Functional studies of two forkhead genes

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av

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Avhandlingen baseras på följande delarbeten:

I. Heglind M, Cederberg A, Aquino J, Lucas G, Ernfors P, Enerback S (2005) Lack of the Central Nervous System- and Neural Crest-Expressed Forkhead Gene *Foxs1* Affects Motor Function and Body Weight. Mol Cell Biol 25:5616-5625.

II. Hjerling-Leffler J, Marmigere F, Heglind M, Cederberg A, Koltzenburg M, Enerback S, Ernfors P (2005) The boundary cap: a source of neural crest stem cells that generate multiple sensory neuron subtypes. Development 132:2623-2632

III. Vidarsson H, Westergren R, Heglind M, Blomqvist SR, Breton S, Enerback S (2009) The Forkhead Transcription Factor Foxi1 Is a Master Regulator of Vacuolar H^+-ATPase Proton Pump Subunits in the Inner Ear, Kidney and Epididymis. PLoS ONE 4:e4471.

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Abstract
Forkhead genes are functionally diverse and several have been linked to human disease. A previous screen for forkhead genes identified the family member *FOXS1*. To characterize the function of this gene, we produced a mouse model in which the *Foxs1* gene was replaced by a *lacZ* marker allele. During embryogenesis, *Foxs1* was most prominently expressed in peripheral sensory neurons and cerebellum, while a more widespread expression was seen in adult animals. Mutant animals displayed a complex phenotype, which included an enhanced coordinated sensorimotor performance and, in male mice, a lowered weight gain on a high-fat diet. We speculate that the relatively mild phenotype may be due to compensatory effects exerted by other forkhead genes.

Genetic tracing of cells of the boundary cap had shown that they contribute to both sensory neurons and glial cells of the peripheral nervous system, suggesting that they could be multipotent stem cells. We investigated their stem cell properties by culturing cells of the dorsal root ganglia and associated boundary caps. This resulted in the formation of neural crest stem cell clones that were shown to be derived from the boundary cap cells. In vitro differentiation of the stem cell clones gave rise to functional sensory neurons of different subclasses. Our results suggest that cells of the boundary cap are multipotent, sensory-specified stem cells that persist throughout embryogenesis.

A second forkhead gene, *Foxi1*, had previously been shown to be of importance in the regulation of the proton-secreting capacity in kidney collecting ducts, endolymphatic sac and epididymis. To gain further knowledge of the mechanisms involved, we investigated the role of Foxi1 in the regulation of V-ATPase subunits B1, a4, A1 and E2. Our results support a direct role of Foxi1 in the regulation of both the specifically expressed B1 and a4 subunits and the ubiquitously expressed subunits A1 and E2 in all of the tissues studied.

Keywords: forkhead genes, Foxs1, Foxi1, vacuolar type H^+-ATPase, boundary cap, neural crest stem cells

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