biological subsets that benefit from the addition of imatinib to existing standard therapeutics.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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HEMOSTASIS

Comment on Jobe et al in the February 1 issue of *Blood*, page 1257

Mitochondria push platelets past their prime

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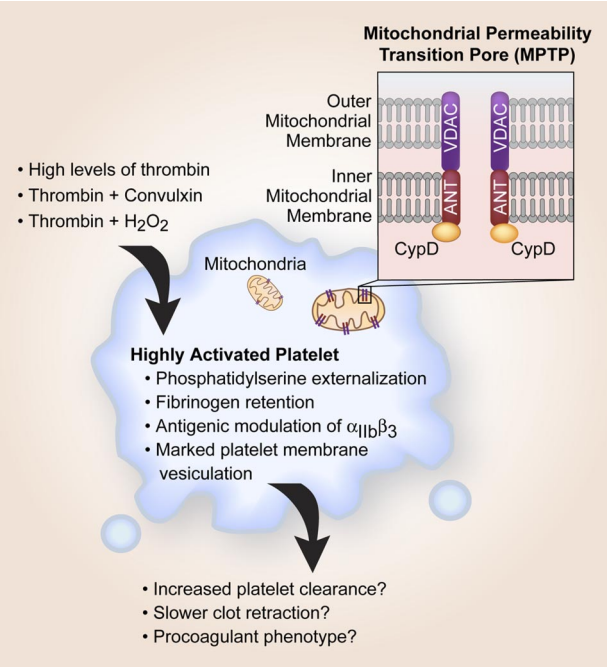
In the February 1 issue of *Blood*, Jobe and colleagues elucidated the function of the mitochondrial permeability transition pore (MPTP), in platelet activation and demonstrated that cyclophilin D (CypD), a regulator of MPTP formation, is a critical factor in the procoagulant response to strong agonists.

Historical roles for platelet mitochondria have been limited to supplying energy for aggregation and secretion. This view, however, continues to be refined and advanced as new functions for this old organelle emerge. It is now well accepted that mitochondria contribute to apoptosis, a process associated with cell death in nucleated cells and recently ascribed to platelets. Mitochondrial membrane potential ($\Delta\Psi_m$) is reduced in platelets that display apoptotic features,[1] and perturbations in the $\Delta\Psi_m$ have been observed in subsets of activated platelets that have high procoagulant activity.[2] Although a reproducible phenomenon, it is generally surmised that compromises in mitochondrial integrity are the consequence of irreversible platelet activation that culminates in cell death. In the February 1 issue of *Blood*, Jobe and colleagues shed new light on these preconceived notions by demonstrating that formation of the mitochondrial permeability transition pore (MPTP) regulates early platelet activation events such as phosphatidylserine externalization, fibrinogen retention, and membrane vesiculation (see figure).



CypD-dependent MPTP formation plays a critical role in pushing a subset of moderately activated platelets into a highly activated state. Highly activated platelets are more likely to be cleared from the circulation, retract clots at a slower rate, and possess procoagulant activity.

MPTP-dependent platelet activation requires cyclophilin D (CypD), a mitochondrial matrix protein that works together with the voltage-dependent anion channel (VDAC) and the adenine nucleotide translocator (ANT) to modulate $\Delta\Psi_m$ (see figure). Although the functional significance of MPTP-dependent platelet activation is not yet known, it appears that MPTP formation pushes a subset of activated platelets past their prime and into a highly activated state. This CypD-dependent transition is regulated by both the quantity and type of agonist(s) used to activate platelets.[1,2] In other words, high concentrations of thrombin or combinations of agonists such as thrombin and H_2O_2 induce the highly activated phenotype.

The fate of highly activated platelets remains undefined, but excessive activation may trigger clearance and thereby contribute to thrombocytopenia, which often occurs in clinical disorders such as sepsis and disseminated intravascular coagulation. High concentrations of thrombin, which are generated in severe sepsis, induce de novo expression of proapoptotic proteins including Bak and Bax,[1] and Mason et al[3] recently demonstrated that an intrinsic program for apoptosis controls platelet survival and clearance. Thus, pharmacological agents that affect MPTP formation may prove useful in the treatment of diseases that are associated with increased peripheral destruction of apoptotic platelets. Similar interventions may also have value in preventing defects in banked platelets that progressively lose their $\Delta\Psi_m$ and become apoptotic during storage.[4]

The surprising findings of Jobe and colleagues continue to highlight the resourcefulness of platelets and raise several new possibilities regarding the function of mitochondria in these anucleate cytoplasts. As an example, it is not a foregone conclusion that highly activated platelets are immediately destined for cell death. Indeed, the authors demonstrate that CypD-dependent responses in platelets can regulate clot retraction, a prolonged process that may contribute to vessel recanalization in vivo. Mitochondrial-dependent signals may also affect thrombus growth, as suggested by the

authors, and variations in the potential to form highly activated platelets may identify subjects at increased thrombotic risk. Other questions remain, including identification of the signaling pathways that link MPTP formation with early platelet activation responses. Regardless of the outcome, it is clear that we are merely on the cusp of discovering new functions for mitochondria in platelets.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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IMMUNOBIOLOGY

Comment on Kambayashi et al in the February 1 issue of *Blood*, page 1489

Mast cells and T-cell expansion

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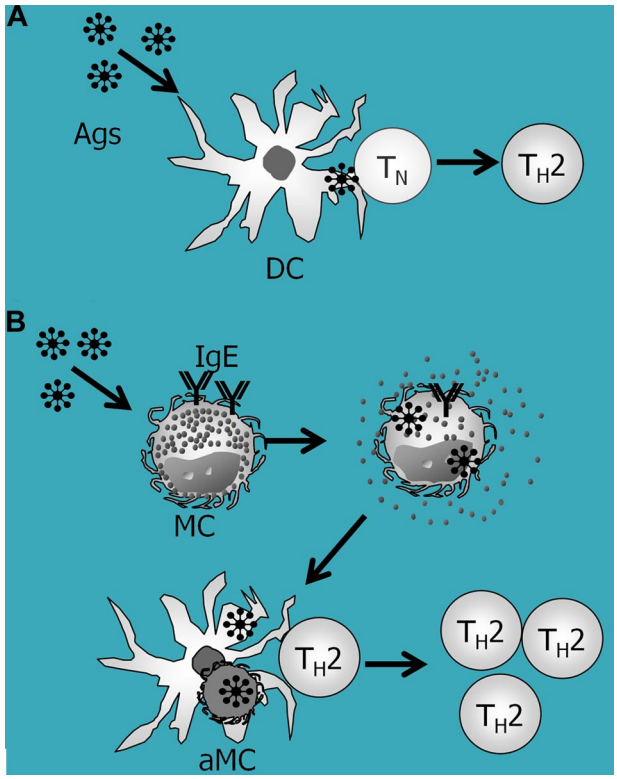
IgE/antigen-FcεRI crosslinking promotes antigen internalization and apoptosis in mouse mast cells. Dendritic cells uptake the apoptotic mast cells carrying internalized antigens, and thus can efficiently present the antigens to memory T cells.

Mast cells (MCs) are responsible for host defenses against bacterial, viral, and parasitic infection through the activation of complement-mediated or Toll-like receptor (TLR)–mediated innate immune responses and IgE/antigen-FcεRI–mediated acquired immune responses.[1] However, excessive or inappropriate MC activation also contributes to the development of certain allergic or autoimmune diseases, which are mediated by allergen- or autoantigen-specific effector T cells.[1]

MCs are capable of presenting antigens to T cells by direct cell-cell interaction through antigen-specific T-cell receptor (TCR) and major histocompatibility complex (MHC) class I– or class II–restricted mechanisms in vitro.[1] Exosomes released from MCs, which contain MHC class II and antigen complexes, participate in antigen-specific T-cell expansion/activation independently of direct cell-cell contact between T cells and MCs in vitro.[1] However, it has remained unclear whether MCs have such functions in vivo.

In the February 1 issue of *Blood*, Kambayashi and coworkers provided a novel molecular mechanism for MHC class II–restricted, antigen-specific T-cell expansion/activation by murine bone marrow–derived cultured MCs (BMCMCs) in a series of well-designed and elegant experiments. Consistent with prior work,[2] they demonstrated that naive BMCMCs showed poor antigen-presenting capabilities to $CD4^+$ T cells from MHC class II–restricted and the ovalbumin (OVA)-specific TCR-transgenic (OTII) stain. However, MHC class II– deficient BMCMCs stimulated in advance with anti-OVA IgE and OVA were found to clearly facilitate OTII T-cell activation without further addition of OVA. In addition, IgE/antigen-FcεRI crosslinking enhanced the internalization of IgE/antigen complexes in MCs, and induced MC apoptosis by down-modulating Bcl-XL expression. The authors also demonstrated that apoptotic MCs carrying intracellularly incorporated antigens were phagocytosed by dendritic cells (DCs). Then, DCs processed the MC-derived intracellular antigens, presented them to $CD4^+$ T cells, and thus induced the expansion/activation of antigen-specific T cells (see figure). These findings suggest that MCs can work as antigen reservoirs and can act as "bridging cells" that transfer the antigen to potent antigen-presenting cells such as DCs.

MCs exist in close proximity with T cells in human tonsils[3] as well as at the inflammatory sites in mice,[2] and in close proximity with DCs in most tissues.[4] In addition, MCs can migrate into draining lymph nodes from antigen entry sites.[5] Based on the present work by Kambayashi and coworkers, it is possible that IgE/antigen-captured MCs become apoptotic in T-cell zones[1] in secondary lymphoid tissues and/or at antigen-challenged inflammatory sites. Thus, DCs can present MC-derived antigens to "antigen-specific," that is, already antigen-sensitized, memory T helper cells. In contrast to a previous report indicating that MC-mediated T-cell activation is Ig/antigen-FcR independent,[2] the findings of Kambayashi and colleagues indicate that MC-mediated T-cell activation is dependent on



Role of MCs in IgE- and dendritic-cell–mediated antigen-specific T-cell expansion. (A) In a conventional antigen-presentation model, dendritic cells (DCs) incorporate antigens (Ags) and present antigen to naive T (T_N) or memory T (T_H2) cells. (B) In the MC-mediated, IgE-mediated, and DC-mediated antigen presentation model, IgE/antigen-FcεRI crosslinking promotes antigen internalization and apoptosis in MCs. DCs then uptake the apoptotic MCs (aMCs) carrying internalized antigens, and thus can efficiently present the antigen to antigen-specific memory T cells.