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Relationship between Thrombopoietin and Interleukin 3: A Review

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Abstract

Thrombopoietin (TPO) is the highest strong cytokine that physiologically controls platelet production. TPO is a hormone constitutively formed by the liver and kidneys. Following a fall in the platelet count thrombopoietin levels rises half maximally by 8 hours and peak by 24 hours. Circulating levels of thrombopoietin are inversely related to platelet mass. Platelets contain an avid thrombopoietin receptor that efficiently binds and removes thrombopoietin from circulation. Interleukin-3 (IL-3) is a multipotent haematopoietic growth factor produced by activated T-cells, monocytes/macrophages and stroma cells. Interleukin 3 stimulates the differentiation of multipotent haematopoietic stem cells into myeloid progenitor cells or, with the addition of IL-7, into lymphoid progenitor cells. In addition, IL-3 stimulates proliferation of all cells in the myeloid lineage (granulocytes, monocytes, and dendritic cells), in conjunction with other cytokines, e.g., Erythropoietin (EPO), Granulocyte macrophage colony-stimulating factor (GM-CSF), and IL-6. It is secreted by basophils and activated T cells to support growth and differentiation of T cells from the bone marrow in an immune response.

Keywords: Thrombopoietin, IL-3, myeloid lineage, GM-CSF.

Introduction

The word thrombopoietin was first applied by Kelemen in 1958 to depict the humoral matter accountable for elevating platelet synthesis after the beginning of thrombocytopenia (Kelemen *et al*., 2008). Thrombopoietin (TPO) also known as c-MpI ligand, mpl ligand, megapoietin, and magakaryocyte growth and development factor, is the highest strong cytokine that physiologically controls platelet production (Wendling *et al*., 2008). TPO is a hormone constitutively formed

by the liver and kidneys. Plasma levels of TPO are controlled via receptor-mediated uptake, internalization and breakdown. TPO has multifactorial effects on hematopoiesis (Kuter, 2006).

Two forms thrombopoietin have been researched in clinical trials. One, termed recombinant human thrombopoietin (rTPO), is a full-length polypeptide. The other, a truncated protein containing only the receptor-binding region, which has been chemically altered by the addition of polyethylene glycol (PEG), is termed PEG-conjugated recombinant human megakaryocyte growth and development factor (peg-MGDF, also known as PEG-rHuMGDF)). The polypeptide has 163 amino acids and is conjugated with polyethylene glycol on the N terminal by reductive alkylation. The biologic activities of both of these proteins are similar (Souryi *et al*., 2010).

Megakaryocyte Development

The production of platelets from the marrow progenitors is a complex process. Each day the adult produce $1x10^{11}$ platelets a number that can increase to 10 fold in times of raised demand. All the formed elements are formed from haematopoietic stem cells, through a series of cell divisions (Wendling, 2009).. This process of cellular proliferation and differentiation requires the support of several interleukins, colony-stimulating factors, and hormones. Thrombopoietin, along with other cytokines, has several actions during megakaryocyte development (Harker, 2006).

One of the earliest identifiable megakaryocyte progenitor is the high proliferative potential colony forming unit - megakaryocyte (HPP CFU-MK). Next stages in the sequentially are burst forming unit-MK (BFU-MK) and CFU-MK, promegakaryoblasts and megakaryoblasts. CFU-MK are initially mitotic cells but then stop cellular division (cytokinesis) while continuing to undergo DNA replication (endomitosis) to produce immature megakaryocytes that are polypoid and contain up to 64 times the normal amount of DNA. The immature MK then develop into larger, mature MK that shed platelets into bone marrow sinusoids (Bartley, 2008).

Physiology

The primary site of thrombopoietin production is the liver. Lesser amounts are seen in the kidneys, brain and testes. Thrombopoietin is synthesized and immediately released as and when required like erythropoiesis. Following a fall in the platelet count thrombopoietin levels rises half maximally by 8 hours and peak by 24 hours.

Regulation of thrombopoietin expression

Circulating levels of thrombopoietin are inversely related to platelet mass. Platelets contain an avid thrombopoietin receptor that efficiently binds and removes thrombopoietin from circulation (Souryi *et al*., 2010). Thus normal or elevated levels of platelets inhibit inhibit the action of TPO on target cells (bone marrow) by binding to circulating TPO. This observation is clinically important because

1. Platelet transfusions may blunt the recovery of magakaryocytes (Kaushansky, 2008).
2. Other cytokines or disorders may modify the constitutive hepatic production of thrombopoietin, similar to reduced erythropoietin levels in renal disease
3. Small molecules could be developed to decrease the platelet's clearance of thrombopoietin and in turn stimulate platelet production
4. Disease related abnormalities in the platelet's ability to clear thrombopoietin may alter thrombopoietin levels. E.g. diminished clearance of thrombopoietin by abnormal platelets may account for the elevated platelet counts seen in myeloproliferative syndromes such as essential thrombocythemia. In conditions associated with marrow failure(e.g. aplastic anemia) thrombopoietin levels are high where as in ITP thrombopoietin levels are low (Kaushansky *et al*., 2005). Thus TPO levels may be used for the differentiation of thrombocytopenia due to bone marrow failure or increased destruction.

Pharmacologic Properties of Thrombopoietin

Of the hematopoietic growth factors thrombopoietin has got the longest half-life i.e. 30hours. PEGylation of thrombopoietin further increases the plasma half-life by 10 fold. Following systemic administration, the platelet count begins to increase after 3-5 days. This is because thrombopoietin acts by stimulating the production and maturation of megakaryocytes (Kaushansky, 2008). The most common adverse events were disturbances of the gastrointestinal system, and arthralgia. In therapeutic doses MGDF doesn't have any effect on platelet function.

Cytokine regulating Thrombopoietin

Thrombopoiesis is regulated by many cytokines in which the rate of platelets production responds to the number or mass of circulating platelets. IL-3, G-CSF,GM-CSF and steel factor(SCF, kit ligand) acts in the progenitor cell stage. Whereas IL-6 acts late in the maturation. TPO and IL-11 stimulate all stages of megakaryocytopoiesis, including the proliferation of progenitors and the development and complete maturation of polypoid megakaryocyte. In addition, thrombopoietin acts in synergy with erythropoietin to stimulate the growth of erythroid progenitor cells (Kaushansky *et al*., 2005), and with interleukin-3 or steel factor it stimulates the proliferation and prolongs the survival of hematopoietic stem cells and all types of blood-cell progenitors. TPO have some role in regulatingneutrophil activation also. Thrombopoietin can sensitise platelets to various agonists (Chen *et al*., 2005) and may predispose to thrombosis when administered therapeutically.

INTERLEUKIN-3

Interleukin-3 (IL-3) is a multipotent haematopoietic growth factor produced by activated T-cells, monocytes/macrophages and stroma cells. Human IL-3 gene is located on chromosome 5 near segment 5q31. The high affinity receptor for human IL-3 is composed of alpha and beta subunits.Interleukin 3 (IL-3) is a protein that in humans is encoded by the *IL3*genelocalised on chromosome 5 (Yang *et al.*, 2006; Ifeanyi *et al.*, 2020; Okorie *et al.*, 2019; Obeagu *et al.*, 2020).

The haematopoietic system is composed of cellular hierarchy and the earliest stem cells, pluripotent stem cell have great potential to self renew, proliferate and differentiate (Metcalf, 2009). This process of blood cell formation is regulated by number of growth factors and interleukins produced from activated T cells, macrophages and stroma cells (Ogawa, 2014). Among such cytokines, stem cell factor (SCF), interleukin-3 (IL-3) and granulocyte-macrophage colony stimulating factor (GM-CSF) stimulates multilineage haematopoietic cells while granulocyte colony stimulating factor (G-CSF), erythropoietin (Epo) and thrombopoietin (Tpo) stimulates more restricted lineage of hematopoietic cells (Ihle, 2012). Human interleukin 3 gene was cloned in 1986 by Metcalf*et al*., and since then it has been used in preclinical studies and clinical trials (Garnick, and D'Reilly, 2009). The major function of IL-3 is to induce proliferation and differentiation of early pluripotent stem cells and committed progenitors (Garland, 2006). The effect of IL-3 depends on the target cell type and presence of other cytokines (McNiece *et al*., 2011).

Discovery of interleukin-3

Interleukin 3 was originally discovered by JN Ihle in mice. He found a T cell derived factor that induced the synthesis of 20alpha-hydroxysteroid dehydrogenase in hematopoietic cells and termed it interleukin-3 (Ihle, Pepersack and Rebar, 1981). In the early 1960s Ginsberg and Sachs discovered that IL-3 is a potent mast cell growth factor produced from activated T cells(Delves, 1998).

BIOLOGICAL EFFECTS OF IL-3

Recombinant IL-3 protein produced in E-Coli or in CHO cells has been used to characterise various biological activities including their effects on normal bane marrow cells and cloned celllines (Yang and Clark, 2009). There are various levels

at which IL-3 affects hematopoiesis. The addition of IL-3 to human bane marrow and peripheral blood stem cells induce growth of stem cell subsets including CFU-GEMM, CFU-GM, BFU-E, CFUMeg. It also induces growth of CFU-baso and CFU-eo in higher doses (Mayer *et al*., 2009). The proliferative stimulus in early progenitors is transmitted only slowly to the other compartments, suggesting that even in vivo, other molecules may play a key role in the regulation of terminal phases of these differentiation processes. IL-3 may act by modifying the sensitivity of marrow cells to the action of cytokines effective in terminal phases of myelopoietic differentiation (Fraser,Lill and Figlin, 2006).

Functions of interleukin-3

Interleukin 3 is an interleukin, a type of biological signal (cytokine) that can improve the body's natural response to disease as part of the immune system. It acts by binding to the interleukin-3 receptor.

Interleukin 3 stimulates the differentiation of multipotent haematopoietic stem cells into myeloid progenitor cells or, with the addition of IL-7, into lymphoid progenitor cells. In addition, IL-3 stimulates proliferation of all cells in the myeloid lineage (granulocytes, monocytes, and dendritic cells), in conjunction with other cytokines, e.g., Erythropoietin (EPO), Granulocyte macrophage colony-stimulating factor (GM-CSF), and IL-6. It is secreted by basophils and activated T cells to support growth and differentiation of T cells from the bone marrow in an immune response. Activated T cells can either induce their own proliferation and differentiation (autocrinesignalling), or that of other T cells (paracrinesignalling) – both involve IL-2 binding to the IL-2 receptor on T cells (upregulated upon cell activation, under the induction of macrophage-secreted IL-1). The human IL-3 gene encodes a protein 152 amino acids long, and the naturally occurring IL-3 is glycosylated. The human IL-3 gene is located on chromosome 5, only 9 kilobases from the GM-CSF gene, and its function is quite similar to GM-CSF.

Receptor for IL-3

IL-3 is a T cell-derived, pluripotent and hematopoietic factor required for survival and proliferation of hematopoietic progenitor cells. The signal transmission is ensured by high affinity between cell surface interleukin-3 receptor and IL-3. This high affinity receptor contains α and β subunits. IL-3 shares the β subunit with IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF). This β subunit sharing explains the biological functional similarities of different hematopoietic growth factors (Manzoor and Adrian, 2008).

IL-3/Receptor complex induces JAK2/STAT5 cell signalisation pathway. It can stimulate transcription factor c-myc (activation of gene expression) and Ras pathway (suppression of apoptosis).

Conclusion

Thrombopoietin (TPO), also referred to as c-MpI ligand, mpl ligand, megapoietin, and magakaryocyte growth and development factor, is the most potent cytokine that physiologically regulates platelet production.TPO is a hormone constitutively produced by the liver and kidneys. Plasma levels of TPO are regulated through receptor-mediated uptake, internalization and catabolism. TPO has pleiotropic effects on hematopoiesis.

Interleukin-3 (IL-3) is a multipotent hematopoietic growth factor produced by activated T-cells, monocytes/macrophages and stroma cells.

Thrombopoiesis is regulated by many cytokines in which the rate of platelets production responds to the number or mass of circulating platelets. IL-3, G-CSF,GM-CSF and steel factor(SCF, kit ligand) acts in the progenitor cell stage. Whereas IL-6 acts late in the maturation. TPO and IL-11 stimulate all stages of megakaryocytopoiesis, including the proliferation of progenitors and the development and complete maturation of polypoid megakaryocyte. In addition,

thrombopoietin acts in synergy with erythropoietin to stimulate the growth of erythroid progenitor cells, and with interleukin-3 or steel factor it stimulates the proliferation and prolongs the survival of hematopoietic stem cells and all types of blood-cell progenitors. TPO have some role in regulatingneutrophil activation also. Thrombopoietin can sensitise platelets to various agonists and may predispose to thrombosis when administered therapeutically

Thrombopoietin and interleukin-3 are both cytokines and growth factors. A lot of cytokines are involved in hematopoiesis (blood production). Among such cytokines, stem cell factor (SCF), interleukin-3 (IL-3) and granulocyte-macrophage colony stimulating factor (GM-CSF) stimulates multilineage hematopoietic cells while granulocyte colony stimulating factor (G-CSF), erythropoietin (Epo) and thrombopoietin (Tpo) stimulates more restricted lineage of hematopoietic cells.

Thrombopoietin (TPO) is the highest strong cytokine that physiologically controls platelet production. TPO is a hormone constitutively formed by the liver and kidneys. Following a fall in the platelet count thrombopoietin levels rises half maximally by 8 hours and peak by 24 hours. Circulating levels of thrombopoietin are inversely related to platelet mass. Platelets contain an avid thrombopoietin receptor that efficiently binds and removes thrombopoietin from circulation. Interleukin-3 (IL-3) is a multipotent haematopoietic growth factor produced by activated T-cells, monocytes/macrophages and stroma cells. Interleukin 3 stimulates the differentiation of multipotent haematopoietic stem cells into myeloid progenitor cells or, with the addition of IL-7, into lymphoid progenitor cells.

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