The ribosomal RNA processing gene *nucleolar protein 9* (*nol9*) is essential for normal exocrine pancreas development in zebrafish

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Abstract

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Zebrafish are an excellent model organism for the study of development and disease, as they are amenable to genetic manipulation and imaging techniques. Genetic screens in zebrafish have identified several mutations in genes involved in pancreas development and research of these mutants has furthered our knowledge of pancreatic disorders and syndromes. A zebrafish mutant in *nucleolar protein 9* (*nol9*) gene, *nol9*^{sa1022}, was found to be associated with a pancreas phenotype in the Zebrafish Mutation Project (ZMP). The main aim of this thesis is to determine the role of *nol9* in pancreas development by studying the *nol9*^{sa1022} mutant. This study has demonstrated that the function of Nol9 is conserved between zebrafish and human. The characterisation of *nol9*^{sa1022} mutants revealed that the pancreas, liver and intestine failed to develop normally after 3 days post fertilisation and this was due to impaired cell proliferation for the exocrine pancreas. The development of the endocrine pancreas and all the other organs appeared unaffected. Interestingly, *las1l*^{sa674}, a zebrafish mutant allele of a Nol9-interacting protein with similar function, was also found to exhibit digestive organ defects. Although an up-regulation of Tp53-signalling pathway genes were detected through mRNA expression analysis of *nol9*^{sa1022} mutant, loss of function of Tp53 did not suppress the pancreatic defects suggesting the involvement of a Tp53-independent mechanism. To gain insight into the underlying biology of the mutants, the mRNA expression profiles of four rRNA processing mutants *nol9*^{sa1022}, *las1l*^{sa674}, *tti*^{s450} and *set*^{s453} were compared. This analysis revealed that differentially expressed genes in all four mutants were enriched for ribosome- and translation-related terms, consistent with the known functions of these proteins. Overall, the findings presented here demonstrate that the *nol9*^{sa1022} mutant is an ideal *in vivo* model to study the roles of rRNA in cell proliferation and digestive organ development and can benefit the field of ribosomopathies.

Declaration

This dissertation is the result of my own work and includes nothing which is the outcome of work done in collaboration except where specifically indicated in the text. This dissertation does not exceed the word limit set by the Biology Degree Committee.

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