EXCELLENT PUBLISHERS

International Journal of Current Research in Biosciences and Plant Biology

ISSN: 2349-8080 Volume 2 Number 10 (October-2015) pp. 78-81

www.ijcrbp.com

Review Article

Leukopoietin and HIV Infection: A Review

Emmanuel Ifeanyi Obeagu[1]*, K.C. Ochei[2] and Getrude Uzoma Obeagu[3]

[1]Diagnostic Laboartory Unit, Department of University Health Services, Michael Okpara University of Agriculture, Umudike, Abia State, Nigeria
[2]Department of Medical laboratory Science, Ambrose Alli University, Ekpoma, Edo State, Nigeria
[3]Department of Nursing Science, Faculty of Health Science and Technology, Ebonyi State University, Abakaliki, Nigeria

**Corresponding author.*

Abstract

This papers reviews leukopoietin and HIV infection. Endogenous chemical substances which activate and regulate processes of cell development and maturation are called leukopoietins. The leukopoietins that catalyze the release of the different leukocyte types and their precursors from the production and storage sites of the bone marrow into blood circulation are defined as leukorecruitins.The leukopoietins that catalyze the release of the different leukocyte types and their precursors from the production and storage sites of the bone marrow into blood circulation are defined as leukorecruitins. The target is the barrier between bone marrow production and storage sites on one hand and blood circulation on the other hand. The well regulated, stable leukocyte level in normal man and lower animals indicates a highly refined equilibrium between (a) factors responsible for production of leukocytes and (b), factors controlling their death. Leukocyte production proceeds at an orderly pace in the normal human subject compensating promptly for greater or lesser leucopoiesis. Some of these leukopoietins include Granulocyte Colony Stimulating Factor (G-CSF), Granulocyte Macrophage Colony Stimulating Factor (GM-CSF), Colony -Stimulating Factor-1(CSF-1).Human immunodeficiency virus type 1 (HIV-1) infection of peripheral blood mononuclear cells (PBMCs) can alter the levels and/or activation of STAT5. Additionally, infection of $CD4^+$ T cells with strain X4 of HIV-1 ($HIV_{NL4.3}$) inhibits STAT5 activation in response to IL-2.

Keywords

Colony Stimulating Factor
HIV
Leukopoietin
Leukorecruitins

Introduction

The stimulus to differentiate for committed cells of each cell line is mediated by glycoproteins inducers called haemopoietins such as erythropoietins for red cells, leukopoietins for white cells, and thrombopoietins for platelets. The discovery of erythropoietin, a humoral substance regulating production of erythrocytes has raised the question whether humoral factors for control of leucocytes exist. Endogenous chemical substances which activate and regulate processes of cell development and maturation are called leukopoietins.

The leukopoietins that catalyze the release of the different leukocyte types and their precursors from the production and storage sites of the bone marrow into blood circulation are defined as leukorecruitins. The target is the barrier between bone marrow production and storage sites on one hand and blood circulation on the other hand.

The well regulated, stable leukocyte level in normal man and lower animals indicates a highly refined equilibrium between (a) factors responsible for production of leukocytes and (b), factors controlling their death. Leukocyte production proceeds at an orderly pace in the normal human subject compensating promptly for greater or lesser leucopoiesis. It is highly probable that one or more specific leukocyte stimulants are involved ,controlled or regulated, as it were by opposing forces or substances which rarely permit an excess of leucopoiesis or apoiesis. While the existence of both leukopoietic stimulants and inhibitors has been suggested, their demonstration has not been conclusive (Bierman, 2006). There are probably many leukopoietic stimulants specific for granulocytes, lymphocytes, monocytes, plasmacytes etc also possibly even for neutrophilic, eosinophilic or basophilic granulocytes. Almost these stimulating substances are interrelated, not only among themselves but also with erythropoietins and thrombocytopoietins to maintain a well balanced hematopoietic population. Since the marrow is the major and only site of granulocyte formation in normal man, it is the target organ for granulocytopoietic stimulation, the widespread distribution suggesting that leukopoietic stimulants are probably supplied through the blood to the hematopoietic site. The prompt initiation and promotion of leukopoiesis in the marrow by a circulating stimulant suggests that the leukopoietic substance is of a molecular size such that it can readily transverse capillary and cell membrane enroute to the target site. It is not known at present whether leucopoiesis is promoted by; (a) the addition of a missing metabolite; (b) a mitogenic substance;(c) the release of mature leukocytes, or (d) other modes of action. The removal of large numbers of mature leukocytes (leukaphresis) is followed by intensive leucopoiesis associated with appearance of increased amounts of leukocytic and leukopietic stimulants in the plasma. According to Kakhetelidze and Dolgina (1972) these endogenous substances capable of inducing leucocytosis or of stimulating leucopoiesis have been given many names depending on the conditions and method used for their detection. Options differ regarding the site of formation of these substances. According to some workers, the factor inducing neutrophilic leukocytosis is formed in the liver. Others concluded that the chief source of granulopoietin found in the blood is the kidneys and that leukopoietins may be stored in the kidneys. According to Kakhetelidze and Dolgina (1972), Menkin one of the workers considered that factors inducing leukocytosis and found in the blood and exudates during inflammatory conditions are formed in the inflammatory focus from damage leukocytes. Some of these leukopoietins include Granulocyte Colony Stimulating Factor (G-CSF), Granulocyte Macrophage Colony Stimulating Factor (GM-CSF), Colony -Stimulating Factor-1(CSF-1), etc.

Granulocyte Colony Stimulating Factor (G-CSF)

Granulocyte colony-stimulating factor (G-CSF), also known as colony-stimulating factor 3 (CSF 3), is a glycoprotein that stimulates the bone marrow to produce granulocytes and stem cells and release them into the bloodstream. Functionally, it is a cytokine and hormone, a type of colony-stimulating factor, and is produced by a number of different tissues such as endothelium, macrophages, and a number of other immune cells. G-CSF also stimulates the survival, proliferation, differentiation, and function of neutrophil precursors and mature neutrophils. G-CSF regulates them using Janus kinase (JAK)/signal transducer and activator of transcription (STAT) and Ras/mitogen-activated protein kinase (MAPK) and phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt) signal transduction pathway. The natural human glycoprotein exists in two forms, a 174- and 180-amino-acid-long protein of molecular weight 19,600 grams per mole. The more-abundant and more-active 174-amino acid form has been used in the development of pharmaceutical products by recombinant DNA (rDNA) technology. The G-CSF-receptor is present on precursor cells in the bone marrow, and, in response to stimulation by G-CSF, initiates proliferation and differentiation into mature granulocytes. G-CSF is also a potent inducer of HSCs mobilization from the bone marrow into the blood stream, although it has been shown that it does not directly affect the hematopoietic progenitors that are mobilized.

Clinical use of G-CSF has been approved for several therapeutically application like treatment of neonatal infections, therapy of acute myocardial infarction, in severe infections and sepsis, therapy in chronic auto

immune neutropenia etc. G-CSF is also used to increase the number of hematopoietic stem cells in the blood of the donor before collection by leukapheresis for use in hematopoietic stem cell transplantation. For this purpose, G-CSF appears to be safe in pregnancy during implantation as well as during the second and third trimesters.

Granulocyte Macrophage Colony Stimulating Factor (GM-CSF)

This is one of the families of glycoprotein hemapoietic growth factors which stimulates the proliferation of myeloid precursor cells and activates mature granulocytes and macrophages. It is produced by a number of cell types such as lymphocytes endothelial cells, monocytes, fibroblasts and some malignant cells. It has been detected in conditioned medium from many tissues such as lungs, platelets, spleen etc. The precise role of GM-CSF plays in the control of hemopoiesis or the activation of phagocytic cells is not clear. Also it is not known whether GM-CSF is required for maintaining homeostasis in the granulopoietic system, whether it is involved in the acute or chronic responses to stress like infection, or both.

Monocytes Colony Stimulating Factor (M-CSF)

The M-CSF receptor is a transmembrane protein tyrosine kinase encoded by the c-fms gene that is required for the proliferation and differentiation of monocyte progenitor cells expressed also in vascular cells. It is a glycosylated homodimer with a molecular mass of 45KD and it is also known as CSF-1. It is found *n t*he circulation and certain macrophages populations like Kupffers cells.

Chronic HIV exposure to type 1 IFN (interferon 1) a cytokine which is a leukopoietin may have detrimental consequences on T-cell homeostasis and survival. This can induce proliferation and exhaustion of hematopoietic stem cells (Sato et al., 2009).

HIV 1 on leukopoietins (GM-CSF)

Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a 22-kDa cytokine that promotes the growth and differentiation of cells of monocyte and granulocyte lineages. GM-CSF also enhances the effector functions of macrophages, including their phagocytic capacity as well as their antiparasitic and antimycobacterial activity (Armitage, 1998). The binding of GM-CSF to its receptor (GM-CSFR) triggers a biochemical cascade necessary to relay information required for these functions. GM-CSFR comprises a low-affinity GM-CSF-specific α-subunit (K_d of ~2.7 nM) and a β_c-subunit, shared by interleukin-3 (IL-3) and IL-5, which together with the α-subunit confers high-affinity binding (K_d of ~170 pM) (Warby et al., 2003) .

This high-affinity binding between GM-CSF and the β_c-chain is dependent on glutamine 21 within the first α-helix of GM-CSF.

As the β_c-chain lacks intrinsic kinase activity, receptor binding triggers receptor-associated kinases that mediate the phosphorylation of cytoplasmic proteins. Activation of the Janus kinase (JAK) family and the subsequent activation of signal transducers and activators of transcription (STAT) are the most studied pathways activated in response to GM-CSF and involve members of each family that differ according to cell type (Al-Shami and Naccache, 1999). Janus kinase 2 (JAK2) protein binds constitutively to an intracellular proline-rich motif of the β_c-chain of GM-CSFR, termed box 1, and is phosphorylated after engagement and oligomerization of GM-CSFR in response to GM-CSF (Warby et al., 2003). This phosphorylation is necessary for activation of JAK2 enzyme activity and leads to phosphorylation of eight tyrosine residues on the β_c-chain. The latent transcription factors STAT5A and STAT5B (STAT5A and STAT5B together make up STAT5) are recruited to the activated receptor complex and phosphorylated on tyrosine residues 694 and 699, respectively. STAT5 then forms dimers between the phosphorylated tyrosine of one molecule and the STAT5 SH2 (Src homology 2) domain of another and dissociates from the receptor. Subsequently, STAT5 translocates to the nucleus and promotes GM-CSF-activated transcription of genes, such as A1 and CIS (Warby et al., 2003). In primary monocytes and macrophages, STAT5A is the STAT5 isoform predominantly activated in response to GM-CSF.

Previous investigations have shown that human immunodeficiency virus type 1 (HIV-1) infection of

peripheral blood mononuclear cells (PBMCs) can alter the levels and/or activation of STAT5. Additionally, infection of $CD4^+$ T cells with strain X4 of HIV-1 ($HIV_{NL4.3}$) inhibits STAT5 activation in response to IL-2 (Selliah and Finkel, 2001). These data suggest that aberrant STAT signaling occurs in HIV-infected T cells, contributing to T-cell dysfunction. It has not been shown whether immediate signaling in response to cytokine stimulation of MDM is disrupted by infection with HIV-1.

Given the importance of GM-CSF to macrophage function and the reported effects of HIV-1 infection on STAT5 activity, it is observed that the effect of in vitro HIV-1 infection of human MDM on GM-CSF-induced STAT5A activation in order to determine whether HIV-1 infection may inhibit macrophage function by impairing GM-CSF signaling. Study shows that GM-CSFR β_c-chain-dependent activation of STAT5A is specifically inhibited in HIV-1-infected human MDM. This may contribute to defective macrophage function in HIV-infected individuals. Also HIV-1 inhibits GM-CSF activation of STAT5A without affecting expression of the known components of the signaling pathway. These data provide further evidence of disruption of cellular signaling pathways after HIV-1 infection, which may contribute to immune dysfunction and HIV-1 pathogenesis.

Conclusion

Endogenous chemical substances which activate and regulate processes of cell development and maturation are called leukopoietins. The leukopoietins that catalyze the release of the different leukocyte types and their precursors from the production and storage sites of the bone marrow into blood circulation are defined as leukorecruitins.Chronic HIV exposure to type 1 IFN (interferon 1) a cytokine which is a leukopoietin may have detrimental consequences on T-cell homeostasis and survival. This can induce proliferation and exhaustion of hematopoietic stem cells.

References

Al-Shami, A., Naccache, P.H., 1999. Granulocyte-macrophage colony-stimulating factor-activated signaling pathways in human neutrophils. Involvement of Jak2 in the stimulation of phosphatidylinositol 3-kinase. J. Biol. Chem. 274, 5333-5338.

Armitage, J.O., 1998. Emerging applications of recombinant human granulocyte-macrophage colony-stimulating factor. Blood. 92, 4491- 4508.

Bierman, H.R., 2006. Characteristics of Leukopoietin G. in animal and man. Ann. New York Acad. Sci. 113, 753-765.

Kakhetelidze M.G., Dolgina, Z. M., 1972. Site of Formation of Leukopoietins in Dogs with Aseptic Inflammation. Options differ regarding the site of formation of these substances. Bull. Exp. Biol. Med. 73(3), 23-26.

Sato, T., Onai N., Yoshihara, H., Arai, F., Suda, T., Ohteki, T., 2009. Interferon regulatory factor. 2 Protects quiescent hematopoietic stem cells from type 1 Interferon –dependent exhaustion. Nat. Med. 15, 696-700.

Selliah, N., Finkel, T.H., 2001. HIV-1 NL4-3, but not IIIB, inhibits JAK3/STAT5 activation in $CD4^+$ T cells. Virol. 286, 412-421.

Warby, T.J., Crowe, S.M., Jaworowski, A., 2003. Human Immunodeficiency Virus Type 1 Infection Inhibits Granulocyte- Macrophage Colony-Stimulating Factor-Induced Activation of STAT5A in Human Monocyte-Derived Macrophages. J. Virol. 77(22), 12630-12638.