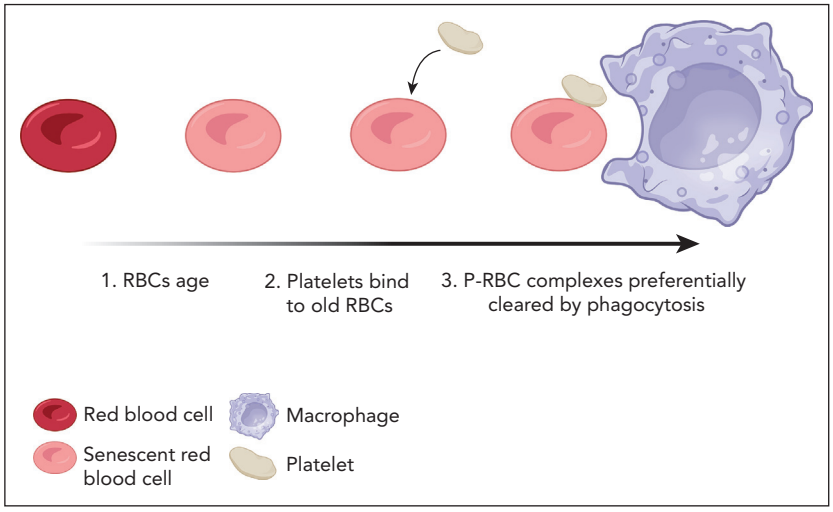

Formation of P-RBCs leads to increased clearance of senescent RBCs. As red cells become senescent, a proportion of them are bound to platelets in circulation, forming P-RBCs. These complexes are cleared in the spleen more rapidly than unbound RBCs. Created with BioRender.com.

stoichiometry of the system being biased greatly in favor of RBCs? RBCs exceed platelets in both number and longevity. Does this mean, therefore, that many platelets are also cleared with an associated RBC by this mechanism? It is also interesting to speculate whether all platelets are able to interact with senescent RBCs or whether it is only a subset, for example, platelets that are also undergoing senescence. This would make sense for biology, allowing clearance of both senescent cells in a single process.

The authors also show the potential clinical importance of the process. Patients with immune thrombocytopenia (ITP) had markedly fewer P-RBCs and greater numbers of aged RBCs expressing increased levels of PS and FasR. Platelet-dependent clearance of PS-exposing RBCs in particular may be important, therefore, in minimizing intravascular coagulation but may underlie mechanisms of enhanced paradoxical thrombosis in ITP and other states of marked thrombcytopenia.[9]

Overall, this elegant study provides foundational work for understanding additional complexities in RBC homeostasis, and possibly platelet homeostasis also, through direct interaction between these 2 cell types. The work opens the door for further research to fully understand its mechanism and clinical implications in health and disease.

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Comment on Kim et al, page 548

Innate capability of clot contraction

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In this issue of *Blood*, Kim et al have discovered that megakaryocyte precursors to platelets are capable of contracting blood clots, paving the way for future studies into molecular pathways of clot contraction and its relevance for hemostasis and thrombosis.[1]

Clot contraction is a poorly understood mechanism that regulates physiological and pathological responses of blood clotting. Clot contraction takes place during normal hemostasis when it helps the clot to reduce in size once the bleeding has been stemmed, prior to other processes of wound healing stepping in to repair the tissue.[2,3] Although we know that clot contraction also happens during thrombosis, the role of this process in thrombosis is less well understood. On one hand, clot contraction reduces the size of the thrombus, thus facilitating restoration of blood flow. On the other hand, however, clot contraction makes the clot more dense and thus potentially harder to break down and remove. Indeed, external fibrinolysis, and thus therapeutic thrombolysis, appears to slow down after clot contraction.[4] Yet, internal fibrinolysis that starts from within the clot appears enhanced by clot contraction.[4] These divergent effects on fibrinolysis and clot breakdown highlight the complex role

that clot contraction plays in thrombosis and vascular occlusion.

Regulation of clot contraction occurs through activated platelets that pull on the highly elastic fibrin fibers within a clot.[5] This process involves platelet pseudopodia interacting and actively pulling on fibrin, and thus both platelet reactivity and the biomechanical properties of fibrin play key roles in the delivery of contraction. Modeling shows that the random pulling direction of platelets on the fibrin network leads to one overall effect: the gradual reduction of the size of the clot.[5,6] The finding by Kim et al that megakaryocytes can also pull at fibrin and drive clot contraction is innovative and important for 3 key reasons.

First, the discovery that megakaryocytes are able to provide clot contraction indicates that the ability for clot contraction is innate to these cells and is not a new function acquired by platelets when they are generated by the megakaryocyte. It will be interesting to study myeloid precursor cells of the megakaryocyte to discover when the ability for clot contraction first arises in this cell lineage. Second, as suggested by the authors, the ability of megakaryocytes to contract clots implies that the molecular pathways involved in clot contraction can be studied through genetic manipulation. Although platelets are anucleate and thus broadly speaking genetically predetermined, the genome of the megakaryocytes can be easily modified to elucidate the gene(s) involved in this remarkable functional capability that dynamically regulates clot size. Third, diseases severely affecting pulmonary function (eg, acute respiratory syndrome and COVID-19) or the bone marrow (eg, myelodysplasia or myeloproliferative disorders) can lead to megakaryocyte egress from the pulmonary or bone marrow space into the circulation.[7] Such increased circulatory levels of megakaryocytes may contribute to thrombosis in these patients, and thus their role in clot contraction is highly relevant.

Kim et al provide a detailed comparison of the relevant forces and structures used by the megakaryocyte vis-à-vis platelet in blood clot contraction. On an individual cell basis, the megakaryocyte was much more potent than the platelet in clot contraction, likely due to its larger size. In fact, when normalized for cell surface, the megakaryocyte and platelet demonstrated largely comparable clot contraction capabilities. The authors further showed that similar to platelets, myosin IIA, the actin network, and fibrin-integrin interactions are essential for clot contraction by the megakaryocyte. The authors also found that although pseudopodia on platelets are responsible for clot contraction by pulling at the fibrin fibers, the megakaryocytes used both pseudopodia and blebs (larger membrane structures) to drive contraction. Further studies are required to detail other cellular mechanisms and structures that are involved in clot contraction, facilitated by the future use of genetic engineering to decipher critical pathways.

There is increasing evidence that clot contraction is a key aspect of clotting that modifies the risk of thrombosis, as well as the duration and removal of vascular occlusion.[8-10] The current study by Kim et al contributes important mechanistic insight with future potential for the study of genetic and cellular regulation of this key pathophysiological process. A final note is reserved for nomenclature. The terms "clot retraction" or "clot contraction" can be found interchangeably in the literature. Although the former indicates a withdrawal of the clot from a surface or object, the latter simply reflects the diminution of size of the clot. In view of the random forces enacted by the megakaryocyte and platelet on the fibrin network, the term "contraction" is preferable since it more accurately describes the mechanistic aspects of the process.

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