transcription factors. Our group contributed to this knowledge with several research, perspective and reviewing papers [see e.g. in (11, 14, 26, 27)]. Typically, cell reprogramming covers dedifferentiation and *de novo* differentiation associated with autophagy and cell cycle regulation [see in (11, 17)]. Interaction within molecular networks relies upon cell origin, actual cell status, within cell distribution and structuration, cell communication and environmental signaling. Biochemical insights tell us that small variation at any level might have large consequences depending on thermodynamics, reactant and product concentrations, intermolecular forces, space organization and time. Consequently, relevant markers for reprogramming including those induced by viruses must be based on complex traits as confirmed by Costa et al. (Preprint 28).

Carbohydrate supply is essential for *in vitro* induction of SE (11, Preprint 28, Preprint 29). Sugars and sugar phosphates interact in plants and animals with hormone pathway networks and play central role in signaling to modulate energy metabolism and energy availability. Down-stream of sugars two important antagonistic protein kinases are involved in energy sensing and physiological adaptation (30–32). While sucrose non-fermenting-1-related protein kinase1 (SNRK1) is activated when energy is depleted (31, 33, 34), TOR (target of rapamycin, mTOR in mammals) is induced in situations of energy excess and stimulates cell cycle progression (G1/S and G2/M transitions) and cell proliferation (35). This stimulation involves transcription factors of the E2F family (36, 37). However, it was shown that a short six-hour pulse of one molar sucrose was sufficient to induce SE in hormone-free medium (16). This observation points to a more complex role of sucrose in cell reprogramming beyond energy supply. Sucrose is known to act as a signaling molecule (32, 38), in addition to acting as an osmotic stressor that can disrupt communication within and between cells (16).

Sucrose was also shown to trigger aerobic alcohol fermentation in support of respiration and synthesis of higher molecular weight compounds, such as, lipids (39). The phytohormone auxin and its distribution play critical roles for SE induction (40). However, sucrose could induce SE even in auxin-depleted medium (14). 2,4-dichlorophenoxyacetic acid (2,4-D), a synthetic herbicide that provides auxin activity, was shown to stimulate ethanol secretion in cultured carrot cells. Ethanol secretion was more dependent on sucrose availability than on oxygen availability, and linked to alcohol dehydrogenase (ADH) activity. Cell differentiation was shown to be critical for the amount of secreted ethanol (41, 42). Recently, Fan et al. (43) identified hormone and alcohol degradation pathways as the most activated during early stages of SE. Ethanol has been

demonstrated to reduce ROS levels in stress performance and led to high induction of alternative oxidase (*AOX*) and glutathione-S-transferase transcripts relative to several other tested genes (44). Aerobic alcohol fermentation was found to play a critical role in controlling tissue level concentration of pyruvate in plants and thereby, adapt respiration rates primarily to energy status rather than to oxygen availability (45).

2,4-D is frequently used in plant biotechnology, because it can induce SE with high efficiency. It seems to impose higher oxidative stress levels than seen for native auxins (46, 47). Reactive oxygen species (ROS) enforced by ROS-induced ROS release (RIRR) and reactive nitrogen species (RNS) can integrate outer and inner cell signals and coordinate together adaptive cell and organism responses (48). Slight variations in ROS and RNS levels can have strong effects on cell fates (49, 50). Excess of nitric oxide (NO) and ROS can lead to production of peroxynitrite ($ONOO^-$), which can cause nitration and subsequent inhibition of a broad range of cellular protein functioning and nitro-oxidative stress (51). ROS are known to interact with redox-sensitive protein cysteine thiol groups relevant for energy metabolism and metabolic channeling linked to cell differentiation and cell cycle regulation (51, 52, pre-print 53, 54). Downstream signaling pathways of NO constitute post-translational protein modifications by S-nitrosylation, including SUMOylation, phosphorylation, persulfidation and acetylation, which plays important role on altering protein functions either positively or negatively (55). Plant alcohol dehydrogenase 2 (ADH2) functions as nitroso-glutathione reductase (GSNOR) (56) and has high similarity to ADH5/GSNOR in human cells (Costa JH, not shown). GSNOR is involved in NO homeostasis and interferes with auxin signaling and polar auxin transport in higher plants (57). In animals, GSNOR was connected to mitochondria maintenance and cell longevity (58, 59). It can modulate redox signaling and, its overexpression in tomato could increase ROS and NO scavenging efficiency (60). Competence for SE induction was shown to be positively linked to the amount of anti-oxidant secondary plant compounds and enzymes (18, 26, 61–65). It is relevant to mention that high levels of NO can counteract SE induction, highly lightening the importance of balanced ROS/RNS homeodynamics in cells. Scavenging of NO by phytoglobins (66, 67) is suggested to integrate oxidative stress and auxin metabolism with the acquisition of SE competence. In plants, NO is produced mainly by the cytosolic nitrate reductase (NR) and mitochondrial electron transport-mediated nitrite to NO reduction (68).

AOX Integrates ROS/RNS Signaling, Aerobic Fermentation and Respiration During Reprogramming - A Learning Tool for Virus Defense?

We hypothesized that a better understanding of the role of AOX during SE induction can help to reveal mechanisms that could be used to confront harmful virus-induced reprogramming in human cells. This hypothesis had been explored through original research (Preprint 28) and confirmed our approach.

AOX functions universally in a vast variety of organisms across all kingdoms (69). Most probably, *AOX* gene got transferred into eukaryotes from prokaryotes *via* primary endosymbiosis (70, 71). However, *AOX* is not present in vertebrates and arthropods and the majority of bacteria lost *AOX* during the course of evolution (72). Nevertheless, in 2005 an Alternative Consortium was created to explore a beneficial role of AOX in mitochondrial oxidative phosphorylation that could alleviate phenotypic effects of widespread OXPHOS deficiencies in human diseases (73, 74). Currently, *AOX* is being explored in animals, which overexpress *AOX* ubiquitously [e.g. (75)] as a tool to understand respiratory control mechanisms (76–78). Studies on transgenic *AOX*-mice revealed differential effects of AOX on acute and chronic hypoxia, which helped to better understand pulmonary oxygen sensing mechanisms vital e.g. for respiratory distress syndromes (79). Recently, it has been shown that viral infection, particularly respiratory viral infections upregulate ROS production [e.g. (80, 81)]. Overexpression of *AOX* in mouse displayed substantially reduced ROS generation (82). Also, cigarette smoke-induced mitochondrial stress and ROS production was shown to be relieved in *AOX*-mice attenuating lung dysfunction and tissue damage linked to chronic obstructive pulmonary disease (known as COPD) (83).

Mitochondrial AOX was proposed as functional marker for plant cell reprogramming (27). It demonstrated significant role in homeostasis, reprogramming and plant growth adaptation in response to diverse abiotic and biotic stresses (26, 84–90). Short- and long-term fine-tuning of *AOX* at transcriptional level was shown to be important for positive effects on performance (85, 91). Recently, relevance of *AOX* for predicting plant robustness from early reprogramming has been substantiated (26). In plants, virus tolerance is essentially regulated by salicylic acid, a hormone that acts on ROS accumulation (92). It involves a highly complex regulatory network, where AOX plays a role by modulating mitochondrial redox/ROS signaling (93). Fu et al. (94) revealed that NO acted as inducer of AOX in response to *Tobacco mosaic virus* (TMV) infection. *AOX* transcript accumulation took place when cytochrome-c-oxidase (COX) was inhibited by TMV, or NO or KCN.

In several applied plant systems of reproducibly stimulated morpho-physiological reprogramming, it was shown that early up- and down-regulation of *AOX* transcript levels is typical and coincides with critical phases of *de novo* induced morpho-physiologic events (induction, initiation, and realization). This included carrot SE induction and seed germination (24, 26), olive root induction for propagation from shoots (95, 96), callus induction from quiescent root tissue (97, 98), and *Hypericum perforatum* germination (99). In carrot seedlings, chilling also induced oscillating *AOX* transcript levels. *AOX* transcripts peaked after 45 minutes and prior to high induction of a specific anti-freezing gene only after 24h (98). These results are in agreement with state-of-the art knowledge on the importance of flexible short- and long-term fine-tuning of

AOX at transcriptional level besides the protein level to enable known positive effects on plant performance (85, 91). To unravel the precise role of *AOX* and its isoforms during reprogramming integrated in complex signaling networks (100–102), it was suggested that measuring transient changes in respiration *in vivo* in seconds to minutes should be performed (103, 104).

The extraordinary role of AOX for reprogramming involves four major aspects for cell and tissue determination: (a) *AOX* is stress-induced and drives ROS level equilibration (105); *AOX* was shown to be involved in both scavenging and generation of NO (68). Cvetkovska and Vanlerberghe (106) demonstrated that overexpression of *AOX* led to lower NO production and *AOX* knockdown led to increasing NO. AOX scavenges electrons, thus it was expected to prevent in the mitochondrial electron transport chain electron leakage to nitrite and concomitant NO formation at the sites of complex III and complex IV. Later, Cvetkovska et al. (107) found that scavenging of NO could prevent NO inhibition of COX. Recently, Vishwakarma et al. (68) showed that bacterial elicitor flg22 treatment led to excess of NO, superoxide, peroxynitrite and tyrosine nitration. Moreover, *AOX* overexpression reduced peroxynitrite and tyrosine nitration suggesting that AOX-mediated NO removal can prevent downstream toxic products, (b) AOX is critical for mitochondrial ROS signal transduction towards mitochondria-nucleus retrograde communication (108–110), (c) AOX contributes to prevent excessive plant cell death by regulating ROS levels (17, 111, 112), and, (d) pyruvate is a major metabolic regulator of AOX (104, 113–117), which links to the role of sugar and the central branch point between respiration and fermentation (118). AOX activation can avoid energy and carbon shortage for anabolism by maintaining the tricarboxylic acid cycle active also when oxygen concentration is reduced (45). In *AOX*-overexpressing transgenic mice, presence of AOX enhanced mitochondrial respiratory rates through forward electron transport from succinate dehydrogenase (cII) both under phosphorylating (presence of ADP) and non-phosphorylating (absence of ADP) conditions (76). Lack of *AOX* in transgenic plants resulted in high ethanol production associated with injuries (118). Thus, AOX can help in decreasing fermentation and, thus can be expected to avoid harmful effects by excessively induced fermentation products (lactic acid, ethanol).

Standard Genes Profile 'ReprogVirus' for Exploring Virus-Induced Early Reprogramming in Relevant Primary Infected Human Cells - A 'Ready-to-Use' Approach

Viruses are known to 'abuse' host cell's competence and structures for reprogramming. Any virus infection provokes struggling for commanding coordination of the host cell program and this starts in the initially infected cells. Therefore, it is challenging to early stop virus-induced harmful reprogramming and avoiding at the same time suppressing the host's defense and survival strategy. As reviewed in Costa et al. (Preprint 28), viruses typically capture host cell signaling and metabolism. Changes in host cell redox homeostasis and central carbon metabolism are recognized as most critical events during viral infection and essential for virus replication. Viruses can influence host cell cycle to arrest or progress in favor of their own replication, where E2F1 of the E2F transcription factor family plays major role. In plants, TOR-suppression by silencing or inhibition resulted in impressively reduced virus replication, resistance or elimination of viral infection. Further, host microtubule (MT) assembly is critical for virus entry, replication and spread. Enzymes catalyzing posttranslational MT modifications were identified as suitable targets for drug development to combat viral infection (119).

Based on this knowledge and the characteristics of 'reprogramming for survival' during SE induction and supported by our validating results on the overall approach (Preprint 28) we selected a set of genes for a 'ready-to-use' standard profile to explore virus-induced early reprogramming. The standard profile consists of genes related to ROS/RNS equilibration, anti-oxidant activities, NO production, G6PDH, MDH1 and 2, lactic fermentation, structural cell organization, energy status-signaling, cell cycle regulation, and regulation of apoptosis/programmed cell death and includes IRF9 and IRF3 as markers for the immune system response plus transcription factors NF-KB1 and NF-KB-RELA. The complete list of genes is given in **Table 1**.

OUTLOOK

Recent advancements in virus research increasingly reveal good relevance of transcriptome data for cell and organism performance (120–123). It is also understood that it will be important to focus on gene sets (Preprint 124). The presented standard profile of selected genes is now available to be broadly applied. It can identify critical early traits of harmful virus-induced cell reprogramming by rapid *in vitro* - screening of a diversity of virus types and variants. It should be applied under commonly accepted standard conditions in relevant human cells or tissues of primary importance for defined diseases. Currently, the profile 'ReprogVirus' was used by our team to trace corona virus-related reprogramming (Preprint 28). Transcriptome profiles were explored by using the data available in public domain from transcriptomic experimental studies in Genbank (NCBI). It proved to be helpful in identifying a complex SARS-CoV-2-induced trait named 'CoV-MAC-TED' (Preprint 28), which covers early ROS/RNS balancing, aerobic fermentation regulation and cell cycle control. Potential impact from this trait is promising to support running and new initiatives of anti-SARS-CoV-2 therapy designs as broadly discussed (Preprint 28).

Here, we announce the initiation of the 'ReprogVirus Platform' to enable appropriate wide data collection under standardized conditions and data processing. The strategic flow diagram in **Figure 1** provides a straightforward instruction for data collection. In parallel, regulatory data of 'ReprogVirus' at

TABLE 1 | List of genes selected as 'ReprogVirus' for analyses in *Homo sapiens*.

Function	ReprogVirus	Gene members (accession numbers)
ROS/RNS equilibration	*ADH* (alcohol dehydrogenase)	*ADH5* (NM_000671.4)
Anti-oxidant activities	*SOD* (superoxide dismutase)	*SOD1* (NM_000454.5)
		SOD2 (M36693.1)
	Catalase	Catalase (NM_001752.4)
	GPX (glutathione peroxidase)	*GPX-1* (NM_000581.4)
		GPX-2 (NM_002083.4)
		GPX-3 (NM_002084.5)
		GPX-4 (NM_002085.5)
		GPX-5 (NM_001509.3)
		GPX-6 (NM_182701.1)
		GPX-7 (NM_015696.5)
		GPX-8 (NM_001008397.4)
	GSR (glutathione reductase)	*GSR* (NM_000637.5)
NO production	*NOS* (nitric oxide synthase)	*NOS1* (NM_000620.5),
		NOS2 (NM_000625.4)
		NOS3 (NM_000603.5)
Lactic fermentation	*LDH* (lactate dehydrogenase)	*LDH-A* (NM_005566.4)
		LDH-B (NM_002300.8)
		LDH-C (NM_002301.4)
		LDH-AL6A (NM_144972.5)
		LDH-AL6B (NM_033195.3)
Structural cell organization	*ACT* (Actin)	*ACT-A1* (NM_001100.4)
		ACT-B (NM_001101.5)
		ACT-G1 (NM_001199954.2)
	TUB (Tubulin)	*TUB-A1B* (NM_006082.3)
		TUB-A1C (NM_001303114.1)
		TUB-A4A (NM_006000.3)
Glycolysis	*ENO* (Enolase)	*Eno1* (NM_001428.5)
		Eno2 (NM_001975.3)
		Eno3 (NM_001976.5)
	HK (Hexokinase)	*HK1* (NM_000188.3)
		HK2 (NM_000189.5)
		HK3 (NM_002115.3)
	PFK-M (Phosphofructokinase)	*PFK-M* (NM_001166686.2)
	GAPDH (Glyceraldehyde-3-phosphate dehydrogenase)	*GAPDH* (NM_002046.7)
	PK (Pyruvate kinase)	*PKLR* (XM_006711386.4)
		PKM (NM_002654.6)
Energy status-signaling	*SNRK* (sucrose non-fermenting-1-related kinase)	*SNRK* (NM_017719.5)
Cell cycle regulation	*mTOR* (target of rapamycin)	*mTOR* (NM_004958.4)
	E2F transcription factor	*E2F1* (NM_005225.3)
Regulation of apoptosis/cell death	*CASP* (Caspase)	Caspase in [*CASP8* (NM_001228.4); *CASP9* (NM_001229.5); *CASP10* (NM_032977.4)]
		Caspase ex [*CASP3* (NM_004346.4); *CASP6* (NM_001226.4); *CASP7* (NM_001227.5)]
	Bcl gene	*BCL-xL* (Z23115.1)
Markers for the immune system response	*IRF* (interferon regulatory factor)	*IRF9* (NM_006084.5), *IRF3* (NM_001571.6),
Viruses-activated transcription factors	*NF-KB1*	*NF-KB1* (NM_003998.4)
	NF-KB-RELA	*NF-KB-RELA* (NM_021975.4)
Other key genes	*G6PDH* (*Glucose-6-phosphate dehydrogenase)*	*G6PDH* (NM_000402.4)
	MDH (Malate dehydrogenase)	*MDH1* (NM_005917.4)
		MDH2 (NM_005918.4)

DNA/RNA and protein levels can be explored and collected. In case of choosing to analyze expression of individual genes (RT-qPCR), regulatory data regarding transcriptome could be obtained by exploring public databases.

The platform will provide integrative data analyses using Artificial Intelligence methodologies to identify final targets for designing specific and/or unspecific anti-viral strategies. More specifically, we intend to apply deep learning techniques to identify gene expression patterns from individual genes or from a combination of genes. These patterns will be automatically correlated with a virus or a set of viruses using a distinct deep neural network. As deep learning architecture we foresee the use of multi-head attention mechanisms in a transformer-based, variational auto-encoder network, allowing the identification of the most relevant parts of the input. Moreover, we will also apply and evaluate other CDNN

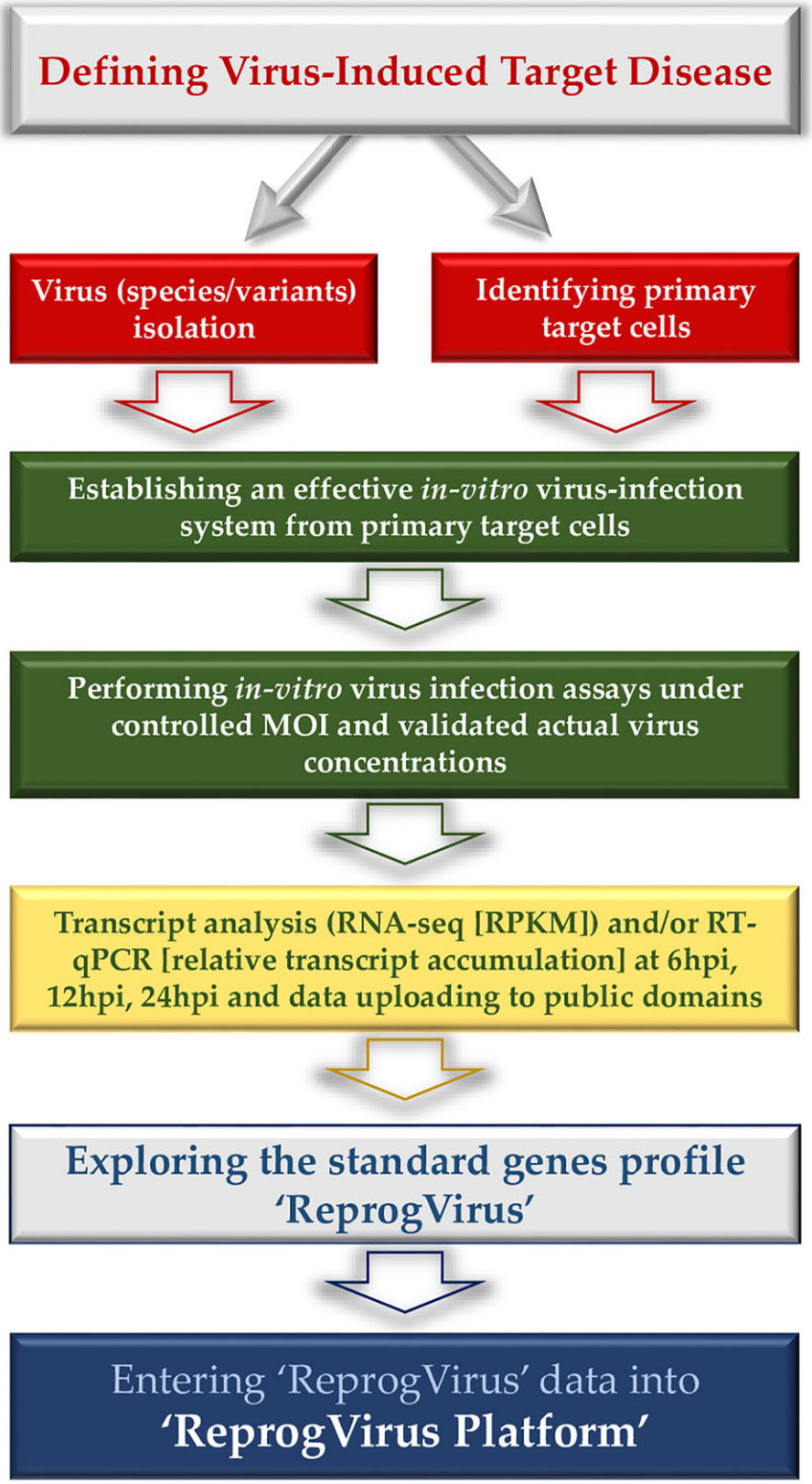

FIGURE 1 | Flow diagram - data collection for 'ReprogVirus Platform'.

(clustering deep neural networks), such as deep embedding clustering and GANs (Generative Adversarial Networks) (125).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS

BA-S initiated scientific approach and concepts in close collaboration with JHC and CN, coordinated their final development for the presented perspective through common discussions among all *FunCROP* net members and wrote the manuscript. RB contributed to manuscript writing and prepared overall ms for submission. PQ supports this initiative through his competence in Artificial Intelligence methodologies. SRK helped BA-S in overall *FunCROP* group coordination. KJG helped in writing manuscript parts related to NO metabolism. All authors contributed to the article and approved the submitted version.

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