The aim of this study is to investigate the molecular mechanisms underlying the tumorigenic transformation of adrenal stem/progenitor cells caused by transcription factor GATA-4, luteinizing hormone (LH) and its receptor (LHCGR).
Adrenocortical tumors are relatively common with benign adrenocortical adenomas present in about 3-7% of the population. Adrenocortical carcinomas are rare, but they are aggressive types of human malignancies with very poor prognosis. Adrenocortical carcinomas appear either during the childhood under 10, or in adults aged 40-50 and are more common in women than men. Untreated malignant tumor most commonly metastasizes to the liver, lungs and bones.
Stem cells play a very important role in the development, as they form the main cell mass at the early stages of embryonic development. Their characteristic feature is the ability to differentiate into specialized cells and self-renewal to produce more stem cells. By differentiation stem cells enable the development of organisms with specialized tissues and organs performing specific functions. In adult organisms, stem cell number is limited. Progenitor or precursor cells (differentiated stem cells) are more dominant and they may still give rise to a few different types of cells only, usually into cells with similar characteristics and origin. Examples of such cells are adult stem /progenitor cells of adrenal glands. Physiologically, adrenal stem cells/progenitor cells are responsible for the regeneration and maintenance of homeostasis by replacing the dead cells. It may happen that the process of differentiation of stem/progenitor cells gets out of control, resulting in stem cells neoplastic transformation and tumor formation. The mechanism of the process of neoplastic transformation of adrenal stem/progenitor cells remains unknown.
It has been suggested that GATA-4 and luteinizing hormone/choriogonadotropin receptor (LHCGR), among others, could be important factors in inducing adrenal stem/progenitor cell transformation into neoplastic cells. The GATA transcription factors bind a consensus A/T-G-A-T-A-A/G sequence in promoters and are conserved in insects and vertebrates. In the fetal period, normal human and murine adrenal express GATA-4 but in adults it is no longer detectable at the protein level. However, during adrenocortical tumorigenesis in mice and human GATA-4 expression is highly upregulated. LHCGR is a transmembrane receptor expressed predominantly in the ovary and testis but also some extragonadal organs such as the uterus, adrenals and breasts may express it. LHCGR interacts with both luteinizing hormone (LH) and chorionic gonadotropins (CG) and represents a G protein-coupled receptor (GPCR). Its activation is necessary for the hormonal functioning during reproduction. Similarly to GATA-4, LHCGR expression is highly upregulated in adrenal tumors.
In this proposed project, we will use sophisticated and advanced molecular biology techniques (transgenic animals, induction of gene expression in cell lines, in vitro knock-down/knock out or knock in of genes) and advanced cell culture techniques (cell immortalization, stem cell differentiation in vitro). The following research tasks will be carried out: 1) Isolation, immortalization and functional characterization of cell lines established from neoplastic adrenocortical A and B cells of TG 21-OH-GATA4 mice, 2) generation and optimization of a working protocol for GATA-4-induced neoplastic transformation of adrenocortical stem/progenitor cells in vitro, and 3) determination of the role of FOG-2 (cofactor of GATA-4) and LHCGR in GATA-4/GDX-induced adrenocortical tumorigenesis.
Results of our planned studies will be very important for understanding the molecular mechanisms underlying the interactions between GATA-4/FOG-2, LHCGR and gonadotropins during adrenal cortex stem/progenitor cells neoplastic transformation. This question is clinically relevant, as GATA-4/LHCGR-positive adrenal tumors were found especially in post-menopausal women in conditions of elevated gonadotropin levels. We will disseminate the results through publication in scientific medical journals and also at international scientific conferences. We are anticipating that for scientific and medical environments our findings would be very interesting and promising.