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The Role of Poietins in the Alleviation of Cytopenias in HIV Infection

Abstract

Safer and greater efficacy biologically occurring 3-O-sulfogalactosylceramide, sulfatide (+/-) poietins for containment of HIV replication and rescue from hematopoietic cell depletion in HIV-1 Infection is our objective. We also discuss novel biomarkers detection with the intention to later design new array of fluorescence molecule (and their protein complexes) labeling methods of monoclonal antibodies using modeling through bioinformatics.

Keywords: HIV/AIDS; Cytopenias; Lumazine; Poietins; Hematopoiesis; Sulfatide

Mini Review

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Introduction

Alleviation of cytopenias which are caused due to the indirect inhibition of hematopoiesis in HIV-1 infection as a result of the retardation or differential differentiation of CD34+ hematopoietic progenitor cells to their terminality of formation of different blood cellular components could be aided by inclusive therapy of Sulfatide (3-O-sulfogalactosylceramide) [1-3]. Since Sulfatide use in preclinical humanized mouse model system could achieve partial but not near complete resurgence of hematopoiesis in HIV-1 infected animals, clinical trials in humans have been proposed to determine the efficacy of different isoforms of this potential drug candidate [3]. We also propose to consider the addition of different poietin drugs (eg. erythropoietin, promegapoietin, angiopoietin, darbepoietinalfa, epoietin, thrombopoietin) in different combinations with sulfatide [3-6]. Moreover sulfatide-poietin combinations could serve as differential CD34+ progenitor cell differentiation mediators of hematopoiesis in the treatment of specific cytopenias (eg. anemia, thrombocytopenia) [3,6]. We intend to determine the efficacy of using singularly the sulfatide and also in parallel therapeutic strategies with combination poeitin therapies, for overcoming multiple or specific cytopenias. Lumazine or lumazine protein (in addition to PerCP) fluorescence [7-9] will be considered for use as an indicator of CD34+ cell differentiation patterns in HIV infection.

Methodology

The use of thrombopoietin (TPO) primarily for megakaryopoiesis and erythropoietin (EPO) for erythropoiesis is well known. TPO and (pro) megapoietin (PMP) are known to promote not only primarily megakaryopoiesis and erythropoiesis respectively but also differentiation of the CD34+ progenitor cells into other lineage types due to interactions with the thrombo poietin receptor, c-Mpl [6-10]. This will occur when interleukin-3 (IL-3) and granulocyte macrophage colony stimulating factor (GM-CSF) also interact with c-Mpl whereas EPO is the ligand for a distinctly different receptor. On the contrary EPO promotes solely erythropoiesis. As a result, IL-3 and GM-CSF, in addition to EPO mixed with the CD34+ cells are added to semi-solid medium, Methocult, to form myeloid and erythroid colonies respectively.

The colony forming potential of these growth factors is not adequate to compensate for the hematopoietic inhibition caused by HIV infection and also the conventional highly active antiretroviral therapy (HAART). Moreover sulfatide exhibited a greater efficacy to retrieve hematopoiesis than AZT in HIV-1 infected severe combined immunodeficient mice carrying human fetal thymus/liver conjoined tissues. Therefore we expect to achieve a potential synergistic effect with use of both the sulfatide and poietins to enhance hematopoiesis and not use the HAART since the latter conventional treatment methods although are improved in recent years due to the development of better protease inhibitors in terms of reduced deleterious effects on hematopoiesis.

Research

Our previous studies on the interactions of c-Mpl with hematopoietic growth factors (as mentioned below) other than its natural ligand thrombopoietin (TPO) yet yielded a multi-lineage enhancement or resurgence of hematopoiesis in its indirect inhibition of the differentiation of CD34+ progenitor cells due to HIV-1 infection of the neighboring thymocytes [11,12]. The action of thrombopoietin is more at the level of CD34+ cells which could also have acquired CD38 but not the lineage markers, CD34+CD38+/-lin-, and also certainly negative for CD45. To the contrary, angiopoietins (ANG-1, ANG-2, ANG-3) which are the ligands for Tie-2 receptor tyrosine kinase [13-16] could when combined with the (+/-) TPO, GM-CSF, interleukin-3 (IL-3),

erythropoietin (EPO), or its functionally equivalent or similar darbepoietin or epoietin, and (+/-) promegapoietin, could also promote the quiescent or primitive CD34-/CD34lowCD38-lin- long term culture initiating cells (LT-CICs) [17] into terminal differentiation via the CD34+/CD34hi progenitor cells, with the acquirement of not only CD38 but also CD45, the latter in particular suggesting expression of lineage markers (lin+). Angiopoietins alone by themselves are not expected to drive the intermediate CD34+ cells to expression of lineage markers. Thus the primitive nature as is assayed of the cobblestone area forming hematopoietic progenitor stem cells (CAFC) is proposed to be driven to differentiation by the ANG-Tie-2 interactions [17-23], whereas the TPO-c-Mpl interactions [6,11] cause further differentiation of the CD34+lin- cells into CD34-CD38+lin+ cells as assayed by CFU-GM, BFU-E, or CFU-MK colonies formed in semi-solid Methocult or Megacult-C, respectively [6]. The lack and loss of CD34 phenotype before advancement of differentiation from quiescence or primitive nature for acquirement of this phenotype and after maturation into lineage phenotype expression respectively does not prevent self-renewal of the CD34+ cells to sustain active hematopoiesis.

Discussion

Whereas the quiescent thymocytes were shown to be activated by HIV-1 infection [24], the same is not suggested with respect to CD34+ hematopoietic progenitor cells due to their resistance to lentivirus infection. Even if the CD34+ cells are permissive to HIV infection, it is not necessary that these cells become HIV+ prior to the acquirement of the T-lymphocyte CD4 subset phenotype coincidentally also this virus' receptor, following terminal differentiation, despite their expression of the HIV co-receptor CXCR4 [25] even during pluripotency. HIV-1 infected T-cell secreted inhibitory factors inhibit the differentiation of adjacent CD34+ cells in an indirect manner which is contrary to the activation of quiescent thymocytes by this virus infection in a direct manner [9,17]. The quiescent thymocytes express the subset CD4 antigen to receive the virus but the primitive hematopoietic precursor progenitor cells do not at that stage express their CD34 phenotype marker, nor is this antigen a receptor for HIV.

Conclusion

Sulfatide delivers greater efficacy that the conventional treatments against HIV infection both in terms of the virus replication and consequently resurgence of inhibited hematopoiesis as well [3]. Thus we suggest a combination of both sulfatide and poietins to further enhance and preserve or protect hematopoiesis in HIV infection.We believe that such sulfatide plus poietin treatments could eliminate the side effects of further contributing to hematological disorders by the HAART. The earlier proposed clinical trials [3] yet to be undertaken could also include poietins as parallel therapeutic strategies to mitigate any deficiencies of using only sulfatide.

Future Directions

A wide spectrum of the terminally differentiated progenitor cells in the hematopoiesis patterns [26] with their respective antigen markers could be analyzed if an array of fluorescence molecules is available for simultaneous labeling of the different monoclonal antibodies that bind to their phenotypic antigens. This would enable a multi-colored FACS analyses and fluorescence molecules like those that our fundamental studies in the 1970's later developed such as the PerCP, or as proposed to be designed Lumazine (LumP) [7]. Different fluorescence instrument gains exhibited varying emission but within a small range, for the same or modified FAD [27]. Thus as suggested, the HIV induced cytopenias are proposed to be alleviated by combination sulfatide plus single or multiple poietin therapies. The variations of the levels of the terminally differentiated blood forming hematopoietic cells from the pluripotent / multipotent CD34+ progenitors by yet to be developed and utilized fluorescence molecules such as lumazine with narrow emission band widths to the existing or currently used molecules in the similar wavelength regions, in this instance the blue colors of the visible light [7,27,28].

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