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Drug-induced thrombocytopenia: Focus on platelet apoptosis

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ABSTRACT

Thrombocytopenia is a serious and potentially fatal complication of drug therapy that results either from a decrease in bone marrow platelet production or the excessive destruction of circulating platelets. Although multiple mechanisms are responsible for deregulated platelet clearance, the role of programmed platelet death (apoptosis) in drug-induced thrombocytopenia has been relatively under-investigated until recently. Here we review apoptotic signaling pathways in platelets, with a focus on current data that provide mechanistic insights into drug-induced apoptosis and thrombocytopenia.

1. Introduction

Platelets are anucleate blood cells essential for hemostasis and wound healing; tight regulation of platelet numbers is crucial for human health. Platelets are synthesized and released from bone marrow megakaryocytes into the circulation where they remain for 7–10 days [1]. In humans, the normal circulating platelet count ranges from 150,000–450,000 platelets/μl of whole blood. A reduction in platelet count below 150,000 platelets/μl is termed thrombocytopenia, a condition that increases the risk of potentially life-threatening hemorrhage [2]. Drug-induced thrombocytopenia (DIT) can occur following administration of a wide range of medications, including antibiotics, cardiac drugs and anti-neoplastic agents [3]. DIT-inducing agents can perturb platelet counts in one of 2 ways: centrally, by exerting cytotoxic effects on bone marrow megakaryocytes, thus reducing platelet synthesis (Fig. 1A); or peripherally, by enhancing clearance of platelets already in circulation (Fig. 1B). Drugs can accelerate the destruction of circulating platelets through both immune- and nonimmune-mediated mechanisms.

2. Immune-mediated platelet destruction

In immune-mediated platelet destruction, drug-dependent antibodies bind to platelets, either directly or alongside accessory proteins [4]. Platelets are then phagocytosed by macrophages that recognize the drug-dependent antibody on the platelet surface. The subject of immune-mediated DIT is covered in-depth by several excellent review articles [3,5–7] and as such is only briefly mentioned here. There are 6 subtypes of immune-mediated DIT that reflect different spatial configurations of the drug and antibody molecules interacting at the platelet surface. These subtypes of immune-mediated platelet destruction are summarized in Table 1.

3. Nonimmune-mediated platelet destruction

In contrast to immune-mediated DIT, nonimmune-mediated platelet destruction is described as a direct cytotoxic effect of the drug molecules on the platelets. For example, thrombocytopenia was previously reported to result from the chemotherapeutic administration of interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α). The purported mechanism was attributed to altered platelet-endothelial cell interactions, and therefore, antibody-independent [8,9]. However, over the past 7 years, considerable evidence has emerged in support of another form of nonimmune-mediated platelet destruction: platelet apoptosis, or programmed cell death. Published evidence from multiple groups clearly indicate that thrombocytopenia-inducing drugs attenuate platelet numbers by triggering pro-apoptotic signaling.

4. Pro-apoptotic signaling in platelets

Apoptosis is a programmed form of cell death that results in a controlled clearance of cells by macrophages, without eliciting an inflammatory response. Apoptosis is essential for the removal of damaged cells from the body and maintaining appropriate cell populations in developing tissues [10]. This form of cell death contrasts with necrosis, which is characterized by the uncontrolled rupture and release of cellular contents [11], resulting in tissue damage. The recognition that platelets undergo apoptosis is a relatively new concept that has been

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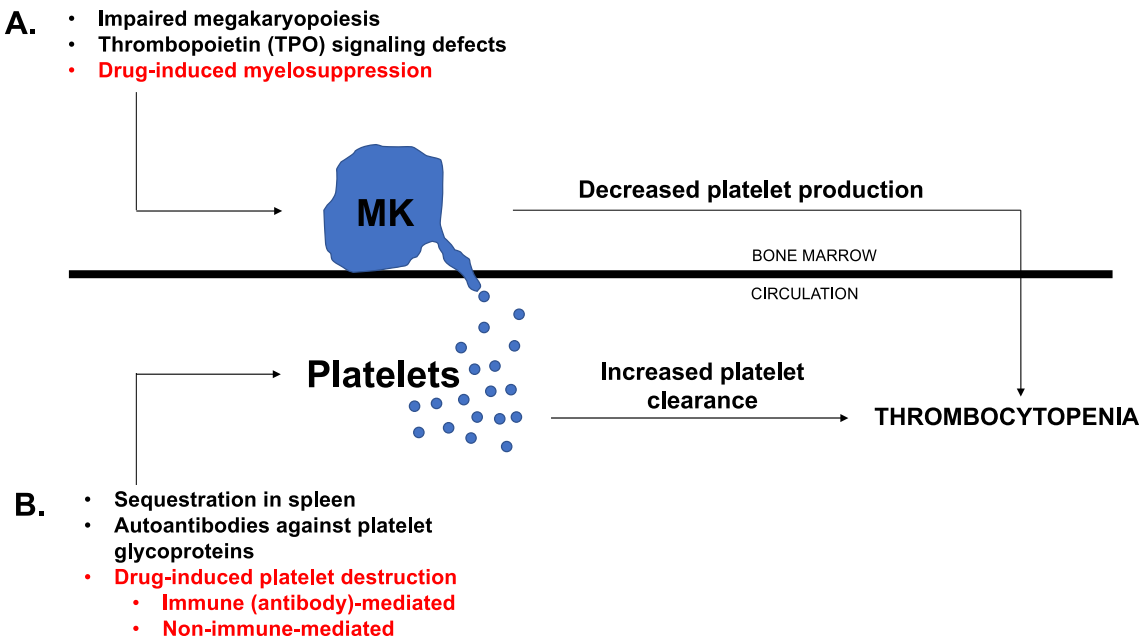

Fig. 1. Platelet production and clearance. A. Decreased platelet production by megakaryocytes (MK) in the bone marrow can result from impaired megakaryopoiesis, thrombopoietin (TPO) signaling defects and drug-induced myelosuppression. B. Circulating platelets may be prematurely cleared due to sequestration in the spleen, autoantibodies against platelet glycoproteins and drug-induced platelet destruction via both immune- and non-immune mediated mechanisms. De-regulation of platelet production and/or clearance can lead to thrombocytopenia.

Table 1
Mechanisms of immune-mediated platelet destruction.

Name	Mechanism	Typical drug	Refs
Hapten-induced antibody	• Drug (hapten) covalently binds to the amine groups of proteins, which elicits an immune response	Antibiotics	[3,5]
Drug-dependent antibody	• Drug associates with platelet glycoproteins that is then targeted by antibodies • Drug exposes glycoprotein sites that are readily recognized by the immune system • Immune response requires a soluble drug	Quinine	[3,5]
Drug-induced autoantibodies	• Autoantibody directly targets platelets • Drug exposes glycoprotein sites that are readily recognized by the immune system, which triggers production of autoantibodies	Procainamide	[5,9]
Immune complex	• Heparin binds and structurally modifies platelet factor 4 causing the formation of antibodies against this complex	Heparin	[3,5,97]
Drug-specific antibody	• A chimeric (human/mouse) Fab domain that binds βA domain of GPIIIa, which is recognized by a naturally occurring antibody or drug-sensitive antibody	Abciximab	[3,5,97]
Fiban-induced thrombocytopenia	• Drug binds to the arginine-glycine-aspartic acid (RGD) recognition site on platelet GPIIb/IIIa receptor, which is recognized by a naturally occurring antibody	Tirofiban	[3,5]

increasingly documented over the past 10–15 years [12–14].

As is observed in nucleated cells, apoptotic platelets typically exhibit cytoplasmic shrinkage, membrane protrusions known as “blebs” and increased cell surface exposure of phosphatidylserine (PS) [10,15] which denotes a cell's slated clearance by phagocytes [16]. Pro-apoptotic signaling pathways are classified as extrinsic or intrinsic (Fig. 2). Extrinsic apoptosis is specifically mediated by extracellular ligand binding to “death” receptors, however, both pathways culminate in the activation of caspases 3 and 7, cysteine proteases that orchestrate cell death by degrading cellular proteins. Therefore, the de-regulation of normal apoptotic signaling mechanisms would plausibly explain amplified platelet destruction observed in drug-induced thrombocytopenia.

4.1. Extrinsic (receptor-mediated) apoptosis

The extrinsic apoptosis pathway is initiated by the binding of extracellular ligands with cell surface receptors. For example, members of the tumor necrosis factor (TNF) receptor superfamily (FasR, TNFR1, DR3, DR4 and DR5) are activated by their respective ligands (FasL, TNF-α, Apo3L, Apo2L, Apo2L) [10]. Death receptor ligation triggers a signaling cascade leading to caspase-8 activation, followed by caspase-3 activation and apoptosis [10]. There is relatively little evidence to suggest that platelets undergo extrinsic apoptosis as they do not express the prototypical Fas death receptor [13]. However, this contention is mitigated by the finding that platelets do express caspase-8, a marker of extrinsic apoptosis [17]. Moreover, thrombin, a platelet agonist and ligand for the protease-activated receptor-1 (PAR-1) [18], reportedly induces caspase-3 activation and cell death [19]. This suggests the existence in platelets of an extrinsic apoptotic pathway that operates independently of the classical death receptors. Consequently, the precise determinants of receptor-mediated platelet apoptosis remain undefined at this time.

4.2. Intrinsic apoptosis

In contrast to the extrinsic apoptosis pathway, intrinsic apoptosis is a receptor-independent process initiated by stimuli such as radiation, toxins, free radicals or an increase in intracellular calcium concentration ($[Ca^{2+}]_i$) [10]. A central feature of intrinsic apoptosis is depolarization of the mitochondria, and this is regulated by several pro-apoptotic and anti-apoptotic accessory proteins (Fig. 2).