Abstract: **P274**

**Novel aspects of chemokine receptor signalling in cardiovascular inflammation**

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**Topic(s):**
Basic Science - Cardiac Biology and Physiology: Leukocytes, Inflammation, Immunity

**Citation:**
Cardiovascular Research (2018) 114 (Supplement 1), S70

**Funding Acknowledgements:**
Oxford BHF Centre for Research Excellence (RE/13/1/30181)

Background: The regulation of monocyte recruitment and macrophage retention into the vascular wall and heart are critical in the progression of cardiovascular disease but also to repair and remodelling after myocardial infarction (MI). Chemokines regulate leukocyte recruitment through G-protein coupled receptor (GPCR) signalling. Although chemokine signalling is a rational therapeutic target in MI, redundancy within the system limits the potential utility of targeting individual chemokines. Downstream modulators such as Regulator of G-Protein Signalling (RGS) proteins, deactivate GPCR signalling by stimulating GTPase activity of the α-subunit. We have found that RGS1 modulates leukocyte chemotactic signalling and regulates leukocyte accumulation in atherosclerosis and aortic aneurysm formation. Rgs1 expression is upregulated in activated inflammatory cells where it functions to inhibit migration, thus promoting inflammation by retention and accumulation of leukocytes, whereas Rgs1-deficiency confers protection.

Methods and Results: In recent experiments, we have identified Rgs1 up-regulation in infarct heart tissue and circulating monocytes after permanent left anterior descending (LAD) ligation to induce acute MI in wild-type mice, at a time point when inflammatory Ly6Chi monocytes infiltrate the infarct. However, an in vivo role for RGS1 in MI has not been investigated. We hypothesise that RGS1 regulates leukocyte recruitment and retention after MI, and has roles in myocardial injury and repair. RGS-1 is up-regulated with monocyte-macrophage activation and during M1 macrophage differentiation. In order to study the role of RGS1 in the recruitment and accumulation of leukocytes in cardiovascular inflammation, we have crossed the Rgs1-/- mouse with the novel Cd68GFP mouse that has GFP under the control of the human Cd68 promoter, enabling visualisation, tracking and isolation of GFP positive resident and recruited monocyte-macrophages in the heart after MI. Rgs1 deficiency reduces macrophage infiltration of the heart 4 days after MI, which may after the later repair phase of MI.

Conclusions: These findings identify a potential role for RGS1 in leukocyte function in cardiac inflammation and suggest that targeting chemokine signalling through RGS1 may provide new approaches to modify post-infarction myocardial remodelling.