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Mini Review

Enhanced Thymopoiesis as an Alternative Therapeutic Option for COVID-19

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Introduction

The pandemic caused by SARS-CoV-2 infection (COVID-19 disease) has expanded worldwide. Currently, it is well known that advanced age is an independent predictor of mortality and severe clinical outcome, apart from other comorbidities [1]. Underlying molecular and cellular mechanisms that could explain the severe clinical outcome among elderly subjects are not well known [2], although it has been described that both immunosenescence and a low-level systemic inflammation (inflamm-aging) could also play a relevant role [3,4].

Now a days, apart from an effective vaccine development, research efforts are focused on therapeutic approaches that could minimize both the viral replication and the further inflammatory cascade driving to respiratory distress and multiorgan failure; however, up to now, no specific therapy for SARS-CoV-2 infection has been established [5]. Awaiting for definitive and conclusive results from prospective clinical trials, antiviral and immunomodulatory drugs currently employed in SARS-CoV-2-infected subjects are based on their biological plausibility according to the mechanism of action or *in vitro* efficacy, but not in a definitive scientific evidences.

Taken altogether, alternative hypothesis about underlying mechanisms driving to an impaired clinical outcome in COVID-19 disease are required. In this sense, even the universally accepted role of the cytokine storm has been questioned [6]. Hence, the greater hypothesis is considered the greater and more beneficial therapeutic options could be tested. Recently, our group has suggested that thymic dysfunction could play a relevant role in the impaired clinical outcome observed in elderly SARS-CoV-2-infected subjects [7]. Thus, the main objective of the present opinion paper is to explore a new therapeutic option for COVID-19 disease, based on enhancing thymic function.

Thymic Function in Adulthood

It has been traditionally accepted that thymic function begins its involution in childhood and continues in adolescence under the effect of sexual hormones, so that just thymic vestiges are observed in the elderly. However, it is well known that thymic function may be present and enhanced in different clinical scenarios. First of all, Mackall et al. [8] reported for the first time how thymic function increased in children and adults with chemotherapy-induced lymphopenia. This observation has been confirmed in other clinical settings [9,10], including HIV-infected subjects under suppressive antiretroviral therapy (Figure 1). Additionally, it has been shown that even in the elderly certain thymopoiesis remains (Figure 2) and it is directly associated with T-cell homeostasis and survival in healthy elderly subjects [11-13].

According to these evidences, thymic function could increase in different clinical scenarios when lymphopenia occurs (chemotherapy, HIV-infection), trying to compensate the lack of T-cells. Besides, thymic function may also be active in healthy elderly subjects, playing a relevant role in the maintenance of the naïve T-cell pool and survival of these people.

Thymic Function and COVID-19 Disease

The potential role of thymic function in the control of acute infections, including SARS-CoV-2, is not well known. Hypothetically, thymic function could have a dual positive role regarding acute infections: 1) First of all, through a direct action against novel antigens (in this case, SARS-CoV-2) by a triple function: elimination of self-reactive cellular clones, generation of naive T-cells and expansion of T-cell receptor repertoire; 2) Secondly, modulating the inflammatory response by regulatory T-cells.

Regarding COVID-19 disease, lymphopenia is developed by around 80% of subjects affecting T-cell, B-cell and NK lymphocytes. Additionally, these affected subjects also show increased exhaustion biomarkers such as PD-1 or TIM-3; the increased levels of those biomarkers could be associated with plasma proinflammatory citokines (IL-6, IL-10, TNFα) and an impaired clinical outcome [14,15].

However, the reason why lymphopenia occurs in the context of severe COVID-19 disease remains still unknown. Different hypothesis have been proposed: direct viral infection against thymus, peripheral T-cell redistribution due to cell migration affecting and colonizating organs including lungs, bone marrow and thymus, despite no ACE receptors (angiotensine converting enzyme, the main SARS-CoV-2 cell receptor) have been described in that lymphoid organ [16]. However, the origin of the distinct lymphopenia that characterizes

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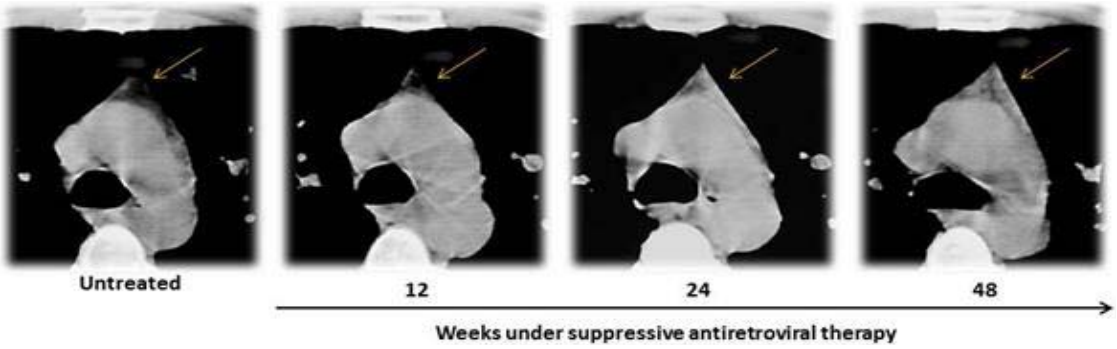

Figure 1: Visualization of thymus slices of a 28-year-old HIV-1 infected patient by Computed Tomography (CT). Enhanced and amplified CT scans at the level of pulmonary artery are shown at baseline and after 12, 24 and 48 weeks under highly active antiretroviral treatment. Thymus outline and density (indicated by yellow arrows at the top centre of each frame) increased progressively after treatment introduction. Images taken by the Laboratorio de Inmunoviología, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío de Sevilla (Spain).

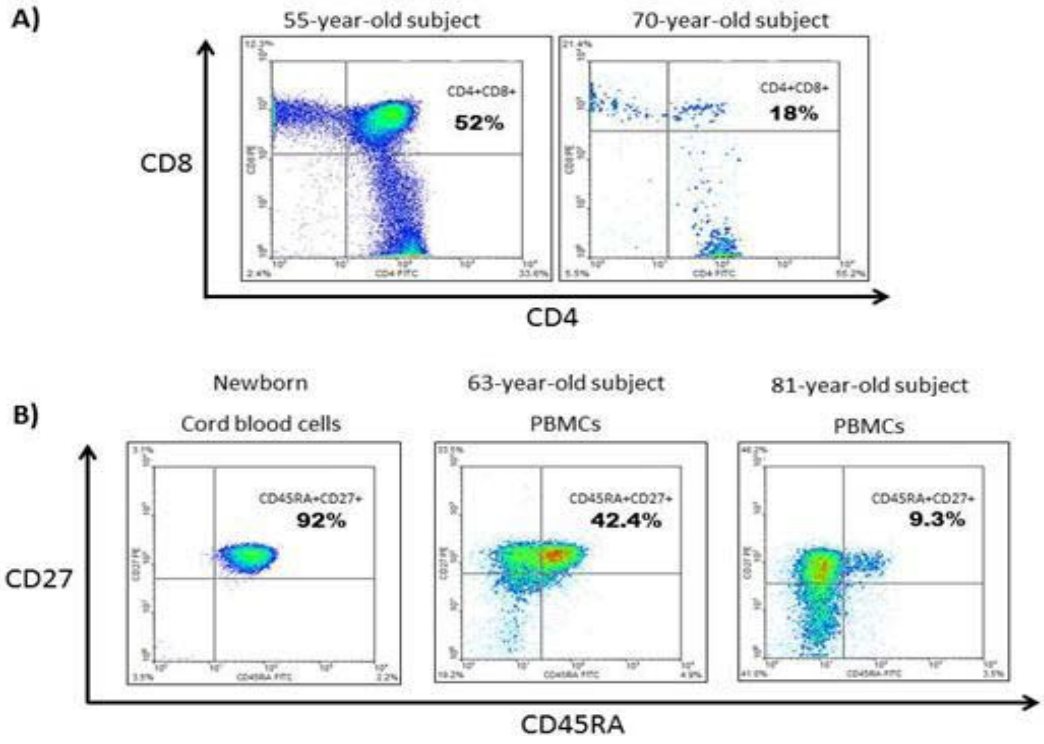

Figure 2: Flow cytometer plots. Percentage of double positive thymocites ($CD4^+CD8^+$) obtained from 55-year-old and 70-year-old subjects. Thymic cells obtained after cardiac surgery and tissue disgregation (A). Plots showing the percentage of thymocites ($CD4^+CD8^+$) and, obtained from two different adults: thymus samples after cardiac surgery. Frequency of naïve $CD4^+$ T-cells based on the expression of $CD45RA^+$ and $CD27^+$ from a newborn cord blood cells, and peripheral blood mononuclear cells of two adults: a 63-year-old and 81-year-old subjects (B). Experiments were performed in a FACSCanto (BD Biosciences) and analysed using Flowjo 8.7.7 (TreeStar, San Carlos, California, USA). Data from Laboratorio de Inmunoviología, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío de Sevilla (Spain).

COVID-19 disease is unknown. We have recently hypothesized that thymic function could play a relevant role in this context [7], an attractive approach that could have subsequent clinical implications.

Enhancing Thymopoiesis: The Role of Alpha-1-Thymosine

In the context of COVID-19 disease, and mainly in elderly subjects because of the greater severity of SARS-CoV-2 infection in this population, the maintenance of a residual thymic function may be critical regarding the further clinical outcome. Moreover, this thymic function may be therapeutically enhanced in order to increased thymopoiesis and improved the cellular immune response to the novel antigen, modifying the natural course of COVID-19 disease (Figure 3A).

The human alpha-1-thymosine (α1Thy) is segregated by the epitelial cells of the thymic tissue and widely distributed through secondary lymphoid organs [17]. The potential immunologic effects of α1Thy are: 1) to mitigate the exacerbated inflammatory response

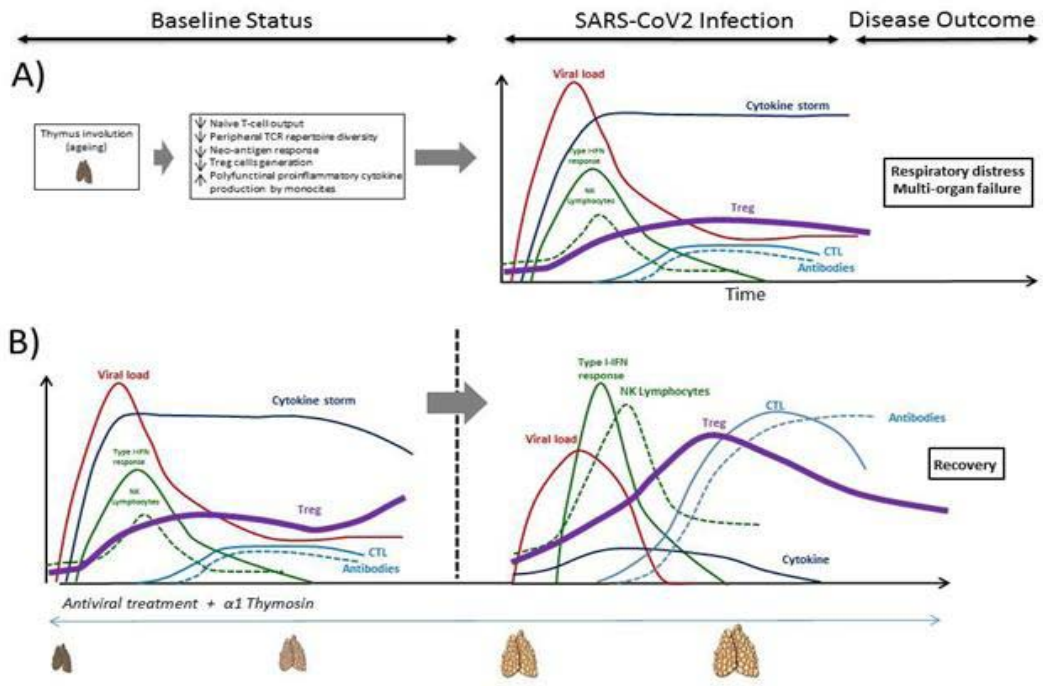

Figure 3: Figurative kinetics of immune system response against SARS-CoV-2, disease evolution and outcome in a status of thymus involution or impairment due to ageing (modified from Genebat et al. Ageing and disease In press) (A). Potential immunomodulatory effect of α1thymosin (α1Thy) as adjuvant in the adaptive and innate immune system restoration and SARS-CoV-2 specific cytotoxic T-response increase (B). The effect of α1Thy could reverse the thymus involution into a status in which thymic function is preserved. Treg: Regulatory T-cell. NK lymphocyte: Natural Killer lymphocyte. CTL: Cytotoxic T lymphocyte. TCR: T-cell Receptor.

favouring the production of regulatory T-cells, that can diminish the production of proinflammatory cytokines [18]; and 2) to favour antigen presentation increasing type I and II MHC expression on antigen-presentation cells [19].

Accordingly to the above commented immunologic effects, clinical use of α1Thy has been tested in different scenarios, with an excellent safety profile [20,21]. Focusing in SARS-CoV-2 infection, it has been recently reported a favourable clinical approach using α1Thy in the context of severe COVID-19 disease, showing a clinical benefit and an immune recovery based on a T-cell count increase [22,23], suggesting that thymus capacity could be partially preserved (Figure 3B). The mechanisms by which α1Thy can participate as an immunomodulatory coadjuvant in therapy and vaccine designs against COVID-19 remain still unknown; however, some evidences has indicated a direct inhibitory property of α1Thy against ACE receptor [24].

Conclusion

In conclusion, we consider that thymic function is critical to control SARS-CoV-2 infection, mainly in the elderly when thymic function is impaired but not absent. Based on the immunologic properties of α1Thy and its preliminary results in different clinical scenarios including COVID-19 disease, prospective studies are required in order to determine the mechanisms and confirm the efficacy of this therapeutic approach as an immunomodulatory adjuvant in therapies against SARS-CoV-2 infection.

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