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Biologicals, platelet apoptosis and human diseases: An outlook

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Abstract

Platelets, once considered mediators of hemostasis and thrombosis, are now known to be involved in wound healing, inflammation, cardiovascular diseases, diabetes, arthritis, and cancer. Recent reports attest that platelets possess the cellular machinery to undergo apoptosis and that platelet apoptosis can be triggered by myriad stimuli including chemical and physical agonists, and pathophysiological conditions. Augmented rate of platelet apoptosis leads to thrombocytopenia, bleeding disorders and microparticle generation. Despite knowing the significant role of platelets in health and disease, and that any alterations in platelet functions can wreak havoc to the health, the offshoot reactions of therapeutic drugs on platelets and the far-reaching consequences are often neglected. The present review focuses on the impact of

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platelet apoptosis and the role of platelet-derived microparticles on different pathophysiological conditions. It also touches upon the effects of biologicals on platelets, and discusses the need to overcome the adverse effects of pro-apoptotic drugs through auxiliary therapy.

Keywords: Platelet apoptosis; Microparticles; Biologicals; Cardiovascular diseases; Cancer

1. Introduction

Platelets were once considered mere mediators of hemostasis and thrombosis. However, rigorous research in the field of platelet biology gave a new insight into their dynamic and versatile characteristics. It is amazing that these seemingly simple anuclear cells, which are unique to mammals, have such a vast array of physiological functions [1]. They play crucial roles in pathophysiological conditions including wound healing, inflammation, cardiovascular diseases (CVDs), diabetes, arthritis, Alzheimer's disease (AD), angiogenesis and metastasis. Till two decades ago, it was not known how exactly their numbers is controlled or how they undergo death. Recent reports prove beyond doubt that platelets do undergo programmed cell death via apoptosis. Apart from cellular senescence, platelet apoptosis is also triggered by various stimuli including chemical agonists (e.g., thrombin, collagen, ADP, hydrogen peroxide, arachidonic acid, epinephrine, calcium ionophore-A23187, etc.), oxidative stress-induced pathological conditions (e.g., hyperlipidemia, Kawasaki disease, Bernard–Soulier syndrome, altered cardiac functions, type-2 diabetes and chronic uremia) and physical factors (e.g., hyperthermia, platelet storage under standard banking conditions, shear stress) [2].

Bone marrow megakaryocytes undergo apoptosis de facto to release platelets. As such, platelets possess the cellular machinery (which is derived from their parent cells) required for normal functioning. This implies that they also undergo apoptosis like any other nucleated cell, except for the nuclear apoptotic events. However, till date there is strong evidence only for the intrinsic apoptotic pathway and very few studies on the extrinsic pathway in platelets. The former occurs through mitochondrial dysfunction in response to stress. Apoptotic platelets display elevated levels of reactive oxygen species (ROS), calcium (Ca^{2+}), cytochrome c, apoptotic protease-activating factor-1 (Apaf1) and caspases-9 and -3, which are all considered markers of apoptosis. In addition, platelets undergoing apoptosis also express surface markers such as phosphatidylserine (PS) (Fig. 1) [3]. Recent reports suggest the involvement of cell signaling pathways such as, p38 MAPK/cPLA2, PI3K, extracellular signal-regulated protein kinase (ERK) and c-Jun NH2-terminal kinase (JNK) in apoptotic platelets [4–7]. Further, there are various lines of evidence suggesting the existence of extrinsic apoptotic pathway in platelets, but none decisively prove it. For instance, though the presence of TNF-α (a prominent cytokine regulating extrinsic apoptotic pathway) in platelets is controversial, accumulation and secretion of a range of TNF-α-related ligands like Fas-L, TRAIL, TWEAK and LIGHT, is observed [8]. Stored platelets are also found to express mRNA and proenzyme for caspases-8 and -10, mRNA for death receptors such as, DR3, DR4, DR5, TRAIL, TNF receptor p55, and RIP, as well as elevated concentration of TNFα [9]. Moreover, caspase-8 activation in platelets stimulated with TPEN and resveratrol was also reported [10,11].

When the rate of platelet apoptosis exceeds the normal physiological level, it may have far-reaching consequences: (i) reduced platelet count (thrombocytopenia) leading to bleeding disorders; (ii) generation of microparticles (MPs), which play a major role in the propagation of various pathological conditions such as, CVDs, cancer, type-2 diabetes and arthritis [12]. Platelet-derived MPs (PMPs) constitute around 80% of circulating MPs. A study by Berckmans et al. determined the concentration of MPs of different cellular origin in fresh blood samples via flowcytometry to be 237×10^6/L (platelet-derived), 28×10^6/L (erythrocytes-derived), 46×10^6/L (granulocyte-derived) and 64×10^6/L (endothelial cell-derived) [13]. MPs are vesicle-like structures surrounded by plasma membrane bilayer enclosing enzymes, transcription factors and mRNA [14,15]. Apoptotic platelets shed MPs via dynamic membrane blebbing that is driven by the contractile force of cytoskeletal structures actin–myosin [16]. Activated Rho-associated kinase augments the actin–myosin force generation. The shed MPs contain a surfeit of biomolecules including proteins (signal proteins, receptors, cytoskeleton, and effector proteins), lipids, and nucleic acids. They express several surface antigens such as, GpIb, PECAM-1, GpIIb-IIIa, P-selectin, CD 63, CD41a, and CD 61 [17]. However, the surface protein content may be different from that of the plasma membrane of the parent cell, since the inclusion of protein molecules into MPs can be selective and regulated by the stimuli from specific agonists or microenvironments of the parental cells [18].

The present review mainly focuses on the impact of platelet apoptosis and the role of MPs on different pathological conditions. Owing to the extremely sensitive nature of platelets, they are very much vulnerable to therapeutic drugs in the circulation. The surfacing of recent reports of commonly used therapeutic drugs provoking platelet apoptosis is of serious concern, considering the prominent role played by platelets in health and disease. Thereby, the review also touches upon the effects of therapeutic drugs on platelet apoptosis and MP generation, and their clinical consequences. Finally, the need to overcome the