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RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Matte et al, page 252

Resolving inflammation and pain of sickle cell

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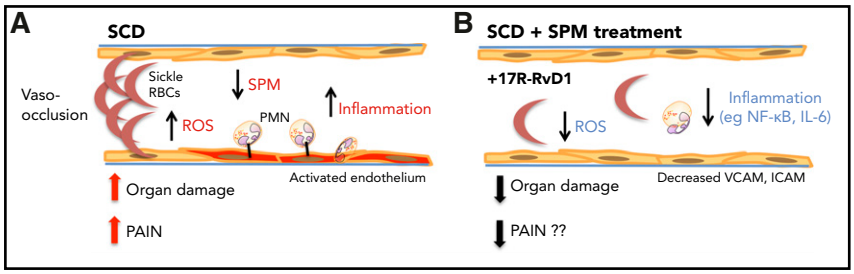
In this issue of *Blood*, Matte et al demonstrate that sickle cell disease (SCD) disrupts inflammation-resolution programs in a mouse model of SCD, giving evidence for an entirely new way to treat this disease.[1]

SCD is a well-known genetic disorder that results in dramatic alteration and function of red blood cells (RBCs).[2] Sickle RBCs can also obstruct the vasculature; activate leukocytes, platelets, and endothelial cells; and exacerbate inflammation.[2] In this regard, SCD is not only characterized by hemolytic anemia, but also vaso-occlusion, progressive organ damage, and pain.[2] The mechanisms that drive unrestrained inflammation and ultimate organ damage in SCD are of immense clinical interest and prior to this report were unclear. Matte et al find clues from clinical samples and a murine model that helps reveal new explanations and provide a potential new treatment strategy for SCD.

The identification of mediators and mechanisms that temper inflammation and maintain tissue homeostasis is an area of active research. Previously, acute inflammation was thought to passively terminate, but we now appreciate that the resolution of inflammation (or inflammation resolution) is an active process that is controlled by a series of biochemical and cellular events.[3] In this context, Charles N. Serhan discovered a family of chemical mediators that govern inflammation resolution, which are collectively referred to as specialized proresolving lipid mediators (SPMs) and include lipoxins, resolvins (Rvs), protectins, and maresins.[3] In general, SPMs temper excessive leukocytic infiltration, limit pathologic platelet-leukocyte interactions, and quell endothelial cell activation in a manner that does not compromise host defense.[3] Moreover, another key feature of SPMs is their ability to enhance the clearance of microbes, dead cells, and debris[3] as well as reduce pain.[4] The discovery of SPM initiated a paradigm shift in our understanding of how inflammation resolution is regulated and has since provided a new framework for the treatment of nonresolving diseases.



SPM limits inflammation in SCD in mice, which has implications for pain control. (A) SCD is characterized by heighted inflammation involving leukocytes, platelets, and endothelial cells. Sickle RBCs can obstruct the vasculature, which can lead to organ damage and pain. (B) 17R-RvD1 decreases inflammation, reactive oxygen species (ROS), vaso-occlusion, and, ultimately, tissue damage. Inflammatory cytokines, and mediators like prostaglandins (which are elevated in SCD) are directly linked to pain. High levels of proinflammatory cytokines like interleukin 6 (IL-6) activate nociceptors to initiate pain. Importantly, 17R-RvD1 decreases NF-κB activation and IL-6 in SCD mice, which implies a mechanistic link for decreasing pain in SCD. PMN, polymorphonuclear neutrophil.

Matte et al are the first to provide evidence that SCD is a disease of failed inflammation resolution. Specifically, they observed that plasma from SCD patients had higher levels of proinflammatory mediators than SPM. To understand this mechanism, Matte et al used a humanized mouse model of SCD and found a significant defect in SPM levels including resolvin D1 (RvD1) compared with controls. This defect was more apparent when these mice were exposed to hypoxia/reoxygenation stress, a process that promotes vaso-occlusive crises and ultimately organ damage. To further explore the mechanism of defective SPM biosynthesis in SCD mice, Matte et al administered docosahexaenoic acid, which is RvD1's biosynthetic precursor, and found that SCD mice were not as readily able to biosynthesize RvD1 as well as control mice.

Defective biosynthesis of SPM or the imbalance between SPM and proinflammatory mediators is associated with several prevalent human diseases, including atherosclerosis.[5] Major unanswered questions in the inflammation-resolution field include why SPMs become defective or imbalanced during nonresolving diseases and what signals or signaling events drive this imbalance. Matte et al first explored the expression levels of SPM biosynthetic enzymes and surprisingly found no difference between the groups. An alternative hypothesis that has yet to be tested in this context could be related to post-translational modifications, including phosphorylation and subcellular localization of key biosynthetic enzymes that may drive

the synthesis of SPM over proinflammatory mediators.[5]

Another major finding was the therapeutic potential of SPMs in SCD. Matte et al demonstrate that the SPM 17R-RvD1 significantly decreased systemic and local inflammation, dampened organ damage, and improved vascular function in this preclinical model, the SCD mice (see figure). The 17R epimer of RvD1 was selected for these studies because it is longer-acting and resists local metabolic rapid inactivation. Moreover, 17R-RvD1 also blunted neutrophil recruitment to endothelial cells exposed to human SCD plasma, which provides important translational relevance. Additionally, Matte et al demonstrate that 17R-RvD1 enhanced the removal and clearance sickle RBCs, which may be a fundamental mechanism that results in decreased inflammation as well as tissue repair by 17R-RvD1. Further mechanisms associated with this clearance process as well as how 17R-RvD1–stimulated macrophages can metabolize the increased cellular intake are important unanswered questions.

Overall, Matte et al provide compelling evidence that SPMs control the inflammatory arm of SCD, which can have profound implications on how pain is regulated during the course of the disease. Pain, which is the number one cause for hospitalizations in SCD, is thought to originate from vaso-occlusion that leads to hypoxia, ischemia, uncontrolled inflammation, and eventual tissue damage.[6] Pain medications for SCD patients vary, but often result in the use of nonsteroidal anti-inflammatory drugs and morphine.[6] Morphine may exacerbate organ dysfunction in SCD and so improving pain management with alternative therapies is a must.[6] Other drugs that block inflammation and inflammatory pain, like cyclooxygenase-2 and tumor necrosis factor inhibitors disrupt necessary host defense mechanisms, which can be detrimental for SCD patients.

As mentioned earlier, SPMs temper inflammation and promote host defense.[3] Moreover, there are numerous reports in the literature that demonstrate how SPMs dampen pain. This emerging body of work demonstrates an intimate link between inflammation resolution and the dissolution of pain. Importantly, key SPMs are significantly more potent than morphine at preventing pain in mice[4] and, as previously mentioned, SPMs are organ protective.[3] Because SPMs are endogenous mediators that are naturally lost during SCD, restoring them may be a safer approach than current treatment of pain and inflammation.

These findings are extremely significant because the current treatment of SCD remains poor.[2] SCD patients are more susceptible to invasive infections, have pain, and are at a significantly higher risk for acute stroke or chronic cerebral ischemia.[2,7] Above and beyond the mechanisms and functions described herein, SPMs boost host defense,[3] limit ischemic stroke,[8] and quell inflammatory pain,[9] which suggests that SPM and/or increasing their endogenous biosynthesis may be a panacea for SCD patients.

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

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