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Thrombopoietin receptor agonists: a new immune modulatory strategy in immune thrombocytopenia?

Alexandra Schifferli*, Thomas Kühne

Department of Oncology/Hematology, University Children's Hospital Basel, Basel, Switzerland

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ABSTRACT

In 2008, new drugs that mimic the effects of thrombopoietin became available for the treatment of primary immune thrombocytopenia, eg, romiplostim and eltrombopag. These drugs activate the thrombopoietin receptor, stimulate the production of megakaryocytes, and increase the production of platelets. Important clinical observation has been gained, such as unexpected long-term remission after stopping thrombopoietin receptor agonists. The pathophysiology of this unforeseen cure is currently the subject of discussion and is investigated in clinical trials and laboratory research projects. Here we evaluate the different hypotheses on how thrombopoietin receptor agonists can affect the immune system, particularly the induction of tolerance, and by which mechanisms this may be achieved.

1. Introduction

Thrombopoietin receptor agonists (TPO-RAs) have been designed to stimulate megakaryopoiesis. In 2008, the US Food and Drug Administration approved two drugs, romiplostim and eltrombopag, for the treatment of primary immune thrombocytopenia (ITP). Both drugs exhibit high efficacy with acceptable adverse effects [1–3]. The success story of TPO-RAs appears to be greater than expected. Data exist suggesting that stimulation of the receptor for thrombopoietin (TPO), the c-MPL receptor, may induce immunological mechanisms to restore immune tolerance in ITP [4,5].

ITP is an autoantibody-mediated bleeding disorder with both accelerated platelet destruction and impaired platelet production. The dysregulation of the immune system in ITP involves the innate and adaptive immune system. Multiple mechanisms underlie the development of autoimmunity, most of which involve disturbances in regulatory circuits, cytokine synthesis, and signaling pathways.

Patients with ITP harbor an imbalance in the T-cell subsets, with a shift toward Th1 and Th17 cells [6,7]. Moreover, it has been shown that there is a decrease in regulatory T and B cells [8,9]. These changes can be defined by the measurement of cytokines. Patients with ITP have a shift toward interleukin-2 (IL-2), interferon-gamma (IFN-γ), and IL-17 cytokines, all corresponding to a pro-inflammatory/immune response, as well as a drop in many cytokines, such as IL-10, transforming growth factor-β1 (TGF-β),IL-4, and IL-35.

In this review article, we will discuss new insights into possible immunomodulatory functions of TPO-RAs.

2. Clinical background

Recently, reports on long-term remission after discontinuation of TPO-RAs in adult patients with chronic ITP have been published. Several case reports, retrospective data, and a clinical trial revealed sustained platelet counts above 100×10^9/L after discontinuation of romiplostim in up to 30% of the patients [10–12].

Červinek et al retrospectively analyzed 46 patients with relapsed and refractory ITP treated with TPO-RAs [10]. In 11 of these cases, TPO-RA therapy (romiplostim, $n = 7$; eltrombopag, $n = 4$) could be successfully stopped, with a median follow-up of 33 months. The probability of remission appeared not to depend on previous treatment, splenectomy, or disease duration. In a case study of eight romiplostim trials, Bussel et al [12] examined patients with sustained remission after discontinuation of romiplostim; remission was identified in 27 patients. No clear predictors of remission were identified; however, a number of patients had ITP for < 1 year and received romiplostim for < 1 year. This observation was supported by a prospective trial in patients with ITP lasting for < 6 months; remission was observed in approximately one third of adult patients who were treated with

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* Corresponding author. Department of Hematology/Oncology, University Children's Hospital Basel, Spitalstrasse 33, 4031 Basel, Switzerland. Tel.: 0041 61 704 12 12; fax: 0041 61 704 12 13.

E-mail address: alexandra.schifferli@ukbb.ch (A. Schifferli).

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romiplostim with a median time (range) to onset of 27 (6–57) weeks [11].

3. Theoretical background

Several theories on the induction of immune tolerance by TPO-RAs are proposed:

- Unknown and unexpected effects of the c-MPL receptor (eg, c-MPL receptor on immune cells)
- Unknown effects of TPO-RAs, which may not directly be related to the stimulation of the c-MPL receptor and involving the immune system (eg, cross-reaction with activation or inhibition of other receptors and pathways of the immune system)
- Immune modulation following increased platelet mass. Two mechanisms may be involved: (1) induction of immune tolerance by exposure to high-dose antigen, or (2) innate platelet immune activity

At present, the latter theory appears to be the most plausible explanation. Platelets are more than just pro-coagulant fragments; indeed, accumulating evidence suggests an immunomodulatory role for platelets and platelet-derived microparticles (PMP). Although they do not replicate or contain nuclei, platelets have multiple roles in host defense against infections and are involved in innate and adaptive immune response mechanisms [13–16]. Thus, platelets seem to be part of the immune response. This theory is also consistent with the evolution of the hematological system. In many invertebrates and early vertebrates, one cell type (the hemocyte) carries out hemostatic as well as host-defense functions. Platelets have the ability to bind to infectious agents, secrete many immunomodulatory cytokines and chemokines (alpha granules), and express receptors for various immune effector and regulatory functions, such as pattern recognition receptors (PRRs) (eg, toll-like receptors), CD40L, and denaturated major histocompatibility complex (MHC) class 1 molecules. Furthermore, platelets contain mRNA that originates from megakaryocytes and are capable of carrying out independent protein synthesis under different environmental stress, and they are able to release membrane microparticles known to be involved in a variety of pathophysiological responses including immune responses, inflammation, angiogenesis, and tissue regeneration. In this respect, platelets are truly immunological cells [17].

4. Research background

TPO-RAs increase platelet production in the bone marrow and subsequently induce a rise in peripheral platelet count. This acute increase in platelet mass could induce tolerance mechanisms. The following five research topics support our theory that TPO-RAs could have an immunomodulatory function (Fig. 1).

4.1. Induction of immune tolerance by exposure to high-dose antigen

T-cell anergy is a key tolerance mechanism suppressing unwanted T-cell activation against self by rendering lymphocytes functionally inactive following antigen contact. Antigen (Ag) plays an important role in anergy induction, where high supra-optimal doses lead to the unresponsive phenotype [18–20]. An antigen density of >100 peptide-MHC complexes/cell was found to be the transition point between dominant activation and inhibition cascades, whereas higher antigen doses induced an anergic functional state [21]. A rapid increase of platelet mass such as TPO-RA effects increase the antigen mass in patients with ITP, and so may inactivate T cells. However, it is unknown how much the Ag density rises with TPO-RAs and if this rise is sufficient to inactivate autoimmune T cells.

4.2. Platelet (microparticles)-mediated immunoregulatory pathways

Microparticles, also known as ectosomes or micro-vesicles, are important mediators of intercellular communication. They are released by budding directly from the cell membrane surface either spontaneously or in response to various stimuli. Microparticles contain cytosolic substances and phosphatidylserine in their membrane. Depending on their cellular origin, microparticles have been associated with a broad spectrum of biological activities. In the last 10 years, it has been shown that PMPs have effects on the innate immune system, as well as on the induction of adaptive immunity with possibly tolerogenic activity [22]. Increasing the mass of platelets, as caused by TPO-RAs, will necessarily increase the mass of circulating microparticles.

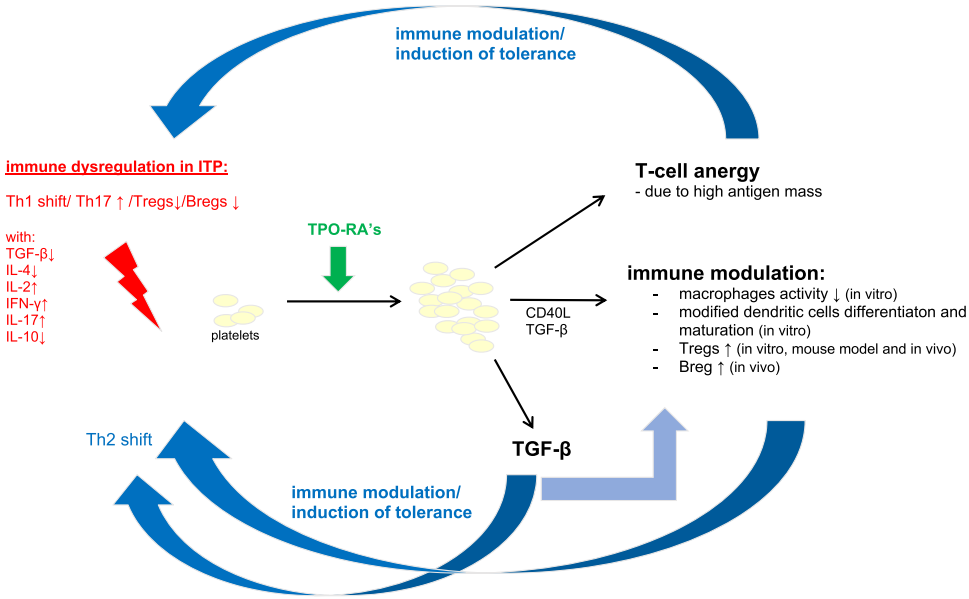

Fig. 1. Hypothesis of immune modulation with TPO-RAs (thrombopoietin receptor agonists) in ITP patients. TGF-β: transforming growth factor β; IL: interleukin.