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Idiopathic thrombocytopenic purpura and dysmegakaryocytopoiesis

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Abstract

Idiopathic thrombocytopenic purpura (ITP) is an autoimmune disorder characterized with thrombocytopenia, primarily caused by platelet destruction. However, the studies of platelet kinetics show platelet turn over are normal or decreased, suggesting that reduced platelet production may lead to severity of ITP. We review recent research progress on abnormal cell events involved in megakaryocytopoiesis contributing to thrombocytopenia.

Keywords: Idiopathic thrombocytopenic purpura; Megakaryocyte; Platelet; Autoantibody; Apoptosis

1. Introduction

Idiopathic thrombocytopenic purpura (ITP) is a bleeding disease in which autoantibodies are directed against an individual's own platelets, leading to increased Fc-mediated platelet destruction by macrophages in the reticuloendothelial system [1].

Most recently, in vitro studies suggest that cell-mediated destruction of autologous platelets may be involved in the pathogenesis of chronic ITP [2,3], which may explain a percentage of patients without detectable antiplatelet antibodies. As a result of the accelerated destruction, platelet production is thought to compensatorily increase. However, the autologous platelet survival studies showed opposite conclusion. Ballem et al. [4] have reported that two-thirds of ITP patients show decreased or normal platelet production. Similarly, Stoll et al. [5] have shown that the rate of platelet production is not increased in most patients with moderate ITP. Furthermore, early light microscopic observations of ITP bone marrow showed increased immature megakaryocytes with manifested degenerative changes in the nucleus and cytoplasm [6]. Various ultrastructural abnormalities of ITP megakaryocytes, including cytoplasmic vacuolization and distended demarcation membrane system (DMS) have also been described [7]. Thus, both platelet destruction and impaired platelet production may contribute to thrombocytopenia.

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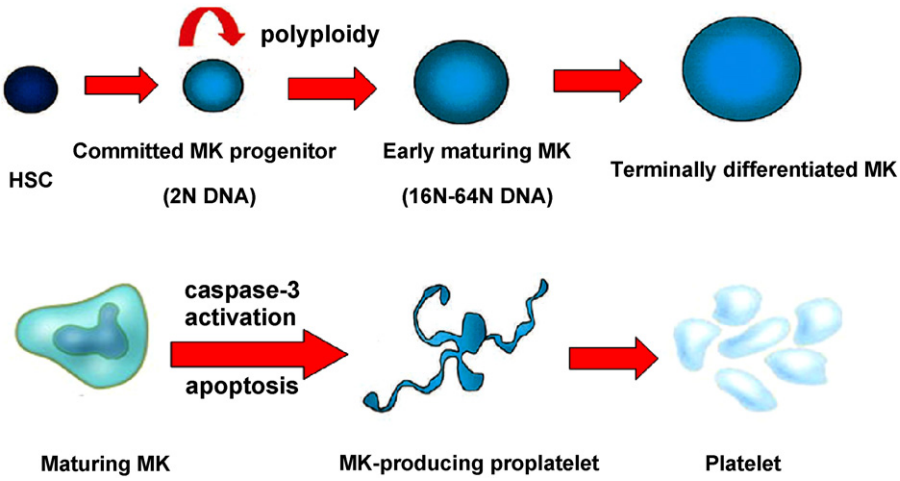

Fig. 1. Megakaryocyte maturation and platelet production. Hematopoietic stem cells (HSC) in the bone marrow go through a process of commitment, proliferation, differentiation, and maturation and become mature megakaryocytes. During the process, endomitosis begins in early maturing megakaryocytes after the standard cell division required to augment numbers of committed megakaryocyte progenitor, resulting in megakaryocyte polyploidy. Primed by a compartmentalization of caspase activation occurring during megakaryocyte maturation, megakaryocyte extends cytoplasmic processes, which is called "proplatelet". Finally, mature platelets are assembled and released at the ends of proplatelets.

Megakaryocytopoiesis is a complex biological process involving a series of cellular events that is initiated with the pluripotent hematopoietic stem cell and eventually results in the biogenesis of platelets shed by mature megakaryocytes. Under appropriate stimulation, pluripotential hemopoietic progenitor cells become committed to the megakaryocytic lineage. During proliferation and differentiation, megakaryocyte progenitors augment number of megakaryocyte and synthesize specific platelet proteins [8,9]. At the end of the proliferative phase, diploid (2N) megakaryocyte precursors undergo a remarkable cellular transformation by increasing their ploidy by the process of endomitosis. Increase in megakaryocytic ploidy is associated with increase in megakaryocytic volume; the large size and abundant cytoplasm allow megakaryocytes to produce several thousand platelets per cell [10]. Mature megakaryocytes extrude long and thin cytoplasmic processes called proplatelet at terminal stage and release platelets at the end of proplatelets [11–13]. Obviously, abnormalities in any stage of megakaryocytopoiesis may influence platelet production (Fig. 1).

2. Serum levels of thrombopoietin, interleukin-6 and -11 in ITP patients

Numerous hematopoietic growth factors regulate different aspects of megakaryocyte biology. Thrombopoietin (TPO) is the predominant regulator of thrombocytopoiesis. As predicted, TPO increases the size, ploidy and number of megakaryocytes and stimulates the expression of platelet-specific markers [14–16]. Other cytokines such as interleukin (IL)-3, -6, -11, and stem cell factor contribute to promote in vitro platelet production with a synergistic action and are capable of inducing platelet shedding by cultured megakaryocyte even in the absence of TPO [17]. Since the platelet destruction is accelerated, the serum levels of thrombopoietic factors in ITP patients are supposed to be elevated. Indeed, ITP patients demonstrate increased endogenous levels of IL-6 and -11, but normal or only slightly increased level of TPO in contrast to the elevated levels found in patients with thrombocytopenia due to bone marrow failure [18–21]. The findings suggest that circulating TPO levels are regulated by all mpl-expressing cells of megakaryocyte lineage [22], not only by the absolute number of circulating platelets.

Though useful in discriminating thrombocytopenia due to decreased production or increased platelet destruction, however, TPO is useless in differentiating ITP from secondary thrombocytopenias [23].

A clinical study of 61 ITP patients showed that TPO levels of the 15 ITP patients who had a poor response to steroid therapy were higher than those of the 22 ITP patients who had a good response to steroid therapy, suggesting that serum TPO levels might be important for the prediction of the outcome of ITP patients who receive steroid therapy [24].

By analogy with autoimmune neutropenia, growth factor for stimulation of megakaryocytopoiesis might be expected to elevate the platelet count in ITP patients. That TPO can increase platelet production without causing thrombus formation in animal models has important implications for its use in treating immune-mediated thrombocytopenia [25]. Indeed, clinical trials of thrombocytopoietic agents, such as PEG-recombinant human MDGF, recombinant human TPO and AMG531, have reported promising response in adults with chronic ITP refractory to other treatment [26,27]. This is in contrast to the lack of effect of recombinant human IL-11 [28]. More data on the long-term efficacy and safety are, however, required and this therapeutic approach is expected to be only suspensive rather than curative.