Neutrophils modulate healing after myocardial infarction

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Purpose: Neutrophils contribute to tissue damage after acute myocardial ischemia and reperfusion, but their role in infarct healing is less well understood. Because neutrophil-derived granule proteins mediate classical monocyte recruitment in acute inflammation, we hypothesized that neutrophil depletion during the acute inflammatory phase will improve infarct healing by reducing the proinflammatory monocyte response in the heart.

Methods and results: In a mouse model of permanent coronary ligation, neutrophil depletion did not affect infarct size (n=5) nor survival (n=35), but decreased blood monocytes and lymphocytes 1 to 7 days post infarction (p<0.05; n=5). This was paralleled by reduced numbers of Ly6Chigh monocytes in the heart, whereas the percentage of Ly6Clow monocytes increased (p<0.05; n=5). Conversely, the number of Ly6Chigh monocytes in the spleen increased, suggesting reduced mobilization. The CD4+ T lymphocyte accumulation in the heart was delayed in neutrophil depleted mice, peaking after 14 days instead of 7 days post infarction in the control group (p<0.05; n=4). The subtype analysis revealed 50% less IFNγ-secreting Th1 cells in the heart and 2.5-fold higher numbers of FoxP3-expressing CD4+CD25+ T cells in neutrophil depleted mice (p<0.05; n=4). We further assessed the effect of neutrophils on healing and scar formation by immunohistochemistry. Our preliminary data suggest increased angiogenesis and fibrosis, evidenced by higher numbers of CD31-stained microvessels, α-smooth muscle actin-positive myofibroblasts and collagen in infarct areas of neutrophil depleted mice 7 to 14 days post-infarction (n=5). Surprisingly, the functional assessment using echocardiography revealed significant decrease of cardiac function (i.e. decreased stroke volume and cardiac output; p<0.05; n=4), probably due to excessive fibrosis and thus stiffness of the heart.

Conclusions: Our data indicate that neutrophils are involved in the regulation of inflammatory cell (i.e. monocyte/macrophage and lymphocyte) responses after myocardial infarction. In this context, neutrophils could represent a key regulator in adverse remodeling by fine-tuning the balance between inflammation and reparative state.