Regulation of BACH1 expression by hemin improves cardiac function and revascularisation in a mouse model of myocardial infarction

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Therapies to induce mature neovascularization formation and moderate oxidative stress after myocardial infarction (MI) are urgently needed. The BACH1 transcription factor is known as a repressor of genes involved in the antioxidant response (1). We have demonstrated BACH1 can regulate neovascularization through modulation of pro-angiogenic genes, particularly angiopoietin-1 (2).

We hypothesise expression of BACH1 after MI contributes to suppression of genes which promote reparative angiogenesis. We propose treatment with hemin (a therapeutic compound known to degrade BACH1) will prevent BACH1 repression of target genes, leading to increased expression of proangiogenic factors and increased neovascularisation and cardiac repair in a mouse MI model.

MI was induced in 8-week old C57/Bl6 male mice by permanent ligation of the left anterior descending coronary artery, n=10-14. Expression of Bach1 and the antioxidant Hmox1 in heart tissue was determined by Western blot at day 3 and 10 post MI, whilst a second group were randomized to receive vehicle, 12.5, 25 or 50mg/kg hemin intraperitoneally every 3 days until 28 days post-MI. On day 28, following echocardiography, mice were euthanised and ventricular tissue collected for histological analysis. Data was analysed by 2-way ANOVA with post-test multiple comparisons.

Compared to sham mice, Bach1 expression significantly increased at both day 3 and 10 post MI (P<0.0001 and P<0.01 respectively). Bach1 expression at day 10 was significantly lower compared to day 3, suggesting a transient effect (P<0.01). Hmox1 expression was significantly decreased at both timepoints (both P<0.001 vs. sham) suggesting in the initial period after MI the antioxidant and angiogenic responses are suboptimal. Treatment of mice with 25mg/kg hemin for 28 days post MI caused significant increases in capillary and arteriole density in the peri-infarct zone (P<0.0002 and P<0.0008 vs. vehicle respectively). There was no effect on capillary or arteriole density in the remote zone. In vehicle-treated mice there was thinning of the left ventricular end-diastolic anterior wall thickness (LVAW) corresponding to the infarct area. Interestingly, a significant increase in the thickness of the LVAW was observed after 25mg/kg hemin treatment (P<0.0001 vs. vehicle), whilst LV internal diameter significantly decreased (P<0.0001 vs. vehicle). Ejection fraction (P<0.0001), fractional shortening (P<0.0009) and stroke volume (P<0.0001) all significantly increased in mice treated with hemin compared to vehicle.

Treatment of mice with 25mg/kg hemin for 28 days post MI was sufficient to induce significantly increased capillary and arteriole density in the peri-infarct region. We also observed hemin exerted benefits on volumetric and contractility indexes. This data suggests hemin has potential to be used therapeutically post MI to improve revascularisation and cardiac function.