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EDITORIAL COMMENT

Therapeutic Treatment Approaches Post–Myocardial Infarction

A Bias Toward Formyl Peptide Receptor Agonists*

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Myocardial infarction (MI) is the leading cause of heart failure globally. Current treatment options consist of thrombolytic agents and interventional procedures to restore blood flow to the ischemic tissue to prevent tissue necrosis. Despite these strategies, death from resultant heart failure remains high, highlighting an unmet need for new therapeutic modalities. Post MI, inflammatory neutrophils and monocytes both enter the ischemic zone. Neutrophils have been traditionally known to add further insult to injury; although emerging reparative functions have been documented (1). Monocyte function is more complex, as they possess both pathological and protective functions that are temporally regulated and associated with differentiation into macrophages. These functions include extracellular matrix degradation, debris clearance, and angiogenesis (1). Inflammatory tissue damage post-MI contributes to adverse left ventricular (LV) remodeling and eventual heart failure development, making it an attractive therapeutic target. In this issue of *JACC: Basic to Translational Science*, García et al. (2) explore the use of formyl peptide receptor (FPR) agonist, Compound 43 (Cmpd43), as a therapeutic agent that targets pattern recognition receptors to promote a more favorable immunological response and improve infarct healing.

SEE PAGE 905

FPRs are G protein–coupled receptors primarily expressed on leukocytes and have been shown to regulate both the initiation and resolution of inflammation post-MI (1). FPRs have unusual biology. For example, FPRs bind to a wide array of ligands and elicit different cellular responses specific to the ligand and cell type, elegantly encapsulated by the concept of biased agonism (3). Biased agonism describes the ability of different FPR ligands to selectively activate only a component of the downstream signaling pathways coupled to that receptor while leaving other pathways either not activated, or potentially suppressed (**Figure 1A**).

FPR2 can be engaged by mitochondria-derived formyl peptides and activate neutrophils in a proinflammatory manner (3). Conversely, $F2Pal_{10}$ also activates neutrophils but fails to induce the characteristic chemotactic response, owing to lack of recruitment of β-arrestin in the signal transduction pathway (3). The FPRs' biased agonism effect appears to be at least partially, if not totally, driven by whether β-arrestin is recruited to the receptor. As opposed to these roles in response to synthetic and self-derived molecules, the earliest descriptions of FPRs were in response to bacterial products, as FPR1 is the well-known receptor for fMLP, a bacterial peptide that is highly chemotactic for neutrophils and induces proinflammatory cytokine production and organ damage (3). Thus, biased agonism can tailor the functional repertoire of FPR-expressing cells such

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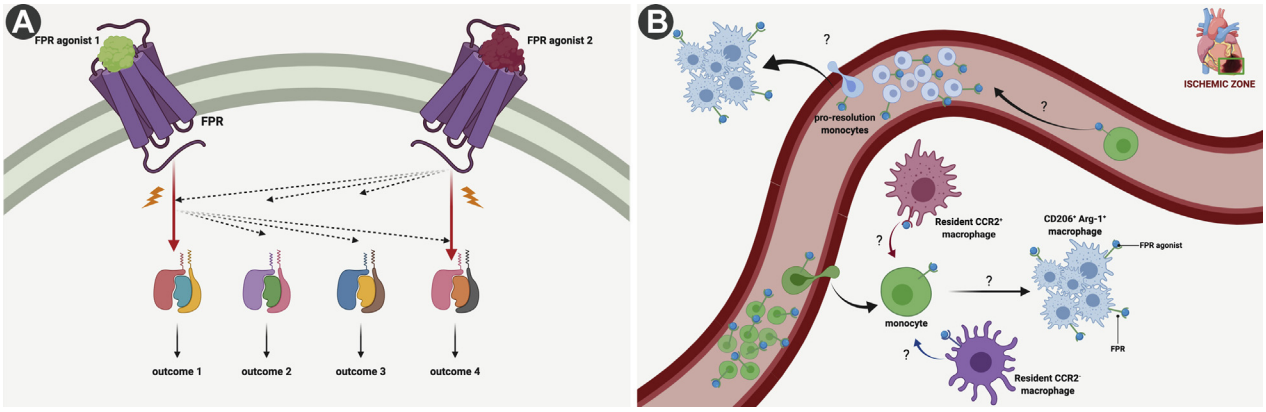
FIGURE 1 Biased Agonism in FPR Signaling During Post-Myocardial Infarction



(A) Different formyl peptide receptor (FPR) ligands can activate the same FPR for a diverse array of possible outcomes depending on the ligand itself. FPR agonist 1 activates a subset of signal transduction pathways for outcome 1 while not activating or suppressing the other outcomes, whereas FPR agonist 2 activates only the pathway leading to outcome 4, which highlight multiple possible combinations. **(B)** Schematic representation of potential mechanisms behind the observation of increased $CD206^{+}$/arginase-1 $(Arg\text{-}1)^{+}$ macrophages in the heart following treatment with FPR agonists. One scenario is that upon engagement with FPR agonists, monocytes are prespecified to a proreparative fate from the systemic effects of the FPR agonist. Thus, after entering the tissue, irrespective of the cardiac microenvironment, the monocytes differentiate into $CD206^{+}/Arg\text{-}1^{+}$ macrophages. Another possibility is that monocytes in circulation, despite engagement with FPR agonists at this stage, are conditioned by the tissue microenvironment, and not FPR stimulation, to adopt a $CD206^{+}/Arg\text{-}1^{+}$ fate within the heart (Created with BioRender).

that the same receptor can be engaged for proinflammatory or anti-inflammatory effects by different ligands. Therapeutic implications of biased FPR signaling have been exploited in clinical trials with pharmaceuticals that activate proinflammatory pathways lacking in immunocompromised patients, and blunt excessive eczematous lesion formation in infants. Thus, the careful selection of agents that can activate only a single component of biased signaling receptors is essential for therapeutic success and limiting off target effects.

García et al. (2) focus on modulating recruited monocytes toward a proresolution phenotype to expedite tissue healing with Cmpd43—a dual FPR1/FPR2 agonist (4). Using in vitro assays, the authors first determined the role of FPR agonism by Cmpd43 on key macrophage functions of chemotaxis, phagocytosis, and cytokine release via receptors FPR1 and FPR2 separately. Despite conservation of signal transduction profiles between FPR1 and FPR2, the receptors appear to have variable influence on different aspects of macrophage function. Peritoneal macrophages from mice deficient of FPR2 displayed defective internalization of zymosan particles, while FPR1-deficient mice were only modestly affected. Absence of both FPR1 and FPR2 inhibited macrophage chemotaxis and oxidative burst, suggesting that both isoforms are involved in these aspects. Treatment of peritoneal macrophages with Cmpd43 in the presence of serum amyloid A triggered FPR2-dependent release of the anti-inflammatory cytokine interleukin-10, which was negated in FPR2-deficient mice. Cmpd43 also was able to partially block interleukin-6 production; however, this response was both dose and receptor dependent. This may be in part related with the ability of these G protein-coupled receptors to either homo- or heterodimerize. Thus, the effects of Cmpd43 are complex, and not yet entirely understood. The studies of García et al. (2) shed light on how macrophages respond to FPR1/FPR2 signaling in vitro. Future work on neutrophils, which both express FPR1 and FPR2, and are recruited in large numbers to the heart post-MI, would be equally valuable.

To assess the in vivo relevance of Cmpd43 treatment, García et al. (2) harvested mouse cardiac tissue 3 days post-MI. Although the total number of macrophages remained unchanged by Cmpd43 treatment, the percentage of macrophages that express arginase-1 (Arg-1) and CD206 increased. Arg-1 and CD206 are markers of resident cardiac macrophages, and also markers of macrophages that adopt a more reparative functional state. These data bring up the classic argument, which happened first? Did Cpmd43 act systemically on recruited monocytes (and other myeloid cells) and prespecify their fate to that of a $CD206^{+}$ macrophage after entry into ischemic tissue? Or did the agonist act locally on the myocardium,

reducing the damage in early phases post-MI? Was altered macrophage composition a result of different environmental signals owing to myocardial effects, or a direct effect on recruited monocytes (**Figure 1B**)? Perhaps it was a combination of both. The long-term effects of Cmpd43 treatment post-MI included an increased LV ejection fraction, reduced LV chamber dilatation, reduced LV wall thinning, and scarring compared with those treated with vehicle in both mouse and rat models. The translational potential of these findings is exciting given that the drug is orally deliverable.

It is interesting to speculate on the role of FPR agonism in the context of cardiac macrophage heterogeneity. Genetic fate mapping in mice has demonstrated that at steady state, cardiac macrophages are composed of heterogeneous populations of embryonic-derived self-renewing macrophages (expressing the receptors TIMD4/LYVE1), and a numerically smaller population of adult bone marrow-derived $CCR2^{+}$ macrophages maintained through monocyte input (5). It may be the case that $CD206^{+}$ cells in the study of García et al. (2) represent the embryonic-derived macrophages that have survived the infarct. Equally interesting would be the idea that recruited monocytes could differentiate into resident macrophage-like cells—an observation previously seen at the single cell level (5).

The work of Garcia et al. (2) adds to the growing body of knowledge, which highlights that modulating individual cell-surface receptors with FPR agonists expedites tissue healing post-MI (1,4). Among these studies, key similarities involve decreased neutrophil accumulation, expedited and increased expression of CD206 and Arg-1 in the ischemic zone, improved infarct healing, and improved cardiac function relative to vehicle-treated control subjects. Future studies using tissue specific or inducible deletion models will help answer the question of which FPR receptor(s) are involved in the beneficial effects of Cmpd43.

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