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GDF11 promotes increased sensitivity of the murine heart to ischemic injury

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Topic(s):
Ischemia, Infarction, Cardioprotection

Citation:
Cardiovascular Research (2018) 114 (Supplement 1), S74

Introduction - Recent studies have implicated a role of TGFβ family members in aging and cardiovascular diseases. Growth Differentiation Factor 11 (GDF11) is a member of TGFβ superfamily with high homology to myostatin/GDF8. Interestingly, in mice its levels decline with age, whereas myostatin and TGFβ1 levels remain unchanged, suggesting involvement of GDF11 in aging. In addition, GDF11 has recently been shown to play a role in cardiac hypertrophy. However, not much is known about its role in the myocardium. The goal of the present study was to investigate whether restoring GDF11 levels of aged mice to the ones observed in young mice by injecting recombinant GDF11 into blood stream would rescue myocardial infarction and provide "youthful" characteristics to the old myocardium.

Purpose - Restoring GDF11 levels in aged mice to the ones observed in young mice would improve the myocardial infarction outcome and provide "youthful" characteristics to the old myocardium.

Methods - 12-14-week-old and 22-24-month-old C57BL/6 male mice were injected daily with either recombinant human GDF11 or vehicle for 30 days. Afterwards mice were subjected to 30 min of ischemia (I) followed by 24h of reperfusion (R). Infarct size was assessed morphologically.

Results - After I/R, both young and aged GDF11-injected mice developed markedly larger infarcts as compared to vehicle-treated group (Fig. 1A and 1B). This was further associated with increased post-ischemic levels of serum cardiac troponin I (Fig. 1C). In addition, both GDF11-injected groups showed accelerated cardiac cell death after I/R as has been assessed by TUNEL on heart cross sections. Of note, both ageing groups showed higher mortality during the GDF11 treatment. Finally, cardiac RISK and SAFE prosurvival pathways were less activated in both GDF11-treated groups.

Conclusions - In summary, present study showed that daily injections of GDF11 promote increased sensitivity of the heart to myocardial infarction. Such GDF11-associated cardiac phenotype is likely to be driven by the increased cell death in the injured myocardium together with impaired function of prosurvival RISK and SAFE pathways. Thus, these results do not support proposed role of GDF11 as "rejuvenation" factor for the heart.
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