14 KIAA1109 IS DIFFERENTIALLY EXPRESSED POST MYOCARDIAL INFARCTION AND IS REQUIRED FOR VASCULAR INTEGRITY IN ZEBRAFISH

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Background We aimed to identify differentially expressed genes (DE) in whole blood following myocardial infarction (MI) or unstable angina (UA), and assess these functionally in zebrafish models.
Methods We performed whole blood microarrays comparing the transcriptome of patients with MI with UA at serial timepoints post-admission. We then examined the effect of knocking down one DE gene (KIAA1109) by morpholino antisense and examining the effect on vascular development in zebrafish embryos.
Results KIAA1109, a gene of completely unknown function was significantly down regulated in MI compared with UA 1d post MI, with no difference at later timepoints. Knockdown of KIAA1109 in developing zebrafish showed KIAA1109 morphants developed normally but developed cerebral haemorrhage (control 10% vs 50% morphants $p<0.05$). Haemorrhage volume was greater in KIAA1109 morphants (control 1.2μm^3 vs morphants 11.3μm^3 $p<0.05$). KIAA1109 knockdown decreased endothelial cell (EC) number in the forebrain (control 73±6 vs 47±4 morphants) and hindbrain (control 95±7 vs 53±4 morphants). Incubation with the VEGF inducer GS4012 completely rescued the hemorrhagic phenotype.

We performed a microarray comparing whole embryo RNA from KIAA1109 morphants with control to assess the transcriptional effect of loss of function of KIAA1109. This identified DE genes that were significantly down regulated such as genes involved in the cadherin-signalling pathway and genes involved in the NOTCH pathway.
Conclusion KIAA1109 is down regulated in peripheral blood early after MI. KIAA1109 knockdown induced cerebral bleeding in zebrafish embryos that is rescued by VEGF induction, suggesting KIAA1109 is required for vascular integrity.

15 CARDIOVASCULAR OXIDATIVE STRESS, INSULIN RESISTANCE, AND LIPID METABOLIC DISORDERS IN AGEING

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Old age has been recognised to be a major risk factor for the development of cardiovascular disease and growing evidence suggests a role for oxidative stress. However, it remains unclear if cardiovascular oxidative stress is associated with ageing-related insulin resistance and metabolic disorders. In this study, we investigated the relationship between metabolic changes and cardiovascular oxidative stress using C57BL/6 mice at young (3–4m) and old (22–24 m) ages. There was no significant difference in the food and water intake between young and aged mice. However, there was a significant increase in bodyweight (24.97±0.75g at 3–4m, 39.34±2.56g at 20m) and the epididymal fat pad weight (0.42±0.03g at 3–4m vs 1.32±0.21g at 22–24m) in ageing mice. Increased body fat deposition in the ageing mice was accompanied with a significant decrease (40%) in fasting serum triglyceride levels, a significant increase in fasting insulin levels (0.69±0.24μg/L at 3-4m, 2.08±0.46μg/L at 21–24m), and impaired glucose tolerance as evidenced by a significantly delayed clearance of glucose ($P<0.05$). These ageing-related metabolic disorders were accompanied with significant increases in superoxide production in aortas and hearts of ageing mice as compared to their young controls. In conclusion, the normal ageing process causes cardiovascular oxidative stress which is associated with metabolic disorders characterised by insulin resistance, increased body fat deposition and reduced fasting serum triglyceride levels in mice.

16 IMAGING REGIONAL DIFFERENCES IN BETA-2 ADRENERGIC RECEPTOR FUNCTION AT THE CELLULAR LEVEL

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A common feature of stress cardiomyopathy is contractile impairment of the left ventricular (LV) apical myocardium, although sympathetic effectors are elevated. We investigated the responsiveness of murine cardiomyocytes (CMs) from different LV regions to beta-2 adrenergic (beta2AR) stimulation. Although, initially positively inotropic, beta2AR may become negatively inotropic via biassed-agonism. The apical myocardium may express more beta-2ARs as it's relatively reliant on inotropic support from circulating adrenaline. High initial beta2AR-cAMP activation may initiate stimulus trafficking to beta2AR-Gi signalling. Contractile response to beta2AR stimulation (1μM Isoprenaline with 300nM CGP20712A) was measured by video microscopy. Whole-cell cAMP production after beta2AR stimulation was measured by FRET-based cAMP sensors. Apical CMs (ApCMs) significantly increased their initial contractility following beta2AR stimulation compared to Basal CMs (BCMs) from rats (ApCM 2.28 fold ±0.12 n=10 vs. BCM 1.32 fold ±0.06 n=8 $p<0.0001$; mean ± sem) and mice (ApCM 2.38 fold ±0.2 n=6 vs. BCM 1.43 fold ±0.1 n=6 $p<0.01$; mean ± sem). The amplitude of the cAMP transients from ApCMs and BCMs didn't differ for either rat (ApCM 46.7%±5.0 n=14 vs. BCM 42.4%±4.5 n=16 p=NS: values are %maximal FRET response; mean ± sem) or mouse (ApCM 9.1%±2.0 n=6 vs. BCM 7.6%±2.5 n=7 P=NS: %max FRET; mean ± sem). In rat ApCM the cAMP response persisted 250 seconds post-stimulation (ACM 2.28%±1.0 n=7 vs. BCM 0.27±0.1 n=10 $p<0.05$: %rawFRET; mean ± sem). ApCMs have a larger beta2AR-Gs-contractile response in two different mammalian species. A persisting cAMP response in the ApCMs may enable this by allowing cAMP greater access to PKA compartments.

17 CHANGES IN THE ROLE OF THE SR IN SAN FUNCTION ACROSS THE LIFESPAN MAY BE RESPONSIBLE FOR CHANGING PACEMAKER STABILITY AND RESPONSE

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Background Intracellular calcium regulation is important for regulating sinoatrial node (SAN) activity. Ventricular expression of the sarcoendoplasmic recticulum (SR) Ca-ATPase pump (SERCA) has been shown to decline with age; a change which if repeated in the SAN may contribute to the well-documented decline in SAN activity, stability and response with advanced age.