FoxF Genes in Development and Disease

Akademisk avhandling

för avläggande av filosofie doktorexamen i Naturvetenskap, inriktning genetik, som kommer att offentligt försvaras i föreläsningssal Carl kylberg, medicinaregatan 7B Göteborg, tisdagen den 3 juni, 2014, kl. 10:00

av

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Prof. Guido Jenster,
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This thesis is composed of following papers, referred to in the text by their Roman numerals:

I. Inversion upstream of FOXF1 in a case of lethal alveolar capillary dysplasia with misalignment of pulmonary veins.

Parris T, Nik AM, Kotecha S, Langston C, Helou K, Platt C, Carlsson P.
American Journal of Medical Genetics Part A
Volume 161, Issue 4, pages 764–770, April 2013

II. Separation of intact intestinal epithelium from mesenchyme.

Nik AM, Carlsson P .
BioTechniques, Vol. 55, No. 1, pp. 42–44, July 2013.

III. Foxf2 in intestinal fibroblasts reduces numbers of Lgr5(+) stem cells and adenoma formation by inhibiting Wnt signaling.

Nik AM, Reyahi A, Pontén F, Carlsson P
Gastroenterology. 2013 May;144(5):1001-11.

IV. *Foxf2* enhances Tgfβ signaling in secondary palate development.

Ali M.Nik, Jeanette Astorga-Johansson, Azadeh Reyahi, Mozhgan Ghiami, Fredrik Pontén and Peter Carlsson
Submitted

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FoxF genes in development and disease

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Abstract

Forkhead transcription factors of the *FoxF* group are important during embryonic development, and mutation of either of the members, *Foxf1* and *Foxf2*, has fatal consequences. In this thesis, I present our recent findings about the mechanism of action of *FoxF* genes in development and disease.

Haploinsufficiency for *FOXF1* in humans causes alveolar capillary dysplasia with misalignment of pulmonary veins (ACDMPV), a rare lethal congenital disorder with incomplete penetrance. We report a new ACDMPV case and define the genomic rearrangement which consists of a pericentric inversion on chromosome 16 (p11.2q24.1), which disrupts the *FOXF1* 5'-flanking region 134 kb upstream of the first exon. We further use this information in combination with chromatin modification data from the ENCODE data set to predict the extent of the *FOXF1* regulatory domain and the critical genomic regions for ACDMPV.

Gastrointestinal cancer, which is the result of uncontrolled proliferation of intestinal stem cells, is one of the most prevalent causes of death in the West. We show that *Foxf2* regulates the number of intestinal stem cells and the proliferation rate in adult mouse intestine, with consequences for initiation and growth of intestinal tumors. *Foxf2* limits the size of the stem cell niche by activating the expression of the extracellular Wnt inhibitor Sfrp1 in mesenchymal cells surrounding the crypts of Lieberkühn. During this work we also developed a novel method for separation of intact intestinal epithelium from mesenchyme.

Cleft palate is a common congenital malformation, associated with many genetic alterations and environmental teratogens. Loss of *Foxf2* results in cleft palate in mouse. We found that the cleft palate is the result of reduced proliferation and decreased extracellular matrix production in the neural crest-derived palatal shelf mesenchyme at a critical stage of palatal formation. The mechanistic basis appears to be a diminished Tgfβ signaling, and decreased expression of integrins required for activation of latent Tgfβ.

Keywords: *Foxf1,* ACMPV, *Foxf2,* Wnt signaling, Adenoma, *sFRP-1*, Intestinal stem cell niche, Lgr5, Intact epithelium, palatogenesis, cleft palate, Tgfβ signaling, LAP, Integrins, extracellular matrix.

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