Abstract: 26O

MiR-558 inhibitor induces cardiac proliferation after myocardial infarction

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Background: Cardiovascular disease, particularly myocardial infarction (MI), and subsequent heart failure, remains the leading cause of death worldwide. Despite significant improvements in post MI management, heart failure remains a significant cause of morbidity and mortality, in a large part due to the formation of myocardial scar, as the adult human heart is unable to undergo cardiac repair. During early-mid gestation, CMs can proliferate. However, large mammals CMs lose their proliferative capacity during late gestation. microRNAs (miRs) have emerged as crucial determinants of cardiac development. Through a gene microarray study, our group has identified two miRs, miR-558 and miR-1538 as critical regulators of CMs. These miRs are differentially expressed depending upon age. In adolescents, these miRs are upregulated, inhibiting expression of proliferative genes. However, in a fetus, these miRs are downregulated, enabling expression of proliferative genes. In a lamb model, we aimed to investigate the role of miR-558 by inducing an MI and administering a miR-558 inhibitor. This may allow us to better understand the molecular mechanisms controlling this switch from proliferative to quiescent CMs.
Methods: 6-month-old Merino lambs underwent surgery using general anaesthesia induced by the intravenous infusion of diazepam (0.3 mg/kg) and ketamine (7 mg/kg). Animals (n=12) underwent thoracotomy and then ligation of a branch of the left anterior descending artery (LAD) to induce infarction. Immediately after the infarct, a 4mg dose of miR-558 inhibitor (n=6) or miR-Scramble (n=6) was injected directly into the infarcted area. Prior to ligation (Baseline), 7 days and 15 days after the ligation, lambs underwent cardiac MRI to assess left ventricular (LV) volumes and function by analysis of short-axis cine images. 2D late gadolinium enhancement (LGE) imaging was performed to quantify MI size. Post-mortem was performed 16 days after the surgery, and the hearts were taken for molecular analysis including qRT-PCR.
Results: Proliferation genes *Ki67* and *PCNA* were significantly upregulated in the infarcted area compared to remote and border regions in the miR-558 inhibitor group. Cardiac hypertrophy genes *NPPA* and *NPPB* were significantly upregulated in the border region compared to remote, but significantly reduced in the infarcted region in the miR-558 inhibitor group. There were no differences in LV end-systolic and diastolic volume (EDV) between groups. LV ejection fraction (LVEF) did not change over time and right ventricular parameters were not different. There was no ventricular dilatation following the MI. LVEDV decreased with time and was lower at day 7 and 15 in scrambles but only at day 7 in miR-558.
Conclusion: Inhibition of miR-558 leads to increased proliferation and decreased cardiac hypertrophy in the infarcted region in a lamb model of MI. Preserved LVEF following MI in both groups may be indicative of the small size of the infarctions induced by the surgery, although quantification of size of MI was not possible by LGE due to inadequate spatial resolution and was limited to visual confirmation at post-mortem. The absence of LV dilatation following an MI may be explained by the small size and extent of MI and warrants further investigation. Employment of quantitative myocardial strain analysis to assess segmental myocardial function in infarcted and remote myocardium may provide more insight into any associated functional deficits.