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Inhibition of FPR2 Impaired Leukocyte Get-in Signal and Triggers Non-Resolving Inflammation in Heart Failure

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Non-resolving inflammation is a prominent trigger for heart failure (HF)-related morbidity and mortality following myocardial infarction (MI). Post-MI activated leukocyte expressed formyl peptide receptor 2 (FPR2) belongs to the essential for inflammation-resolution mechanisms. However, the role of FPR2 in leukocyte kinetics in acute HF is incompletely understood. Here, we aimed to determine whether pharmacological inhibition of FPR2 would impair leukocyte trafficking to the site of cardiac injury using WRW4 (FPR2 antagonist). For this, male C57BL/6 (8 to 12 week) mice were subjected to acute HF using permanent coronary artery ligation. FPR2 inhibitor WRW4 (1µg/kg/day; subcutaneous) was injected 3 hours post-MI and saline-injected- mice served as MI-control. Inhibition of FPR2 impaired leukocyte trafficking ("get-in" signal) that altered post-MI immune responsive clearance in the infarcted LV and spleen. Leukocyte kinetics, measured using flow cytometry, showed there was an overall decrease in CD45⁺/CD11b⁺; 23.3±2% in WRW4-injected mice when compared with MI-control (49.1±2%) in the LV. FPR2 inhibitor, WRW4, decreased FPR2 in the LV and spleen tissue, and mice displayed increase F4/80⁺/Ly6C^{hi} macrophages (14.8±2%) compared to the MI-control group (10±1%) in LV, this is indicative of amplified proinflammatory profile. Inhibition of WRW4 primes immature neutrophil infiltration Ly6G^{int} and intensifies the *Ccl2* (all p<0.05) expression compared to MI-control in the infarcted LV post-MI. WRW4 increased transcripts of pro-inflammatory markers *TNF-α* and *IL-1β*, with a decrease in expression of *Arg-1* (p<0.05) in the infarcted LV compared to MI-controls is suggestive of non-resolving or immune suppressive inflammation. In summary, FPR2 inhibition using WRW4 altered leukocyte get-in signal leading to the onset of frustrated resolution signaling in acute HF post-MI.

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