Characterization of a zebrafish model for pheochromocytoma, an adrenal cancer type

Clinical relevance

Patients with pheochromocytoma have tumors that originate from chromaffin cells in the adrenal gland. Chromaffin cells are neuro-endocrine cells and produce adrenaline or noradrenaline, also called epinephrine and norepinephrine, respectively. Every year, between 100 and 150 new pheochromocytoma cases are reported in The Netherlands. Currently, there is no effective treatment for patients with pheochromocytoma other than removal of a tumor when operable. There is an urgent clinical need for development of therapeutics against this disease, which requires a better understanding of the etiology of pheochromocytoma and therefore generation of relevant animal models.

Background

About 40 percent of the pheochromocytoma can be explained by a mutation in a variety of genes. 15 of such pheochromocytoma-related genes have been identified so far. A mutation in one of these pheochromocytoma-related genes, the succinate dehydrogenase B (SDHB), is the strongest indicator of malignancy of this cancer type. Therefore, we decided to generate an animal model with an SDHB mutation. The SDHB protein is part of a four subunit (A-D) protein complex, the succinate dehydrogenase (SDH) complex. The SDH complex converts succinate to fumarate, one of the steps of the TCA cycle. When this complex is dysfunctional there is a build-up of succinate in the cell. Succinate stabilizes hypoxia-inducible transcription factors (HIFs). HIF-targets are subsequently transcribed and in turn boost proliferation and angiogenesis, two essential processes of tumor formation.

As an animal model we choose zebrafish, since mice with an SDHB mutation do not develop pheochromocytoma and zebrafish with a mutation in the Von Hippel Lindau gene (VHL), another pheochromocytoma-related gene, do show characteristics of pheochromocytoma. To study the disease- causing molecular pathways of pheochromocytoma we generated a whole-animal *sdhb* mutant zebrafish strain with CRISPR/Cas9 and are working on a chromaffin-cell-specific mutant strain to mimic the situation in the patient. Our zebrafish model is the first viable vertebrate animal model for pheochromocytoma and thereby will yield urgently needed insights in the etiology of this cancer type.

Goal

The goal of this project is to further characterize the phenotype of whole-animal and tissue-specific *sdhb* zebrafish mutants with a variety of different assays and techniques. In addition, a drug screening will be performed to identify targets to rescue the observed diseased phenotype in the mutant fish.

We offer:

The possibility to perform and present exciting high-quality research in a professional, multi-cultural and highly-motivating work environment with about 35 colleagues in a well-equipped department. You will have the opportunity to learn a broad range of techniques and skills, such as genotyping and phenotyping of KO zebrafish via fin clipping, PCR, DNA gels, histology, Handling and breeding zebrafish and planning, scientific writing and presenting. The student would be exposed to proteomics and metabolomics via Mass Spectrometry and Nuclear Magnetic Resonance, as these techniques would be performed in another lab as part of a collaboration. All of this would take place under the supervision of an experienced postdoc.

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