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Genetic control of sensory neuron diversification

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ABSTRACT

The somatosensory system of vertebrates transmits information from external and internal environments to the brain. This information relates to various modalities such as touch, temperature, itch and pain. The different modalities require a variety of subtypes of sensory neurons, tuned to detect and transmit specific stimuli. Each of these subtypes expresses a specific set of proteins to serve this highly specialized function and to control the cell type specific gene expression. This thesis explores the development and diversity of sensory neuronal subtypes in the dorsal root ganglion (DRG) of the mouse.

In the five studies included in this thesis, we have investigated the roles of several genes in the development and function of sensory neurons. In Paper I, the focus is on a transcription factor, Cux2. We described that its expression is limited to large, early born neurons, which are mainly mechanosensitive, including a lineage of poorly characterized large $TrkA^+$ neurons. We found no evidence that Cux2 would affect neuronal subtype specification, but instead we showed that it contributes to regulation of mechanosensation.

Transcription factors themselves are closely regulated in order to be expressed at the right time and place in development. In Paper II we identified that FGF signaling from earlier-born neurons triggers the upregulation of the transcription factor Runx1 early in the development of the thermo-nociceptive lineage. Signaling by soluble factors is also involved in the late stages of maturation of neuronal identity, as we demonstrated in Paper IV for the Ret receptor. We reported that the loss of Ret expression caused a hypersensitivity to several sensory modalities and showed that Ret is necessary for the expression of a large number of ion channels and receptors. One of the Ret-regulated genes was the cold receptor TrpM8. In Paper III we showed that TrpM8 expression was confined to a small population of neurons lacking coexpression with most subtype markers. We also characterized the developmental expression of all members of the TrpM family in the DRG and showed that most of them were expressed with individual temporal patterns.

Finally, in Paper V, we characterized the expression pattern of the enzyme Tyrosine hydroxylase (TH), the function of which is unknown in the DRG. TH is central in the catecholamine synthesis pathway, but whether or not that pathway is active in the DRG is uncertain. We showed that neurons expressing TH belong to the Ret^+ population and that the expression of TH depends on Runx1 but not Ret.

In summary, we have described a number of novel sensory neuron populations as well as genetic mechanisms governing development and diversification of specific populations. These results lead to a better understanding of the somatosensory system and hopefully in extension to better treatments for patients with somatosensory disturbances such as chronic pain conditions.

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