Hutchinson-Gilford Progeria Syndrome

A new treatment strategy and the role of prelamin A in oncogenesis

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I. **Ibrahim MX**, Sayin VI, Akula MK, Liu M, Fong LG, Young SG, Bergo MO. Targeting isoprenylcysteine methylation ameliorates disease in a mouse model of progeria. *Science*. 2013 Jun 14;340(6138):1330-3.

II. **Ibrahim MX**, Sayin VI, Bergo MO. Prelamin A inhibits K-RAS and B-Raf induced invasion but is dispensable for tumorgenesis. *Manuscript.*

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ABSTRACT

Prelamin A, a *CaaX*-protein is a key structural protein of the inner nuclear lamina, a meshwork lining the inner nuclear envelope. Farnesylated prelamin A is cleaved just upstream of the farnesylcysteine residue to produce mature lamin A. We generated Zmpste24 knockout mice and documented a striking accumulation of farnesylated and methylated prelamin A in cells. Zmpste24 knockout cells exhibit premature senescence and misshapen cell nuclei. Zmpste24 knockout mice show slow growth, hair loss, micrognathia, bone fractures, muscle weakness, and premature death. These phenotypes are similar to those in HGPS. HGPS is caused by a LMNA point mutation that leads to the deletion of 50 amino acids in the carboxyl terminus of prelamin A (eliminating the ZMPSTE24 cleavage site and preventing formation of mature lamin A). Consequently, a mutant farnesylated and methylated prelamin A accumulates at the nuclear rim in HGPS cells, interfering with the nuclear lamina and causing misshapen cell nuclei.

Specific Aim and Results of Paper 1: To define the importance of ICMT in the pathogenesis and treatment of progeria. In this project we bred Zmpste24 knockout mice with mice harboring a hypomorphic (reduced expression) allele of Icmt. We found that these mice where protected from most aspects of progeroid disease. They had an increased survival, lack of osteoporosis, and increased strength. Icmt inhibition in cells derived from Zmpste24 KO mice and cells from human progeria patients also showed increased proliferative and somatrophic activity, without affecting the frequency of nuclear shape abnormalities which is one of the hallmark phenotypes of progeria.

Specific Aim and Results of Paper 2: To test the hypothesis that prelamin A is a tumor suppressor. We bred *Zmpste24* knockout mice with mice expressing a Cre-inducible endogenous oncogenic K-RAS and B-Raf alleles (K-RAS$^{LSL/+}$ and B-Raf^{CA}). Groups of mice where then allowed to inhale a Cre- adenovirus to activate the expression of oncogenic K-RAS$^{G12D/+}$ and B-Raf^{V600E} in lung cells (these mice normally develop lung adenomas to adenocarcinoma without metastases). 10 and 8 weeks post inhalation mice were euthanized and lungs where prepared for routine histology. Surprisingly, *Zmpste24*-deficiency had no impact on the development K-RAS$^{G12D/+}$ and B-Raf^{V600E} driven tumor except for a reduction in grade. Furthermore, fibroblasts derived from the same mice could be readily transformed and proliferated at the same rate as *Zmpste24 competent cells.* Finally, K-RAS$^{G12D/+}$, B-Raf^{V600E} *Zmpste24*-fibroblasts had significantly reduced basement membrane invasiveness.

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