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

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Spleen is adept at removing old or damaged red blood cells (RBCs) from circulation on a daily basis, where approximately 1 % of RBCs (~ 1,7 x 10^{11} cells) are replaced by new cells. This process involves erythrophagocytosis, a vital physiological process that is accomplished by splenic macrophages, *a.k.a* red pulp macrophage (RPMs). These macrophages are integral for maintaining a healthy pool of circulating mature red blood (RBCs) by enabling the macrophages to efficiently clear damaged or aged RBCs, especially during times of increased demand or "erythroid stress". A defect in this system can impact physiological iron recycling leading to anemia and deficits in immunity. A long-standing question that is less well understood is how these RPMs can accomplish such a metabolically demanding feat without getting "burnt out" by the excessive iron, heme, and free radicals at steady state erythropoiesis.

In this report, Asplund et al demonstrate that arachidonic acid, a polyunsaturated fatty acid (PUFA), metabolism to bioactive lipid mediators via the 15-lipoxygenase (Alox15), a non-heme iron-containing dioxygenase, in the form of specialized proresolving mediators (SPMs) such as lipoxin A4 (LXA4) help in the maintenance of RBC homeostasis[(1)]. These bioactives 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 RBCs 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.

Asplund et al systematically address the questions using a *Fpr2*$^{-/-}$ mouse strain as well as a myeloid-specific deletion of *Fpr2*, which display an unhealthy and aged RBC pool accompanied by reduced signs of RBC turnover in their spleens. Interestingly, the RPMs also showed changes in heme metabolism, which is also 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 greatly altered transcriptomic phenotype that could impact their ability to effectively respond to inflammatory stimuli or efficiently uptake stressed RBCs and facilitate their turnover and maintain a healthy erythroid pool. These experiments raise an important question of the source of these bioactives within the splenic environment. Transcriptomic analysis revealed that non-RPM populations as the primary producers of SPMs, with RPMs 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 SPMs, which in turn promoted macrophage-mediated RBC uptake via the ALX/FPR2 receptor.

Through meticulous experimentation, the study concludes that the ALX/FPR2 signaling axis serves as a necessary component for the maintenance of RBC health, and LXA4 activation of ALX/FPR2 is a critical part of how RPMs respond to basal levels of RBCs or during situations where they need to quickly ramp up clearing a large number of damaged RBCs. This exciting work provides new leads into the endogenous production of SPMs and their cognate receptor in combating physiological and pathologic hemolytic stress, which may have clinical implications in treating systemic unresolved inflammation or 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, an unexpected discovery that non-RPMs are also major producers of SPMs leads to the question which specific cell type is the source of SPMs and their role in 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]. Fpr2 activation by SPMs and its downregulation of ferroptosis still remains unclear, despite the 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]. However, it is not clear how SPMs 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 the resolution mechanisms during steady state erythropoiesis, where erythrophagocytosis plays a central role.

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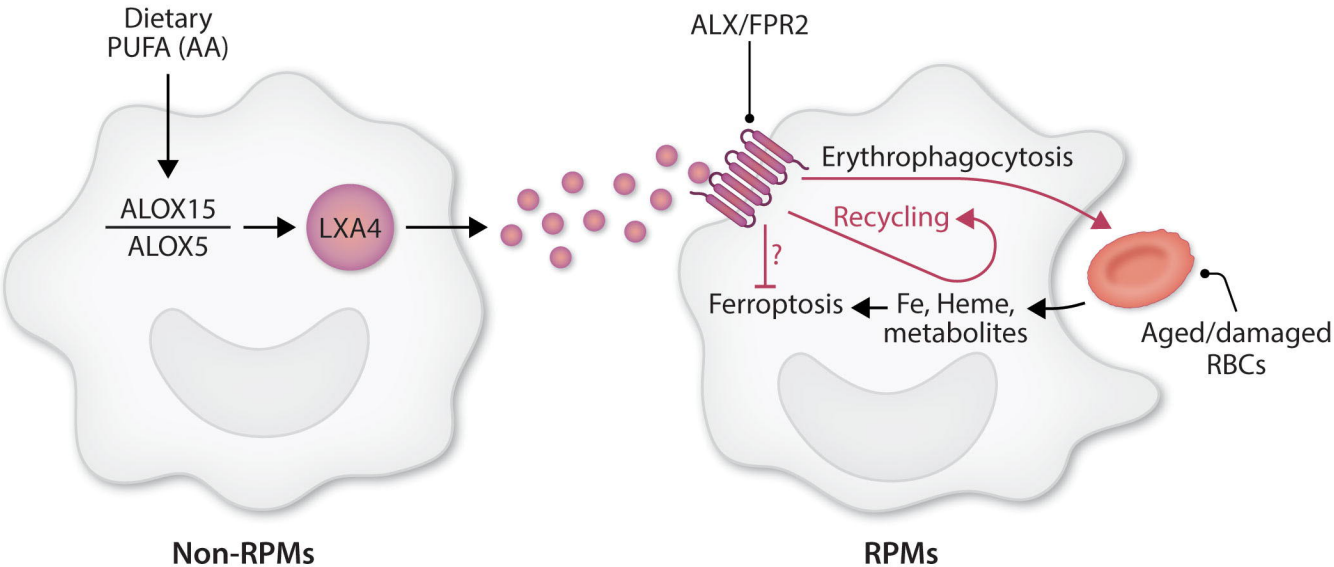
Legend to figure

Schematic representation of LXA4-ALX/FPR2 signaling axis in the disposal of aged or damaged erythrocytes in the spleen. Dietary PUFA derived LXA4 (and other SPMs) through the coordinated action of lipoxygenases, e.g., Alox15 and Alox5, which activates ALX/FPR2 in the red pulp macrophages (RPMs) to activate pathways of erythrophagocytosis of aged and/or damaged RBCs. This is accompanied by cellular mechanisms of resolution involving inhibition of ferroptosis and recycling of heme and iron.


Dietary
PUFA (AA)
ALOX15
ALOX5
LXA4
ALX/FPR2
Erythrophagocytosis
Recycling
?
Ferroptosis
Fe, Heme,
metabolites
Aged/damaged
RBCs
Non-RPMs
RPMs