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Preface:
Epigenetic control of hippocampal stem cells

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Preface

The adult brain has the ability to structurally and functionally adapt to changes in its environment¹. Examples of these adaptations are the addition of new neurons to discrete neurogenic regions such as the hippocampal dentate gyrus (DG), termed adult hippocampal neurogenesis (AHN), and alterations in neuronal connections at synaptic sites². Both of these forms of plasticity are heavily regulated at multiple molecular levels, not all of which are fully understood.

Concerning AHN, a number of crucial events occur before newly born neurons in the adult hippocampus can functionally contribute to the pre-existing network³. Exit of the neural precursor cells (NPCs) from their quiescent state, proliferation of these activated NPCs, NPCs cell fate decisions and selection through apoptosis are some of the cellular changes that together control the neurogenic cascade, ultimately establishing a balanced level of new neurons that contribute to hippocampal plasticity and cognition³. This plethora of events can all take place within a time-span of several days, and as such require rapid yet carefully orchestrated changes in the molecular machinery of these cells⁴. This rapid coordinated action can be achieved through multiple layers of molecular control, many of which are of epigenetic nature, such as alterations in gene promoter DNA methylation and microRNA-mediated control of mRNA translation. Furthermore, specific alterations in any of these layers of molecular control, and in the corresponding cellular phenotypes, can also be induced by cell extrinsic factors such as e.g. circuit hyper-activation⁵ and alterations in glucocorticoid hormone (CORT) exposure or stress⁶.

Therefore, the overall aim of this thesis is the identification of novel epigenetic mechanisms governing phenotypical changes of NPCs and newborn neurons such as quiescence, proliferation, apoptosis and differentiation, induced by some of the aforementioned cell extrinsic factors.

Outline of this thesis

In **Chapter 1** we provide a review of the literature on the different neurogenic steps that are differentially affected by aging. We

propose a role for small non-coding RNAs in the molecular control of adult hippocampal neurogenesis, and the changes as a result of aging. In this review, an interplay between age-dependent changes in endocrine profiles, steroid receptors and microRNAs is proposed as a way to explain some of the factors that contribute to an age-related decline of cognition.

Chapter 2 reviews the literature on how stressors can lastingly alter neuronal plasticity through epigenetics, with a particular focus on microRNA. Furthermore, we propose the concept of microRNA cooperativity as a mechanism in microRNA biology.

In **Chapter 3** we describe molecular changes, with a particular focus on mitochondrial dysfunction, occurring shortly after kainic acid induced hyper-activation in the adult mouse DG. We show that kainic acid induces a particular expression pattern of microRNAs and proteins involved in mitochondrial function, and how the cooperative action of miR-124&137 control caspase3 activity through BCL2L13, thereby favoring NPC survival and differentiation.

In **Chapter 4** we describe a working protocol for structural illumination microscopy (SIM) that helps to overcome the limitation of conventional microscopy's resolution limits. This allowed the identification of subtle morphological changes in small but functionally important cellular compartments such as the head and neck of dendritic spines.

In **Chapter 5** we focus on how glucocorticoid receptor (GR) activation can induce NPC quiescence and compare a constant CORT treatment scheme commonly used in the literature with a pulsatile CORT exposure regimen. We found that deviations from basal CORT rhythmicity induce long lasting changes as demonstrated by an attenuated promoter methylation profile and concomitant altered responsiveness to a subsequent CORT exposure.

Chapter 6 describes how aging differentially influences the decay kinetics of specific NPC subsets and how GR expression in NPCs predicts the decay kinetics of different NPC subsets. Given the previously described role of the GR in regulating multiple

NPC phenotypes including quiescence, proliferation, apoptosis and differentiation, this chapter suggests the GR is critically involved in maintaining NPC populations with advancing age.

In **Chapter 7** we provide a general discussion on the topics considered in this thesis and provide future directions.

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