Transcription Factors in the Nervous System

Development, Brain Function, and Diseases

Edited by
Gerald Thiel

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Neuron of a hippocampal cell culture ten days after plating. (Courtesy of Thomas Dresbach and Nils Brose.)

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Contents

Preface

Sequencing of the human genome, "the blueprint for life" has revealed that 5% of our genes encode transcription factors [Tupler et al., 2001], demonstrating the importance of gene regulatory proteins in the organization of life. This book provides a comprehensive overview of how transcription factors operate as key regulators for the development and function of the brain. The knowledge of the molecular structure and function of these proteins are essential for understanding how the nervous system develops and how the brain works.

The phenotype of every cell, including the cells of the nervous system, is defined by the set of active genes. Cellular diversity is a remarkable feature of the nervous system structure. There are thousands of distinct neuronal and glial cell types. This complexity excludes the existence of a single "master gene" responsible for the entire gene expression program leading to the many differentiated phenotypes. Rather, the combinatorial action of numerous transcription factors is required for the development and function of the nervous system. Research in the last years in the field of molecular neurogenetics has aimed to decipher these transcription factor codes, and this book tells some of those exciting stories.

The development of the nervous system requires tightly controlled expression of transcription factors and their target genes. The identification of transcription factors that regulate this process offers a mechanism in answer to a key question of neurobiologists, how neuronal and glial fates are determined. Along with control of the formation of neurons and glia cells from uncomitted progenitor cells, transcription factors also determine the subtype of neurons, are involved in the glial subtype determination, and play a pivotal role in neuronal migration.

In the adult nervous system, synaptic activity is a major stimulus for induction of neuronal gene transcription. The induction is mediated by transcription factors that respond to synaptic activity. These proteins have been shown to be essential for long-lasting neuronal plasticity, but are also involved in neuronal survival and differentiation. Naturally, a dysfunction of transcription factors in the nervous system has severe effects, as demonstrated by transcriptional defects in Alzheimers´ and Huntington´s disease. Moreover, a molecular explanation for spinocerebellar ataxia type 1 has recently been offered, involving a complex of the mutated ataxin–1 protein with the transcription factor Gfi–1 [Tsuda et al., 2005].

The stimulating results of gene targeting experiments, in combination with new imaging techniques, should not let us forget that understanding of the functions of transcription factors always involves the identification of transcription factor target genes that are activated or repressed and are responsible for the phenotypic changes. In this context, the chromatin immunoprecipitation technique, a state-of-the-art method to examine transcription factor interaction *in vivo* with chromatin-packed genes, has increased our knowledge about the interaction of transcription factors with DNA in its natural chromosomal context. Moreover, the "ChIP on chip" technique, the combination of chromatin immunoprecipitation with microarray analysis [Kirmizis and Farnham, 2004], will certainly help to identify additional transcription factor targets in the genome.

A recent genome-scale transcription factor expression analysis identified over 300 transcription factors expressed in the brain of developing mice [Gray at al., 2004]. This book covers many but not all transcription factors involved in the development and function of the nervous system. The balance of death or survival of neurons, for instance, is regulated by p53 and the forkhead transcription factors. A very important issue in brain function are the Ca^{2+}-regulated signaling pathways that are initiated by the influx of Ca^{2+}-ions through L-type voltage-sensitive Ca^{2+}-channels and the NMDA receptors as a result of neuronal activity and depolarization. In addition to the here described transcription factors NFAT, CREB, NF-κB, MEF2 and Egr–1 the transcription factors DREAM (downstream response element antagonist modulator) and CaRF (Calcium-response factor) have to be added to the list of Ca^{2+}-responsive transcription factors, indicating that neurons have many ways to connect an increase in the intracellular calcium concentration with enhanced gene transcription. The proteins described in this book normally bind to DNA via a distinct DNA-binding domain. They can recruit other proteins, termed co-activators or co-repressors that bind via protein-protein interaction and often function via altering the chromatin structure. The discovery that transcription factors are able to recruit chromatin-modifying enzymes has revolutionized our thinking about the regulation of gene transcription [Orphanides and Reinberg, 2002] and has focussed attention on those proteins that modify the chromatin.

Many new and exciting discoveries are anticipated in the near future in the investigation of transcription factors in the nervous system. This book provides a snapshot of the current knowledge of key transcription factors that are essential for proper brain development and function. I thank my editorial partner, Dr. Andreas Sendtko at Wiley-VCH, for the initial suggestion and promotion of the project.

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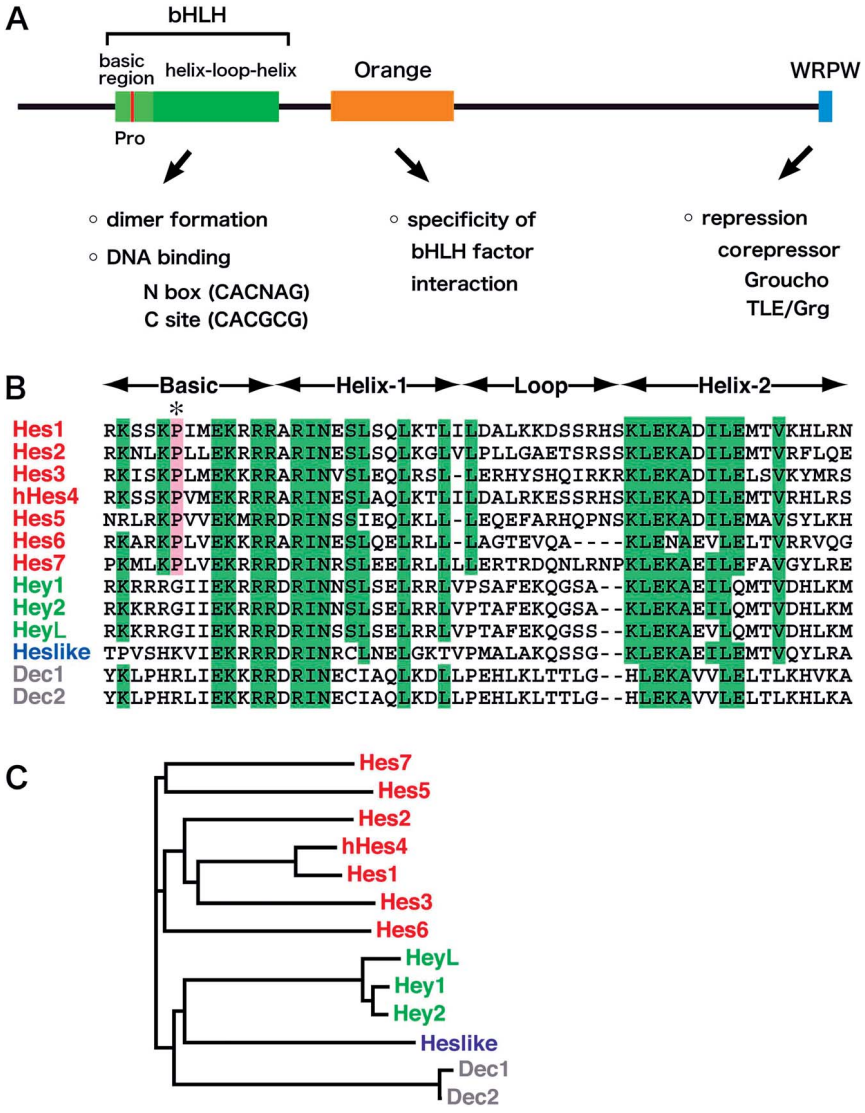

Fig. 1.2 Features of Hes bHLH factors. (A) Three conserved domains of Hes factors, the bHLH, Orange and WRPW domains. (B) Sequence alignment of the bHLH domain of Hes and related factors. Proline is conserved in the middle of the basic region of Hes factors (asterisk). (C) Phylogenetic tree of Hes and related factors. This figure also appears on page 6.

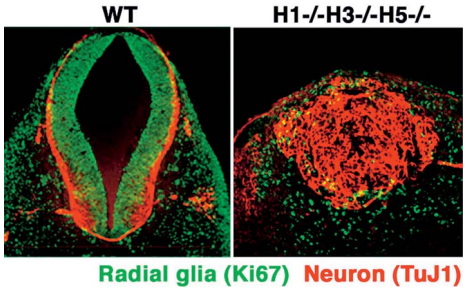

Fig. 1.7 Premature neuronal differentiation in *Hes1:Hes3:Hes5* triple knockout mice. The horizontal sections of the neural tube of mouse embryos at day 10. In the wild type, cell bodies of radial glia ($Ki67^+$) are located in the ventricular zone while neurons ($TuJ1^+$) reside in the outer layers. In the absence of *Hes1*, *Hes3* and *Hes5*, neuronal differentiation is severely accelerated. As a result, virtually all cells become neurons and neural stem cells are depleted. Adopted from Hatakeyama et al. (2004). This figure also appears on page 12.