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EDITORIAL COMMENT

Leveraging FPR2 Agonists to Resolve Inflammation and Improve Outcomes Following Myocardial Infarction*

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The immune response has become increasingly recognized for its importance following myocardial injury. The innate and adaptive immune system is involved in cardiac homeostasis, conduction, inflammation, tissue repair, left ventricular (LV) remodeling, and heart failure. Recent studies have demonstrated enormous and previously recognized diversity among myeloid cells. These studied have challenged the classical M1-M2 macrophage dichotomy, in which inflammatory macrophages are categorized as M1 and wound healing or reparative macrophages are classified as M2. Although this concept can still be applied in vitro, we now understand that macrophages and other myeloid cells exist as a remarkably heterogeneous population with diverse genetic profiles and functions (1). Although the precise roles of different cardiac monocytes and macrophages remain incompletely defined, it has become increasingly apparent that modulation of these cell types represents an untapped opportunity to suppress inflammation and limit adverse cardiac events across a broad spectrum of cardiac pathologies.

These recent advances have rekindled interest in identifying therapeutic targets within cardiac monocyte and macrophage populations. Historically studied anti-inflammatory agents including steroids and tumor necrosis factor antagonists were largely unsuccessful due to limited efficacy and serious adverse events potentially related to interrupted wound healing. Current efforts within this field are focused on discovering targets that suppress proinflammatory responses and preserve reparative functions of cardiac macrophages.

In this issue of *JACC: Basic to Translational Science*, García et al (2) build on prior studies uncovering the existence of proresolving mediators, factors that promote the resolution of inflammation. This strategy represents an alternative to inhibiting proinflammatory responses. The authors investigate a compound that binds and modulates signaling downstream of formyl peptide receptor 2 (FPR2). Ligand engagement of FPR2 can lead to either proinflammatory or proresolution effects. Indeed, endogenous lipid ligands for FPR2 promote resolution of inflammation and polarize macrophages toward a M2 phenotype in vitro. The therapeutic impact of these endogenous lipid ligands is limited by poor stability and bioavailability. The authors circumvented these challenges by utilizing a selective small molecule FPR2 agonist.

García et al (2) leveraged prior studies utilizing small molecule dual agonists of FPR1 and FPR2, which implicated FPR2 as the dominant proresolution mediator (3,4). They hypothesized that selective activation of FPR2 would serve as an effective strategy to limit myocardial inflammation and remodeling. The authors utilized in vitro studies and in vivo models of myocardial infarction in mice and rats to explore the therapeutic potential of the small

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molecule FPR2 agonist BMS-986235. The investigators confirm that BMS-986235 activates FPR2 Gi signaling in rodent and human homologs of the receptor and establish selectivity of BMS-986235 for FPR2 using cultured macrophages with targeted deletion of FPR1 or FPR2.

Interestingly, BMS-986235 increased chemotaxis toward FPR2 agonists in both FPR1 and FPR2 knockout HL-60 cells with differing dose-response relationships. The investigators hypothesize that FPR1/FPR2 heterodimers may selectively regulate chemotactic responses. This observation warrants further study into possible interactions between FPR1 and FPR2 in the presence of BMS-986235. Prior studies have demonstrated that FPR heterodimerization influences ligand binding and downstream signaling (5).

BMS-986235 drove expression of interleukin-10 and monocyte chemoattractant protein-1 in human blood cells and enhanced human neutrophil apoptosis in response to amyloid A. The latter represents an important finding, as neutrophil apoptosis is necessary to stimulate macrophages recruitment, efferocytosis, and acquisition of proresolving macrophage phenotypes. Neutrophils rapidly accumulate at the site of tissue injury, where they undergo apoptosis and stimulate recruitment of monocytes and macrophages. Efferocytosis is recognized as a critical step in the transition from inflammation to tissue repair. When clearance of apoptotic neutrophils is delayed or inefficient, inflammation and tissue damage is exacerbated (6). These data implicated that BMS-986235 as a candidate to promote inflammatory resolution.

The therapeutic efficacy of BMS-986235 was then tested in vivo. In mice, treatment with BMS-986235 resulted in increased expression of the anti-inflammatory cytokine interleukin-10 3 days after lipopolysaccharide challenge. Administration of BMS-986235 following permanent coronary artery occlusion in mice potentiated indices of infarct healing including increased collagen deposition and decreased matrix metalloproteinase-2 expression. The authors also observed decreased neutrophil abundance and increased numbers of $CD206^{+}$ and $arginase\text{-}1^{+}$ macrophages, populations implicated in wound healing. In both mice and rats, treatment with BMS-986235 improved survival, reduced infarct size, preserved LV systolic function, and suppressed LV remodeling following permanent coronary artery occlusion. Additional experiments utilizing ischemia-reperfusion injury in rats, a model more closely resembling human myocardial infarction, recapitulated these key findings. Collectively, these data provide promising evidence that BMS-986235 given in a timely manner following myocardial infarction may limit infarct size, reduce LV remodeling, and decrease subsequent heart failure.

In conclusion, García et al (2) present compelling evidence that targeting FPR2 with the small molecule agonist BMS-986235 may represent a strategy to augment inflammatory resolution, augment infarct healing, and improve outcomes following myocardial infarction. Although a detailed time course was not presented in the study, it is likely that the timing of treatment delivery is a key determinant of efficacy. Such information will be necessary to generate optimized protocols for clinical translation. In addition, the mechanism by which FPR2 agonists result in inflammatory resolution in the heart remains incompletely defined. Further studies delineating the relevant cell types involved in FPR2 signaling, downstream signaling events, and subsequent impact on immune phenotypes including monocyte fate specification and macrophage behavior (extending beyond M1/M2 classification) will yield key information regarding mechanisms of inflammatory resolution in the heart. Much remains to be learned regarding this process. Future studies in this area are poised to uncover exciting new opportunities to target inflammation in the cardiovascular system.

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