FoxF genes in embryonic development

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Abstract

In this thesis I summarize three papers where we present the expression patterns and functions of the two *Foxf* genes in mouse embryonic development. Both genes are expressed in similar patterns in mesodermally derived tissues from gastrulation to adulthood, but there are also some important differences in the expression resulting in both radically different and similar mutant phenotypes.

We have knocked out *Foxf1* and show that it is strongly expressed in lateral plate and extraembryonic mesoderm resulting in a severe mutant phenotype with posterior truncation of the embryo, impaired coelom formation and malformations in all of the extraembryonic membranes, leading to necrosis and resorption of all homozygous null mutants before embryonic day 10. Altered adhesion properties in the mesoderm, probably caused by the misexpression of the cell adhesion molecule VCAM1, lead to enhanced intramesodermal cohesion and adherence between yolk sac and amnion. *Foxf2* null mutants on the other hand develop to term, but die at birth due to a cleft in the secondary palate. We demonstrate that both *Foxf2* null mutants and $Foxf1^{+/-}$;$Foxf2^{+/-}$ compound heterozygotes have a range of intestinal defects such as agangliosis, megacolon and colorectal muscle hypoplasia. Both *Foxf1* and *Foxf2* are regulated by Hedgehog signaling from the endoderm and we demonstrate that mesenchymal expression of *Bmp4* is reduced and *Wnt5a* expression is increased in *Foxf* mutants. The extracellular matrix is depleted of mainly collagens causing tissue disintegration and epithelial depolarization. The combination of these properties results in a complex phenotype that both show signs of epithelial overproliferation and resistance to apoptosis as a result of hyperactive Wnt signaling, as well as epithelial depolarization and tissue disintegration.

The Foxf transcription factors have been shown to be at the crossroads of several of the main developmental pathways during embryonic development, connecting Hedgehog, BMP and Wnt signaling. In addition, the intestinal phenotypes observed in *Foxf* mutants support the increasing body of evidence implying the importance of the stroma and extracellular matrix in the maintenance of epithelial homeostasis and tumor initiation.

Keywords: Foxf1, Foxf2, Hedgehog, Wnt, Bmp, forkhead, transcription, mesoderm, development, extraembryonic, intestine