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A Commentary on the Role of 6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 3 in Atherosclerosis

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Commentary

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ABOUT THE STUDY

Atherosclerotic plaque formation and progression are a result of a chronic non-resolving inflammatory response involving a constant expansion and infiltration of monocytes and impaired clearance of dying macrophages within the plaque [1]. Therefore, the mechanisms regulating the expansion and recruitment of monocytes as well as the death and elimination of lipid-laden macrophages in lesions are crucial for atherosclerosis.

Macrophages are highly adaptive cells, which respond to a plenty of atherogenic stimuli by acquiring distinct functional phenotypes and adjusting their metabolism to sustain their specific bioenergetic demand. Activated monocytes and pro-inflammatory macrophages highly depend on glycolysis for their energy [2]. This glycolytic switch relies predominantly on the enzyme 6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase (PFKFB3), which serves as a potent source for inducible glycolysis [3]. Publicly available single-cell RNA-seq data showed PFKFB3 expression mainly in macrophages in human and mouse atherosclerotic plaques, indicating PFKFB3 probably an attractive target to interfere with macrophage function in atherogenesis [4,5].

A few studies have indeed demonstrated that small-molecule inhibitors of PFKFB3, such as 3PO and PFK158, exhibit efficacy in decreasing total plaque burden and improving plaque stabilization, respectively, in preclinical models [6,7]. However, systemic pharmacological PFKFB3 inhibition could not identify which cell type confers these positive effects and genetic intervention targeting PFKFB3 is lack. Using Apoe$^{-/-}$ mice with global heterozygous Pfkfb3 deficiency, our group demonstrated that genetic targeting of PFKFB3 decreased plaque formation but had no effect on plaque stability, similar to effects observed with 3PO inhibition. At the cellular level, the impaired systemic monocytosis and reduced monocyte infiltration into the lesions were observed in Pfkfb3 heterozygous Apoe$^{-/-}$ mice, provoking us to check whether the myeloid PFKFB3-mediated glycolysis might contribute to atherogenesis. Using Apoe$^{-/-}$ mice with myeloid cell-specific Pfkfb3 haplodeficiency, we showed that partial myeloid knockdown of Pfkfb3 phenocopies the global heterozygous deletion of this enzyme regarding atherogenesis [8].

To mechanistically understand how PFKFB3 could control systemic monocytosis and monocyte recruitment in atherosclerosis, PFKFB3 level was examined in monocytes. PFKFB3 is predominantly expressed in murine inflammatory Ly6Chi monocytes and their human counterparts, thus promoting the expansion of these inflammatory monocytes and their infiltration into atherosclerotic lesions. This is consistent with the idea that PFKFB3-driven glycolysis could aid the proliferation and migration of multiple cell types [9,10].

To complicate things, using Apoe$^{-/-}$ mice with myeloid cell homozygous deletion of Pfkfb3, we surprisingly found that homozygous loss of Pfkfb3 impaired macrophage efferocytosis and sensitized the Apoe$^{-/-}$ mice to Western diet-induced atherosclerosis. Mechanistically, PFKFB3 co-localizes with F-actin in macrophages and aids actin polymerization to meet the efferocytotic function of macrophages. Importantly, our study, together with the work of Morioka and colleagues, highlighted the role of aerobic glycolysis in fueling active actin filament assembly. In summary, our study unveiled the double-edged sword effect of myeloid PFKFB3 on the pathogenesis of atherosclerosis in a gene dose-dependent manner, and demonstrated that caution should be warranted with PFKFB3 inhibitor-based therapeutics [11].

Previous mentioned single-cell RNA-seq data showed that PFKFB3 was also expressed in many other plaque cells, including lymphocytes, Endothelial Cells (ECs), and Vascular Smooth Muscle Cells (VSMCs). PFKFB3 has been shown to regulate the activation of lymphocytes and ECs [12,13]. Our recent work revealed that PFKFB3-mediated glycolysis promotes the VSMC phenotypic switching and the resulting vascular remodeling [14]. In future research, it would be of interest to investigate whether PFKFB3 in these cell types exerts the double-edged sword effect in atherosclerosis.

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