ALX/FPR2 - the spleen's cellular cleanup crew!

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Spleen is adept at removing old or damaged red blood cells (RBC) from the circulation on a daily basis, with approximately 1% of circulating RBC (~1,7x10^{11} cells) being replaced by new cells. This process involves erythrophagocytosis, a vital physiological process that is accomplished by splenic macrophages, a.k.a red pulp macrophages (RPM). These macrophages are integral to maintaining a healthy pool of circulating mature RBC by enabling efficient clearance of damaged or aged RBC, especially during times of increased demand or "erythroid stress". A defect in this system can affect physiological iron recycling, leading to anemia and impairments in immunity. A long-standing issue that is poorly understood is how these RPM can accomplish such a metabolically demanding feat without getting "burnt out" by the excessive iron, heme, and free radicals during steady-state erythropoiesis.

In a study published in this issue of *Haematologica*, Asplund *et al*. demonstrate that the metabolism of arachidonic acid, a polyunsaturated fatty acid, to bioactive lipid mediators via 15-lipoxygenase (Alox15), a non-heme iron-containing dioxygenase, in the form of specialized proresolving mediators (SPM) such as lipoxin A4 (LXA4) helps in the maintenance of RBC homeostasis.[1] These bioactive mediators activate the G-protein coupled receptor ALX/FPR2 signaling axis, which is well known to promote macrophage clearance of pathogens, cellular debris, and apoptotic cells, including dead or dying RBC, facilitating resolution mechanisms.[2] Asplund *et al*. provide novel evidence that the LXA4-ALX/FPR2 axis regulates clearance of aged or damaged erythrocytes, advancing our understanding of basal erythroid homeostasis.

The authors systematically addressed the issues using a *Fpr2*$^{-/-}$ mouse strain as well as a myeloid-specific deletion of *Fpr2*, such that animals displayed an unhealthy and aged RBC pool accompanied by reduced signs of RBC turnover in their spleens. Interestingly, the RPM also showed changes in heme metabolism, which was an unexpected discovery that may highlight new signaling mechanisms downstream of ALX/FPR2. Another interesting observation was the significant downregulation of Alox5 and Alox15 in the *Fpr2*$^{-/-}$ macrophages, leading to a greatly altered transcriptomic phenotype that could have an impact on the ability of the animals to respond effectively to inflammatory stimuli or take up stressed RBC efficiently, facilitate their turnover and maintain a healthy erythroid pool. These experiments raise an important question about the source of these bioactives within the splenic environment. Transcriptomic analysis revealed that non-RPM populations are the primary producers of SPM, with RPM functioning mainly as targets of these lipid mediators. This cooperativity further aligns with the original designation of these mediators as "lipoxins" by Serhan and colleagues, reflecting their origin as lipoxygenase-derived products generated through intercellular interactions.[3,4] Erythrophagocytosis markedly increased LXA4 and its precursor, 15(*S*)-HETE, and other SPM, which in turn promoted macrophage-mediated RBC uptake via the ALX/FPR2 receptor.

Through meticulous experimentation, Asplund *et al*. conclude that the ALX/FPR2 signaling axis serves as a necessary component for the maintenance of RBC health, and that LXA4 activation of ALX/FPR2 is a critical part of how RPM respond to basal levels of RBC or during situations in which they need to quickly ramp up to clear a large number of damaged RBC. This exciting work provides new insights into the endogenous production of SPM and their cognate receptor and their role in combating physiological and pathological hemolytic stress, which may have clinical implications in treating systemic unresolved inflammation or in the development of new therapies for transfusion-related immunomodulation or even acute hemolytic stress. However, before translating these interesting findings more broadly to humans, many questions remain. For instance, the unexpected discovery that non-RPM are also producers of SPM leads to the questions of which specific cell type is the source of SPM and what is their role in the resolution of erythroid stress leading to erythroblast development. The ability of *Fpr2*$^{-/-}$ macrophages that have a defective heme metabolism links Fpr2 to intermediary metabolism and other mechanisms, which are poorly understood. The ability to activate pathways of ferroptosis is well known.[5]

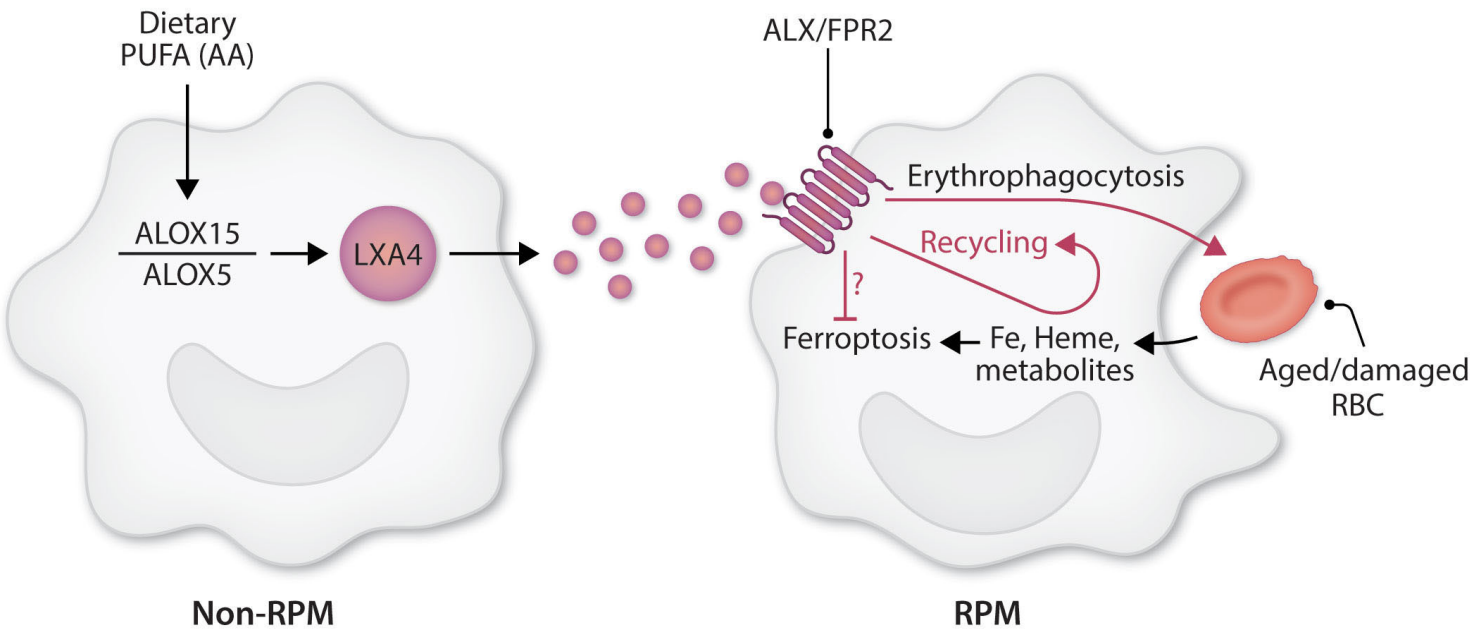

Figure 1. Schematic representation of the LXA4-ALX/FPR2 signaling axis in the disposal of aged or damaged erythrocytes in the spleen. Lipoxin A4 (and other specialized proresolving mediators) derived from dietary polyunsaturated fatty acids through the coordinated action of lipoxygenases, e.g., Alox15 and Alox5, activates ALX/FPR2 in red pulp macrophages to trigger pathways of erythrophagocytosis of aged and/or damaged red blood cells. This is accompanied by cellular mechanisms of resolution involving inhibition of ferroptosis and recycling of heme and iron. PUFA: polyunsaturated fatty acids; AA: arachidonic acid; RPM: red pulp macrophage; ALOX15: arachidonate 15-lipoxygenase; ALOX5: arachidonate 5-lipoxygenase; LXA4: lipoxin A4; ALX/FPR2: lipoxin receptor; Fe: iron; RBC: red blood cell.

Fpr2 activation by SPM and its downregulation of ferroptosis still remain unclear, despite recent reports on the role of resistance pathways involving redox mechanisms via the cystine transporter (Slc7a11/Xct), modulation of glutathione peroxidase 4 (GPX4) and Nrf2 activation.[6] It is not clear how SPM impact ferroptosis suppressor protein 1 (FSP1), heme transporters, alterations in the labile iron pool, or other mechanisms such as the recently reported downregulation of p38 MAPK.[7] Elucidating these pathways will advance our understanding of the intersection between iron and lipid metabolism in resolution mechanisms during steady-state erythropoiesis, in which erythrophagocytosis plays a central role.

Disclosures

No conflicts of interest to disclose.

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