

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

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Abstract

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

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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}*, *ttr^{sa450}* and *set^{sa453}* 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.

Laure Lam Hung,

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Table of Contents

Chapter 1 Introduction.....	7
1.1 Pancreas	7
1.1.1 Pancreas development in humans	8
1.1.2 Congenital disorders of the pancreas	8
1.2 Zebrafish as a model organism.....	13
1.2.1 Zebrafish genome	13
1.2.2 Forward genetic approaches.....	14
1.2.3 Reverse genetic approaches	15
1.2.4 Transgenic approaches.....	19
1.2.5 Gene inactivation tools.....	21
1.2.6 Gene knockdown tools	22
1.3 Zebrafish pancreas development.....	25
1.3.1 Endoderm induction, patterning and regionalisation	25
1.3.2 Morphogenesis of pancreas	29
1.3.3 Differentiation of pancreatic progenitor cells.....	30
1.3.4 Role of ribosomal biogenesis genes in exocrine pancreas development.....	35
1.4 Ribosome.....	39
1.4.1 Ribosome biogenesis	41
1.4.2 Ribosomopathies	46

1.5 Thesis aims and objectives.....	51
Chapter 2 Materials & Methods.....	54
2.1 Zebrafish husbandry and genotyping.....	54
2.1.1 General husbandry.....	54
2.1.2 Genotyping of zebrafish embryos, larvae and adults.....	55
2.2 RNA extraction and DNase treatment.....	56
2.3 RNA and protein expression detection	57
2.3.1 Embryo fixation.....	57
2.3.2 Whole-mount RNA <i>in situ</i> hybridisation	57
2.3.3 Immunohistochemistry	60
2.3.4 Microscopy	60
2.4 Characterisation of loss of function mutants	62
2.4.1 Morpholino injections	62
2.4.2 Inhibition of Notch-signalling	62
2.4.3 Flow cytometry analysis.....	62
2.4.4 Cell Proliferation.....	62
2.4.5 Cell Death	63
2.4.6 Alcian blue staining.....	63
2.4.7 O-dianisidine staining.....	63
2.4.8 Statistical approaches.....	64
2.5 Study of rRNA processing and ribosome biogenesis	65

2.5.1	Bioanalyser & Northern Blot analysis	65
2.5.2	Polysome fractionation	65
2.6	Differential Expression Transcript Counting Technique (DeTCT)	67
2.6.1	DeTCT Library preparation.....	67
2.6.2	DeTCT analysis	70
2.6.3	Comparisons between <i>nol9^{sa1022}</i> , <i>las1^{sa674}</i> , <i>tts⁴⁵⁰</i> and <i>set^{s453}</i> mutants	71
2.6.4	Gene ontology enrichment analysis	71
2.6.5	KEGG pathways enrichment analysis	72
Chapter 3	Characterisation of <i>nol9^{sa1022}</i> mutants.....	73
3.1	Introduction	73
3.2	Results.....	76
3.2.1	Gross morphology of <i>nol9^{sa1022}</i> mutants.....	76
3.2.2	The <i>nol9^{sa1022}</i> mutants have smaller exocrine pancreas	77
3.2.3	Knockdown of <i>nol9</i> results in smaller exocrine pancreas	79
3.2.4	Early development of digestive organs is normal in <i>nol9^{sa1022}</i> mutants	81
3.2.5	Expansion growth of the exocrine pancreas and formation of pancreatic ducts are impaired in <i>nol9^{sa1022}</i> mutants	83
3.2.6	Pancreatic endocrine cells are formed and are differentiated in <i>nol9^{sa1022}</i> mutants	85
3.2.7	Secondary islets cells expressing <i>insulin</i> are present in <i>nol9^{sa1022}</i> mutants ..	87
3.2.8	Expansion growths of liver and intestine are impaired in <i>nol9^{sa1022}</i> mutants ..	89

3.2.9	The <i>nol9^{sa1022}</i> mutants have different proportion of cells in <i>G1</i> , <i>S</i> and <i>G2</i> phases of cell cycle	91
3.2.10	The pancreas of <i>nol9^{sa1022}</i> mutants show impaired cell proliferation.....	93
3.2.11	The pancreas of <i>nol9^{sa1022}</i> mutants do not show increased cell death.....	95
3.2.12	Development of the jaw cartilage and erythrocyte is normal in <i>nol9^{sa1022}</i> mutants	97
3.2.13	Developmental expression pattern of <i>nol9</i>	99
3.2.14	The processing of 28S rRNA is impaired in <i>nol9^{sa1022}</i> mutants	100
3.2.15	Formation of 60S ribosomal subunit is impaired in <i>nol9^{sa1022}</i> mutants	103
3.3	Discussion	104
Chapter 4	Characterisation of <i>las1^{sa674}</i> mutants	109
4.1	Introduction	109
4.2	Results.....	111
4.2.1	Gross morphology of <i>las1^{sa674}</i> mutants	111
4.2.2	The <i>las1^{sa674}</i> mutants have smaller exocrine pancreas.....	112
4.2.3	The pancreas of <i>las1^{sa674}</i> mutants do not show increased cell death.....	115
4.2.4	Development of the jaw cartilage and erythrocyte is normal in <i>las1^{sa674}</i> mutants	117
4.3	Discussion	119
Chapter 5	Analysis of mRNA expression profiles of <i>nol9^{sa1022}</i>, <i>las1^{sa674}</i>, <i>tti^{sa450}</i> and <i>set^{sa453}</i> mutants	123
5.1	Introduction	123
5.2	Results.....	127

5.2.1	The mRNA expression profile of <i>noI9^{sa1022}</i> mutants	127
5.2.2	Enriched Gene Ontology categories in <i>noI9^{sa1022}</i> mutants.....	131
5.2.3	Enriched KEGG pathways in <i>noI9^{sa022}</i> mutants	135
5.2.4	The small pancreas phenotype of <i>noI9^{sa1022}</i> mutant is Tp53-independent	138
5.2.5	The mRNA expression profile of <i>las1^{sa674}</i> mutants	140
5.2.6	Enriched Gene Ontology categories in <i>las1^{sa674}</i> mutants.....	143
5.2.7	Comparison of the mRNA expression profiles of <i>noI9^{sa1022}</i> , <i>las1^{sa674}</i> , <i>tti^{sa450}</i> and <i>set^{sa453}</i> mutants	147
5.3	Discussion	151
Chapter 6	Discussion.....	157
Appendices	163
Bibliography	175

