Abstract Title: scar-6 lncRNA epigenetically regulates PROZ and modulates blood coagulation and vascular homeostasis

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Zebrafish serves as an exemplary model for studying human vascular diseases. Research from our lab has shown the role of long non-coding RNAs (lncRNAs) such as VEAL2 in regulating PRKCB2 for modulating junctional dynamics and maintenance of endothelial cell permeability in zebrafish and diabetic retinopathy patients (Sehgal et al 2021). Next we intended to investigated the epigenetic regulation of protein-coding genes by lncRNAs and their relevance to human diseases. We uncovered a previously uncharacterized lncRNA, Syntenic Cardiovascular Conserved Region-Associated lncRNA-6 (scar-6) and elucidate its pivotal role in coagulation and vascular function. Targeted mutation in the scar-6 locus in zebrafish demonstrated its indispensable role in maintaining vascular integrity, substantiated by the occurrence of cranial haemorrhage. Molecular investigations uncovered scar-6's regulatory control over prozb, an inhibitor of coagulation factor Xa, facilitated through an regulatory element on its locus. The scar-6 mutant zebrafish exhibited disruption in the active suppression role of the enhancer-promoter loop formation between prozb and scar-6. This disruption was identified to be associated with CpG island methylation, orchestrated by the epigenetic regulatory complex prdm14-PRC2. Our findings underscore the pivotal role of the scar-6 locus in epigenetically regulating the coagulation cascade gene prozb, contributing to the maintenance of vascular homeostasis. This study advances our understanding of lncRNA-mediated epigenetic mechanisms in vascular biology and highlights the potential implications for therapeutic interventions in maintaining cardiovascular health.

Area of expertise: Genomics, Genetics, Zebrafish, Human Diseases