Internship Proposal

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Project Title:
Regulation of the somatotropic signaling by FOXM1

Level:

Trainee

Project Summary:

Hutchinson-Gilford progeria syndrome (HGPS), also known as progeria, is a fatal genetic condition of accelerated aging. Affected children have severe clinical manifestations such as growth impairment, lipodystrophy, dermal and bone abnormalities, alopecia, and cardiovascular alterations which are the leading cause of death.

Previously, our group showed that an extra copy of FOXM1(FOXM1tg) acts prophylactically improving major progeroid features of the LAKI mice (HGPS mouse model), such as loss of weight and body fat, skeleton abnormalities (e.g. kyphosis) and aortic dysfunction (main cause of death). Moreover, an increased body size was observed upon FOXM1tg induction. This raised the question whether FOXM1 improves the somatotropic axis (growth hormone (Gh)/ insulin-like growth factor), the key endocrine mechanism that regulates organismal growth.

In progeria models, downregulation of IGF-1 driven by DNA damage, via mir-1 upregulation. In line with FOXM1 role as a master regulator of DNA repair, we proposed that FOXM1tg induction improves IGF1 levels by improving DNA repair. Our preliminary data show that in progeroid LAKI mice FOXM1tg induction improve IGF1 levels rebalancing the somatotropic axis in liver, at the same time FOXM1tg induction is also able to downregulate mir-1. Our goal now is to mechanistic link FOXM1tg overexpression to Igf-1 restoration via DNA damage targeting.

Work to be developed by the student:

We will use hepatocytes from LAKI mice to determine if FOXM1tg induction upregulates IGF-1 via inhibition of miR-1 expression. miR-1 is up-regulated in response to persistent DNA damage in both progeroid zmpste-/- mice and human HGPS cells, directly contributing to reduced IGF-1 mRNA levels via miR-1 upregulation. To demonstrate that FOXM1tg

modulates miR-1/IGF-1 expression by improving DNA repair, we will treat FOXM1tg-LAKI hepatocytes with small-molecule inhibitors of major DNA repair proteins (DNA-PK, ATM, ATR, PARP1) and check by RT-qPCR if miR-1 repression and Igf-1 upregulation are abrogated.

References:

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