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Selective Interleukin-6 trans-signalling antagonism with sgp130Fc reduces infarct size in a rat model of myocardial infarction whereas pan-blockade with an anti-IL-6 antibody does not

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Introduction: Interleukin-6 (IL-6) is elevated during Acute Myocardial Infarction (AMI) particularly after reperfusion and is associated with the development of heart failure and mortality (1). Therefore IL-6 is a potential therapeutic target in AMI. IL-6 has both pro and anti-inflammatory effects; the anti-inflammatory effects are mediated by classic signalling (2), whereas the pro-inflammatory effects are mediated by trans-signalling (3). We hypothesised that selective blockade of IL-6 trans-signalling with the novel sgp130Fc protein during AMI would result in reduced infarct size (IS) whereas pan-IL-6 blockade with an anti-IL-6-Ab would not.

Methods: AMI was induced in male Sprague-Dawley rats by occluding the left-anterior descending artery for 50 minutes prior to reperfusion. The model was characterised by measuring IL-6 and sIL-6R within heart tissue and plasma by ELISA at 6 time-points post reperfusion (2h-7 days, n=3-4/group). In addition, cardiac leukocyte infiltration (flow-cytometry of cells obtained from heart digests) was measured. In therapeutic experiments, rats received either 0.5µg/g of sgp130Fc, 0.1µg/g anti-IL-6-Ab or vehicle alone given intravenously immediately prior to reperfusion. IS (as a percentage of area-at-risk (AAR)) was measured histologically at 24 hours (n=7-8/group). LVEF was measured by cardiac magnetic resonance imaging at 28 days in a group receiving sgp130Fc and compared to age-matched naïve rats and vehicle-controls (n=6-8/group).

Results:

Characterisation: IL-6 levels in the heart were biphasic; with peaks at 4 and 72 hours. Only the early peak was associated with elevated circulating IL-6. The early peak was temporally associated with neutrophil influx and the second with mononuclear phagocytes (MPs). Plasma sIL-6R peaked at 24 hours.

Therapeutic studies: IS/AAR was significantly reduced by the administration of sgp130Fc but not by the anti-IL-6-Ab (vehicle: 46.1%, anti-IL6-Ab: 45.6%, sgp130Fc: 26.3%, one-way ANOVA with multiple comparisons: sgp130Fc v vehicle $p<0.001$). At 28 days sgp130Fc ameliorated the reduction in LVEF associated with AMI (naïve 72.35%, vehicle: 62.58%, sgp130Fc 69.51%, one-way ANOVA with multiple comparisons: naïve vs vehicle $p<0.01$, naïve vs sgp130Fc ns).

Conclusions: Our results suggest that specific targeting of IL-6 trans-signalling with the novel sgp130Fc protein reduces IS in an animal model of AMI with reperfusion, whereas pan-blockade with an anti-IL-6-Ab does not. Furthermore, administration of sgp130Fc preserves LVEF at 28 days.

Reference:

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3. Tilg H *et al.* (1994). *Blood* **83**:113-8.