UMEÅ UNIVERSITET

# Vitamin A regulated neuronal regeneration and homeostasis

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Akademisk avhandling

som med vederbörligt tillstånd av Rektor vid Umeå universitet för avläggande av filosofie doktorsexamen framläggs till offentligt försvar i A103, Byggnad 6A, Norrlands universitetssjukhus
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Avhandlingen kommer att försvaras på engelska.

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**Abstract**
The olfactory epithelium is a dynamic tissue maintained by continuous neurogenesis throughout life. Upon injury, neurons and other olfactory cell types are regenerated through proliferation of horizontal stem cells. Some genes that regulate vitamin A metabolism are spatially expressed in the olfactory epithelium. Retinoic acid is a vitamin A derivate, a key regulator of proliferation and stem cell activity. Retinoic acid is generated and inactivated by enzymes with opposing expression patterns which create local variations in retinoic acid levels in the olfactory epithelium. The overall aim of this thesis is to elucidate functional relationships between retinoic acid metabolism and the regulation of temporal and spatial features of normal tissue homeostasis and regeneration of neurons within the olfactory epithelium.

I have studied the association between the activity-dependent retinoic acid inactivating enzyme CYP26B1 and neurogenesis. During doubled stimulation by odorants and air flow the level of CYP26B1 was further induced in olfactory sensory neurons and proliferation of progenitor/stem cells was increased. In the absence of stimuli, CYP26B1 expression was reduced and proliferation decreased. Stimuli-independent transgenic over-expression of CYP26B1 resulted in increased proliferation, which was compared to acute intranasal administration of retinoic acid that reduced the number of proliferating cells.

The region of the olfactory epithelium with low CYP26B1 and high levels of retinoic acid synthesizing enzymes had the greatest level of proliferation and regenerated efficiently after chemical induced injury. Furthermore, neurons in this region differentiated surprisingly fast. In the region with high CYP26B1 and low levels of retinoic acid synthesizing enzymes the proliferation rate was low and the regeneration after injury was incomplete. Together these results indicate that retinoic acid within the olfactory epithelial stem cell niche regulates local differences in functional neuronal diversity, neurogenesis, and generative capacity of olfactory epithelial progenitor/stem cells.

My research has revealed that ageing as well as constitutive transgenic over-expression of CYP26B1 activated dormant horizontal basal stem cells in the olfactory epithelium in an injury like manner. Continuous stem cell activation by constitutive CYP26B1 expression, repeated injuries or old age results in the appearance of epithelial patches devoid of normal olfactory epithelial cells, containing metaplastic respiratory cells. The respiratory patches either contained ciliated cells or a previously unidentified columnar secretory cell type. Moreover, we investigated whether increased proliferation of stem cells affected their regenerative potential over time. Repeated injury-repair cycles maximized the number of stem cell division, which decreased their potential to regenerate olfactory epithelial cells. Together these results indicate a premature exhaustion of the stem cell niche upon reduced levels of retinoic acid, repeated injury induced regeneration, and ageing.

**Keywords**
Activity dependent, Adult stem cells, Ageing, CYP26B1, Homeostasis, Metaplasia, Neurogenesis, Olfactory epithelium, Regeneration, Respiratory epithelium, Retinoic acid, Sensory map, Vitamin A

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