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Commentary

Modulation of macrophage polarity for treatment of acute pancreatitis: Are we there yet?

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Acute pancreatitis (AP) is a common cause of hospitalizations, morbidity and mortality in the USA [1]. Today, it is clear that the novel therapeutics against this formidable disease will have to target inflammation. Given the central role of Monocytes/macrophages in orchestrating the inflammation during AP, they have emerged as an obvious cellular target [2]. However, it has also become clear that we need to modulate, and not completely abrogate this important player. Depending on its phenotypic characteristics, various subtypes or states of polarization of this important regulator of inflammation may in fact be critical for quietening inflammation and beginning repair. To take things in perspective, the polarization of macrophages should be considered as a spectrum, of which the classical (M1) and alternative (M2) activation states represent the two extremes [3]. Studies till date suggest that while M1 macrophages are believed to initiate as well as promote inflammation during acute phase, M2 phenotype dominates and potentially promotes repair during recovery. For instance, it has been demonstrated that Ly-6C^{hi} monocyte subset (which may correspond to M1 macrophages) increases the severity of AP by producing TNF-α, and their depletion (using diphtheria toxin inducible Ly-6C^{hi} monocyte depletion) prior to induction of AP in CD11b-DTR mice, reduces AP severity [4]. The Yin-Yang of macrophage is further underscored by the fact that while prophylactic depletion of macrophages using clodronate 24 h before initiation of injury has a protective effect [5], depletion of macrophage later in the process led to decrease in PDX-1 positive cells and failure of regeneration [6]. To complicate the matter even more, it has recently been shown that Systemic Immune Response Syndrome (SIRS) and Compensatory anti-inflammatory response (CARS) in AP are initiated early on and progress simultaneously, but not sequentially as was the previous consensus [7,8]. It appears that while the cellular target for novel therapeutic strategies i.e., macrophages, is in our plain sight, we need to better understand its pathobiology to develop next generation of therapies.

In this article of EBioMedicine, Jinghua Wu and colleagues investigated the dynamic phenotype of macrophages during caerulein AP development and repair/regeneration and have taken us one step closer to better understanding the dynamics of macrophage during AP [9]. This study again confirms the well-known dual role of macrophages in AP with M1 predominating the early stages and potentially exacerbating the injury as well as Acinar to ductal metaplasia (ADM) formation, and M2 being crucial for pancreatic regeneration. Congruent with this notion, depletion of macrophages right after the acute inflammatory response (before day 3) led to decrease, while in the later phase (after day 3) led to increase in severity of AP. They further showed that alternative activation of macrophages was partially dependent on IL4RA signalling and ECM/AKT activation.

To understand the molecular mechanism and pathways manifested in macrophages which modulate pancreatic regeneration, authors performed RNA-seq analysis of pancreatic macrophages. RNA-seq data suggests that genes related to ECM-receptor interaction and PI3K-AKT signalling pathway as well as regulation of cell cycle are highly expressed in ADM stage. Activation of PI3K/AKT is essential for M2 polarization and inhibition of PI3K/AKT pathway abrogates the upregulation of M2 polarizing genes and pathways. Further analysis revealed 80% of these genes to have a function in crosstalk between macrophages and neighbouring parenchymal cells. Blocking of PI3K/AKT signalling at ADM stage and not before, using a specific inhibitor of PI3K δ/γ (TG100-115) which is primarily expressed on pancreatic macrophages, significantly reduced the extent of pancreatic regeneration. Authors also showed that PGE2 released by duct like cells induces M2 activation and enhances pancreatic recovery by limiting ADM formation.

In this study, authors have not only dissected the molecular pathways, but also shed an important light on the metabolic interactions during AP progression. Their results suggest that in acute inflammatory phase glycolytic pathways are predominantly active, which are essential for M1 polarization, phagocytic activity, ROS production and secretion of pro-inflammatory cytokines. In ADM phase, metabolic processes shift to support M2 polarization, which is demonstrated by upregulation of genes involved in amino acid metabolism. During acinar re-differentiation phase, glutathione metabolism and fatty acid beta-oxidation is upregulated in macrophages, which supports alleviation of inflammatory process to enhance tissue recovery. While there is a need to further define and better understand the

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molecular mechanisms responsible for M2 macrophage polarization, this important work is a significant step to better understand the idiosyncrasies of macrophages during AP and thus better 'tame' it for therapeutic gains.

Contributors

P.S., E.P.B, S.I. and V.D. were responsible for the literature search, data analysis and interpretation, and writing the manuscript.

Declaration Competing Interest

The author declares no conflicting interests.

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