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PERSPECTIVE

The Anti-Viral Activity of Stem Cells: A Rational Explanation for their Use in Clinical Application

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Abstract: It is well established the importance of stem cells (SCs) in tissue growth, regeneration and repair, given their ability to self-renew and differentiate into mature cells. Stem cells are present in all individuals and are potentially active to the end of life. However, less is known about their unique function within the immune system as immune regulators and their important task in viral protection. Antiviral resistance is a common mechanism in all cells though stem cells utilize an antiviral RNA interference (RNAi) mechanism, while adult cells react by using the interferon-dependent repression pathway *via* interferon-associated protein-based response to induce an antiviral response. Therefore, the idea behind this review is to highlight the mechanisms of viral evasion of host defense, which would then allow us to highlight the rationale use of autologous stem cells and their biochemical and immunological ability to reset the subverted immune responses. Recently, scientists have highlighted their use in the field of immune-therapy, establishing the possibilities of using them outside the conventional protocol with the advancement in manipulating these cells in such a way that specific body activity can be restored. This paper describes the remarkable SCs profile and discusses some ideas regarding their promising use *in vivo*.

Keywords: Stem cells (SCs), mesenchymal stem cells (MSCs), cluster of differentiation, anti-viral activity, SARS-CoV-2, pandemic.

1. INTRODUCTION

The term Stem Cells (SCs) indicates a category of undifferentiated special cells that are categorized based on surface markers, otherwise known as "cluster of differentiation" (CD marker), and their potency, which refers to the ability of differentiating into specialized cell types or based on their source indicating their growth of stage, adult or embryonic [1]. The overall accepted way to categorize stem cells is by classifying them into two groups: embryonic and adult. Early stem cells, often called embryonic stem cells, are found in the inner cell mass of a blastocyst approximately within five days of development. Mature stem cells are found in specific mature body tissues as well as the umbilical cord, cord blood, placenta, amniotic fluid, peripheral blood, fat tissue and bone marrow after birth [1].

Centered on the potency classification, SCs are classified based on the hierarchy of cell potency, as follows. (i), Totipotent stem cells capable of giving rise to any of the 220 cell types found in an embryo as well as extra-embryonic cells such as placenta, obtained from the early cell-mass, blastocysts. (ii), Pluripotent stem cells capable of giving rise to all cell types of the body (but not the placenta), derived from the early germ layers ectoderm, endoderm and mesoderm. (iii), multipotent stem cells that can develop into a limited number of cell types of a particular phenotype, for instance, hematopoietic stem cells that can become white cells, red cells and platelets (iv), oligopotent stem cells, stem cells with a lesser ability of differentiating, this group includes adult stem cells that can develop only to specific tissues such as neural stem cells, lymphoid stem cells, osteo stem cells. (v),

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unipotent stem cells, cells able to replicate cells of their kind tissue such as muscle stem cells [1, 2].

However, there is not a clear consensus as the CD markers classification may refer to phenotypic differences rather than their sources or biological phase. CD markers may denote the mesenchymal stem cells (MSCs) phenotype, whether they come from placenta, fat tissue, dental tissues, bone marrow or peripheral blood, to distinguish them from stem cells like the hematopoietic stem cells (HSCs), neural stem cells (NSCs) or embryonic like stem cells (ElSCs) that can be found together within the same source. Most of the CD markers are ubiquitous as they may simultaneously indicate different stem cell types. The most common surface markers expressed by MSCs include STRO-1, CD29, CD44, CD73, CD90, CD105, CD106, CD146, SSEA-1 and SSEA-4. Other types of stem cells, such as HESCs and ElSCs, share many of these markers, for instance, SSEA-1, CD90 and CD133 [1-5].

Thanks to their unique biological nature, stem cells play a key role not only in maintaining proper tissue structure and regenerative function but in regulating immunity as well. The effects on growth and regeneration must be protected from damage and loss and should be exposed to the microenvironment to receive physiological indications for cell replacement and repair. To achieve the correct homeostasis between protection and exposure, stem cells are either maintained in a specialized niche or in a special silent mode to facilitate their interactions with local and systemic humoral and immunity factors *via* the vascular and central nervous system network [5, 6].

2. THE STEM CELLS ANTI-PATHOGEN ABILITY

Stem cells circulating within the peripheral blood are at risk of viral infection; in humans, retroviruses and herpesviruses are able to target hematopoietic stem cells, especially once infiltrated into the bone marrow [7]. However, it is well accepted that some of the stem cells, such as the ESCs and MSCs, are able to adopt special tools to resist viral infection. These assertions have been confirmed by several lines of studies conducted towards different viruses, including SARS-CoV2, HIV1, West Nile virus, cytomegalovirus and myxoma virus, which are also unable to infect adult stem cells efficiently [7-10]. The conclusion showed viral resistance ability as adjunctive distinctive feature of stem cells. This paper will focus on the unique traits of stem cells and their role in viral immunity.

The SCs, MSCs and ESCs are particularly able to perform immune-modulatory activities by different ways. The most known is performed by the secretion of different growth factors, cytokines and interleukins. The keratinocyte growth factor, prostaglandin E2, granulocyte-macrophage colony-stimulating factor, pro-inflammatory cytokines and interleukins such as IL-6, IL-2, IL-4, IL-10 and IL-13, TNF-α, TNF- β and IFN-γ are molecules and factors that can determine the way of innate and adaptive immune cells, which may respond to the cellular environment. This is the precise mechanism that could induce alveolar macrophage phagocytosis to modify the cytokine profile released by immune cells locally T, B lymphocytes, natural killer cells (NK) and dendritic cells (DCs) [11].

Several studies observed that, in general, no matter the source, the MSCs (umbilical cord, peripheral blood, fat tissues, bone marrow) were able to exert a beneficial activity on the lungs reducing the proportion of lesions derived from virus infection, either HIV or Sars-CoV2, especially those lesions with solid appearance [10-13]. In those studies, either autologous or from donor, SCs transplantation was followed by a decrease in ground-glass lesions and viral loading significantly once compared to individuals who did not receive SC treatment. It was also observed a significant improvement in oxygenation index, compared to baseline values, together with a significant decrease in the following inflammatory cytokines after treatment: GM-CSF (pro-inflammatory M1 macrophage phenotype inducer), IFN-γ, IL-5, IL-6, IL-7, TNF-α, TNF- β. All articles confirmed that cell therapy was a safe and well-tolerated alternative therapy [10-13].

The SCs inflammatory modulatory effect takes place by interacting with pro-inflammatory T cell phenotypes. This ability was confirmed by investigating their behavior against allogeneic T- cells; the low stimulation *in vitro* towards allogeneic T-cells showed a definite inhibition towards further autoimmune reaction. According to the authors, SCs in general, MSCs in particular, express low levels of MHC class I molecules with a complete absence of MHC class II and costimulatory molecules CD80, CD86 and CD28 that are crucial in T-cell further engagement of antigen presenting cells (APCs) [13]. Expression of both MHC class I and class II can only be upregulated upon stimulation with IFN-γ, which is considered the main mechanism of defense of differentiated adult somatic cells. In addition, SCs immunogenicity resides in their suppressor ability of memory and naïve T cells induced by mitogens, allogens and CD3 and CD28 antibodies [13, 14].

Another special trait of SCs is the lack of the IFN-γ mechanism, a crucial weapon against viral/pathogen aggression that is otherwise replaced by the RNA interference (RNAi) mechanism, a distinguishing expedient preserved across eukaryotes that allows for specific gene silencing *via* sequence-dependent targeting by small RNAs of 20–30 nucleotides in length. This mechanism is based on the ability to respond to double-stranded RNA (dsRNA) microorganisms, a common intermediate in the replication of RNA viruses with the exception of retroviruses. The RNAi process involves several mediators, such as the cytoplasmic enzyme RNase Dicer, which identifies and cleaves the dsRNA substrates to produce small interfering RNAs (siRNAs). The siRNAs are loaded onto special carrier proteins, known Argonaute (Ago), together with different proteins to form the RNA-induced silencing complex (RISC). The mature RISC then cleaves target RNA following the siRNA sequence complementarity. The final intent is to cleave viral dsRNA replication intermediates to suppress viral accumulation within the host's cells, a successful strategy adopted by plants, flies, nematodes and mammalians [15-20] (Figs. **1** and **2**).

The results were eventually confirmed by using infected ESCs from the mouse by using two procedures: (i), using mouse ESCs infected with encephalomyocarditis virus (EMCV) that developed highly specific EMCV-derived siRNAs with 3' overhangs; (ii), mouse ESCs infected with a

mutant Nodamura virus (NoV) without the ability to antagonize the RNAi pathway, in this case, the production of higher levels of NoV-derived siRNAs compared to wild-type NoV infection was noted. The results showed a profound impairment of the RISC-mediated silencing mechanism; mutant NoV replication was technically compromised. Intriguingly, once scientists knockout Ago proteins that were able to restore the RISC functionality [19].

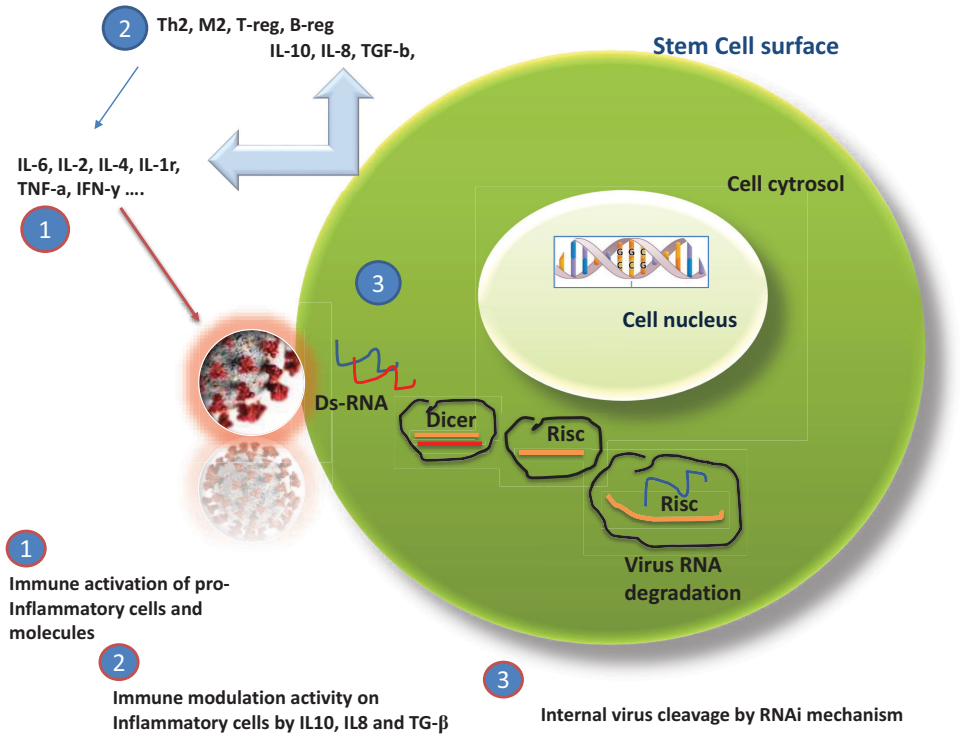

Fig. (1). Stem cells use the RNA interference (RNAi) mechanism to protect themselves and their environment from virus aggression. Virus double-stranded RNA induces the activation of protein complexes Dice and RISC to get to viral structure degradation. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

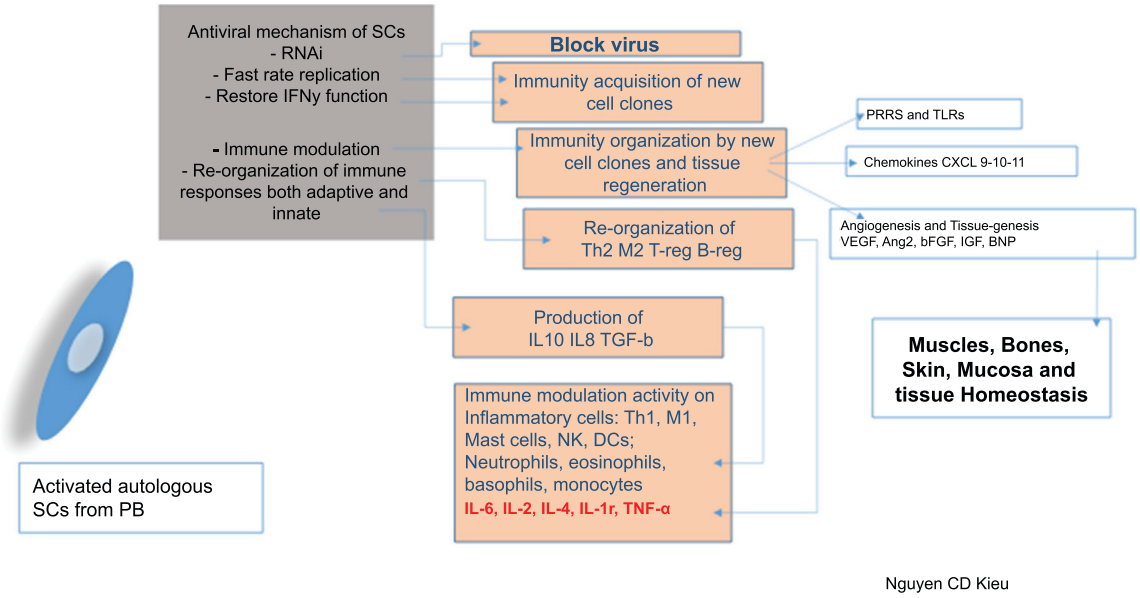

Fig. (2). The SCs multiple ways of fighting pathogens. The steps are linear and sequential and take place at multiple levels: tissue homeostasis, tissue repair and tissue regeneration, modulation of inflammation, immune modulation, re-organization of immune responses, both adaptive and innate, and use of RNAi and PRRs. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Nevertheless, the RNAi partial loss with the gain of a functional IFN-γ mechanism is also suggestive of a highly functional antiviral immunity mechanism since both IFN and RNAi tend to perform almost redundantly; it seems that RNAi would eventually set-in in case of IFN responsiveness in differentiated affected cells [21]. Of note, it was shown that IFN-competent mammalian somatic cells infected with the influenza A virus were still able to produce virus-derived siRNAs co-immunoprecipitated with Ago [22]. There is only one of the many points that can be found regarding the controversy over RNAi's role in SCs and somatic cells (Fig. **2**).

However, what was seen during the COVID-19 pandemic is that a certain number of individuals were heavily infected by the virus while the majority either revealed low symptoms or were completely unaffected. A possible explanation may reside in individual's genetic makeup due to the presence of single nucleotide polymorphisms (SNPs) on genes such as IFN-γ gene, which eventually compromise gene expression. Of interest, recent studies have confirmed that human SCs have kept a subset of interferon stimulated gene (ISGs). Therefore, given a lack of interferon reaction, it seems reasonable to assert that SCs may rely on different signaling pathways other than the JAK/STAT signaling pathway for IFN expression, allowing inferring the existence of a distinct transcriptional regulatory mechanism [22].

This intrinsic ISG expression varies depending on stem cell type and may appear towards the final stage of differentiation. Intrinsic ISG expression is gradually lost after reaching this latter stage, becoming completely interferon responsive [22, 23]. The authors found that this is a pool of well conserved cells across many species, including humans. These SCs are capable to express ISGs that remain an intrinsic expression. In this view, the study refers to ISGs function as a mechanism enhancing innate pathogen-sensing activities whilst inhibiting signaling through the JAK-STAT pathway. ISGs regulate a wide range of activities. Many ISGs regulate viral, bacterial, and parasite infection by directly controlling specific gene immune pathways through either the upregulation of chemokines and chemokine receptors that allow the cell-to-cell communication or by the use of negative regulators that by switching off IFN signaling allow the return to cellular homeostasis [23, 24] (Fig. **3**).

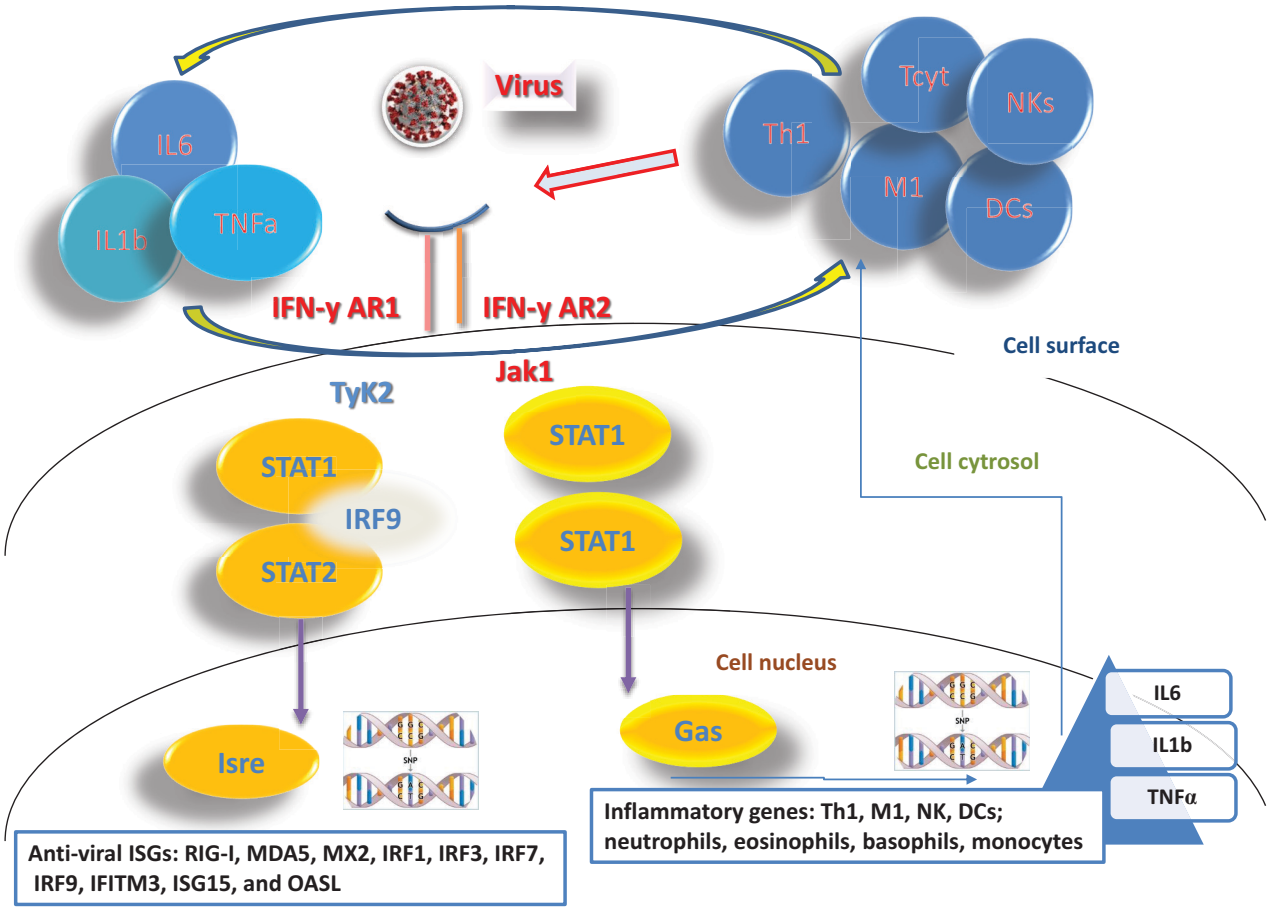

Fig. (3). Antiviral mechanisms of IFN-γ. The IFN-γ inhibits viral entry extracellularly and intracellularly by disrupting replication mechanism *via* inhibition of virus gene expression, translation and by impeding nucleocapsid assembly; the IFN-γ breaks the disulfide bond of a necessary cellular interaction partner and suppresses the transcription of a viral master regulator. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Therefore, it is legitimate to confirm the existence of two antiviral ISG processes that take place within the differentiation phase that allow SCs to preserve a certain amount of ISGs to be used as prophylactic mediators against viral infection. Of course, regarding the ISG expression, one should also consider the involvement of other immune cell mediators that could have antiviral functions as a direct consequence of SCs activation, as in the case of CD141+ dendritic cells and NK cells that constitutively resist viral infection due to expression of vesicle-trafficking proteins that group to prevent viral fusion to cells [25, 26].

3. VIRUS ADOPTING EVASION STRATEGIES FROM IMMUNE SURVEILLANCE

3.1. Regulation of Host DNA Methylation and its Implications for Immune Elusion

The first step for a virus, either enveloped or non-enveloped, after initial attachment to the cell surface is the invasion by fusion and endocytosis. Viruses evolution brought different strategies to inhibit and avoid immune detection and counter-responses by using special devices against T cell receptors and antibodies, mainly by modifying the ligands for particular receptors. Viruses, besides the ability to edit human DNA by inserting their own genetic code to multiply and survive along DNA replication, are also able to mute the immune system by epigenetic regulation intercepting the expression of particular genes, a mechanism known as DNA methylation. *Via* DNA methylation, viruses built parts over DNA promoter regions to hide them from being read and thus silencing gene expression. This transcriptional repression occurs by the assemblage of multiple repressive nucleoprotein complexes because single methylation alone would not be enough to cause gene silencing. Data confirmed that the inactivation is based on the number of methylated sites; the higher the methylated sites, the higher the impact on transcriptional repression [27-31]. Those viruses are capable of using the human syncytin genes to adhere to the targeted cell membrane and commence to penetrate deep into the tissues. *Via* demethylation of host syncytin 1 and 2 genes, these viruses up-regulate gene transcription inducing syncytium formation in specific tissues starting diseases such as multiple sclerosis and even amyotrophic lateral sclerosis. Syncytium formation by SARS-CoV-2 is the main cause of the virulence intensity and is one of the key factors responsible for cytokine storm. Viruses such as SARS-CoV-2, ZIKAV, congenital cytomegalovirus (CMV), Epstein-Barr virus (EBV) and congenital toxoplasmosis are capable of downregulating genes involved in severe inherited forms of degenerative diseases. These viruses alter gene expression *via* DNA methylation, including gene pathways that influence endothelial, neural and tissue development [32-34]. Common underlying epigenetic bases include disruption of the normal pattern of expression of genes involved in virus/host cell interactions, genes that regulate immune response, or genes that directly regulate developmental pathways in organs and tissues such as lungs, kidneys, brain and heart [31-37].

Thus, epigenetic mechanisms are involved in multiple processes by which viruses infect the human host, which allows us to speculate on the importance of individual's genetic makeup, designating those who are more susceptible to some virus infections such as SARS-CoV-2. Those SNPs are different and might be detected on different genes as those involved in immunity and blood clotting mechanism such as ACE, MTHFR, IL10, IL1β, Il6, tumor necrosis factor alpha (TNF-α) and the interferon genes such the case of interferon gamma (IFN-γ) [37-39].

3.2. Viral Escape Mechanisms: Sabotage, Shape Changing and Camouflage

Bacteria and viruses are also known for their ability to interfere with either innate or adaptive immune responses by camouflaging, mimicking and or sabotaging the inner mechanism of defense. These abilities reside in the virus's capacity of producing specific enzymes such as proteases that degrade host defense factors, producing an exact replica of human cytokines and interleukins that modulate immune responses, evading complement activation, blocking the employment of macrophages type 1 and 2 (M1 and M2), escaping neutrophil extracellular traps (NET), dendritic cells and NK cells activation [40,41]. Often there is an overlap between the viral persistence and immune escape mechanisms; immune evasion strategies contribute to pathogen persistence at both the population and individual levels, making it difficult to develop effective vaccines or effective counter-measures. Examples of pathogens using such types of evading strategies may include herpes simplex virus (HSV), human immuno-deficiency virus (HIV), respiratory syncytial virus (RSV), and cytomegalovirus (CMV) among viruses; *M. tuberculosis*, *H. pylori*, and *S. aureus* among bacteria; and *Leishmania, Trypanosoma*, and *Filaria* species among parasites [40-42].

The RNA viruses expose very peculiar features, which is their ability to continue mutation once inside a cell, unveiling the role of the immune response in the natural selection of 'escape mutants' centering attention on the role of T and B cells in this mechanism. Intercepting the immune tolerance performed by regulatory T cells (Tregs) and M2 is one of the best tools that pathogens adopt to dampen immune responses. These types of viruses are also able to delete T cell epitopes to evade recognition by human T cells, and the deimmunization mechanism has been observed in the course of infection by RNA viruses such as in the case of HIV, HCV and SARS-CoV-2. Deletion of total T cell epitope appears to be also a mechanism adopted by selected bacteria. However, T cell epitope deletion also involves antibody titers reduction and diminished antibody affinity, indicating that this mechanism may eventually compromise the B cell integrity as it happens in COVID-19 disease. A few experiments data showed that viral loading is a key point. If levels were low, virus infection was rapidly cleared; on the other hand, as soon as the dose of infection increased, the selection capacity leading to the up-rising of viruses which were not recognized by the host T cell receptor (TCR) also increased, suggesting that a high viral load and a strong/focused selective force are required to see the evading modes [42-45].

In addition, RNA viruses are equipped with an ingenious immune evading mechanism based on the ncRNAs (non-coding RNAs) highly correlated with viral infection activity. The internal structure of ncRNAs up to 200bp indicates two main groups of long ncRNA, circular and linear ncRNAs. The

ncRNAs are not presented *via* major histocompatibility complex (MHC) therefore, are not recognized as a danger by the adaptive immune system, which facilitates them to overwhelm host cell functions by controlling the expression of viral genes, influences host cell regulation and evades host innate and specific immune responses [46]. The ncRNA allows the virus to escape detection also *via* the dsRNA that, in turn, induces the activation of both dsRNA dependent-PKR (pattern recognition receptors) and TLRs (Toll-like receptors), which results in type I IFN response. For instance, EBV and HIV act as a trap to inhibit PKR activation. Another benefit of ncRNA viruses is their ability to modify cytokines and chemokines secretion that can directly take place by binding to RIG-1 mRNA, thereby impairing the production of IFN in association with host-derived miR-197, generating a weakened production of IL-6, a well-known pro-inflammatory cytokine [46-48].

Thus, the inhibition of IFN production remains one of the most important tools adopted by viruses to block antiviral response. A common feature of flavivirus as Zika virus, Japanese encephalitis virus (JEV), West Nile Virus (WNV) and dengue virus is the production of viral non-coding subgenomic RNAs known as subgenomic flavivirus RNAs (sfRNAs) involved in immune evasion *via* inhibition of IFN production by targeting the STAT2 pathway [46-48]. The SARS-CoV-2 virus is equipped with ncRNAs usually upregulated in COVID-19 active infection that would be eventually used as a biomarker for disease progression and severity. Understanding these mechanisms could provide further insight into the SCs possible options against COVID-19 [49].

4. THE RATIONALE USE OF AUTOLOGOUS STEM CELLS FROM ALREADY INFECTED PATIENTS IN THE TREATMENT OF PATHOGEN INFECTION

It appears that one of the strongest points in using autologous SCs from affected patients in treating infections is possibly based on their biological capacity of restoring and reorganizing the functions of immune responses, at both adaptive and innate levels lost during viral and bacterial infections. Newly isolated and re-activated SCs obtained from affected patients may thus constitute a strategic anti-viral tool against virus infection [10].

The first step is probably the reorganization of the altered micro-environment which is followed by a sequential anti-pathogen activity based on SCs RNAi mechanism. Until very recently, the lack of biochemical and genetic evidence for the existence of siRNA suggests that the RNAi mechanism was not considered a key mechanism in antiviral immunity in humans. However, outcomes from pluripotent cell studies showed a different scenario. Using mice ESCs as a model system, it was demonstrated that siRNA of viral origin was detected in infected ESCs with encephalomyocarditis virus or Nodamura virus, suggesting that the RNAi pathway might be functional in these cells [49, 50].

Biologically adult somatic cells do not utilize RNAi since they use the IFN-based innate immunity and adaptive immune system to protect the cells from viral infection. Therefore, the RNAi mechanism may reside only in SCs or young somatic progenies. Evidence suggest that the two mechanisms may either have some conflict in their mechanisms of action, which appears to be due to the incompatibility between the IFN system and siRNA/miRNA biogenesis in differentiated cells or simply refer to two different biological stages of cell life [16, 17, 50].

Following Guo in 2017, we, therefore, proposed that the IFN-based system can be considered a functional antiviral mechanism in adult somatic cells in the absence of the RNAi mechanism, although the entire molecular mechanism responsible for both biogenesis remains to be determined. Furthermore, we assume that the successful use of SCs is based on the reorganization of the microenvironment and their ability to restore and regenerate damaged tissues and cells (T, B lymphocytes, new DC and NK cells) with a renewed anti-pathogen IFN-γ mechanism. To this must be added the natural immunomodulatory capacity of SCs in controlling the inflammatory process through the production of new anti-inflammatory cytokines and interleukins such as TGF-β and IL10 [50, 51].

Since antigen presentation through the Class I MHC pathway is a key point of interference by some viruses, it is worth assuming that SCs may also exert a beneficial effect on MHC-class I. The SCs tend to regulate the presenting antigen pathway, inducing the peptides loading in an appropriate length (9–11 amino acids) and appropriate motif into stable complexes with Class I-MHC molecules and beta-2 microglobulin. Another important trait that we assume the newly injected SCs would support is the HLA-G5 soluble molecule, a non-classical human MHC class I protein that protects the fetus against rejection from the maternal immune system. The HLA-G5 contributes to the immunomodulatory properties of SCs, as this molecule can suppress allogeneic T cell proliferation and can also induce the expansion of CD4 + CD25 high FOXP3 + Tregs. The presence of HLA-G5 inhibits the lysis of MSCs mediated by NK cells, as well as the secretion of IFN-γ by these cells [44-51]. Natural killer (NK) cells, which are considered the major effector cells of innate immunity, are also influenced by the immunomodulatory potential of SCs. In previous works, we showed that autologous PB-SCs, once re-injected into HIV and T Gondii infected patients, showed an increase of NK CD 16+ and CD56+ together with a decrease of IFN-γ secretion. Likewise, a marked decrease in the cytolytic capacity of NK cells was also observed. The expression of MHC class I molecules by MSCs protects them against certain detection mechanisms by NK cells. Tumor cells, as well as virus-infected cells, which have little or no expression of MHC class I, are usually killed by NK cells [13, 52-54].

Furthermore, we speculate that SCs may also be able to adopt an additional tool in fighting viruses probably based on the pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), retinoic acid-inducible gene-I (RIG-1), and protein kinase R (PKR) allowing SCs to recognize foreign nucleic acids, as viral RNAs. In fact, by Toll-like receptor activation, SCs would be able to restore the intracellular signaling pathways leading to the induction of inflammatory cytokines such as type I IFNs within the adult somatic cells, and to upregulate the whole group of co-stimulatory molecules that drive to the activation of the innate and adaptive immune responses [55-57]. Assumption was

confirmed by some studies on hFT-MSCs that showed their ability to express almost the totality of TLRs with highly functional TLR2, TLR3, and TLR4 capable of initiating downstream signaling events. These studies demonstrated that those SCs expressed PRRs that recognized nucleic acids, including TLR3, RIG-I, and IFI16. The poly(I:C), a synthetic dsRNA, activating TLR3 and RIG-I, and HSV60, a synthetic fragment of the DNA sequence of herpes simplex virus (HSV), activating IFI16, induced innate immune responses through the expression of type I interferons and antiviral proteins in hAD-MSCs [57-59].

CONCLUSION

The evident immunomodulatory properties of SCs over immune system cells, as well as their capacity for multi-differentiation and their validation in the regeneration of damaged tissue suggest that autologous SCs could be of great potential for use in immunotherapy in viral and bacterial infections. However, well-delineated *in vivo* studies regarding immunogenicity, mechanisms of immunomodulation and anti-pathogen capacity of autologous SCs, as well as the safe use of these cells in the long term, are necessary for their long term application for different infectious diseases.

AUTHORS' CONTRIBUTIONS

Conceptualization, M.G.B., C.G.I., K.C.D.N. and A.B.; methodology, all the authors; investigation, C.G.I., K.C.D.N. and A.B.; data curation, M.G.B., P.D., R.L., E.D., A.N., F.I., G.D. (Gianna Dipalma), D.T., E.M.S., A.B., K.C.D.N. and C.G.I.; writing-original draft preparation, M.G.B., C.G.I., F.I. and A.B.; bibliographic research: C.G.I. and A.B.; writing-review and editing, M.G.B., C.G.I., A.B. and K.C.D.N.; supervision, M.G.B., C.G.I., A.B. and P.D.; project administration, M.G.B., D.T., C.G.I. Contributed equally, K.C.D.N. and C.G.I. All authors have read and agreed to the published version of the manuscript.

LIST OF ABBREVIATIONS

HSV	=	Herpes Simplex Virus
NET	=	Neutrophil Extracellular Traps
PKR	=	Protein Kinase R
PRRs	=	Pattern Recognition Receptors

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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Declared none.

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