

Meis: New friends of Pax

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The generation of neuronal diversity in the mammalian brain is a multi-step process, beginning with the regional patterning of neural stem- and progenitor cell domains, the commitment of these cells toward a general neuronal fate, followed by the selection of a particular neuronal subtype and the differentiation of postmitotic neurons. Each of these steps as well as the transitions between them require precisely controlled changes in transcriptional programs. Although a large number of transcription factors are known to regulate neurogenesis in the embryonic and adult central nervous system, the sheer number of neuronal cell types in the brain and the complexity of the cellular processes that accompany their production suggest that transcription factors act cooperatively to control individual steps in neurogenesis. In fact, combinatorial regulation by sets of transcription factors has emerged as a versatile mode to control cell fate specification. Here, I discuss our recent finding that members of the MEIS-subfamily of TALE-transcription factors, originally identified as HOX cofactors in non-neural tissues, function in concert with PAX-proteins in the regulation of cell fate specification and neuronal differentiation in the embryonic and adult brain.

TALE (3 amino acid loop extension) proteins are atypical homeodomain-containing transcription factors, which take their name from the insertion of a proline-tyrosine-proline motive between the first and second helix of the homeodomain. In animals, the TALE-homeodomain superfamily comprise 4 subclasses. Among them, the MEIS-family, consisting of

homothorax (hth) in *Drosophila melanogaster*, *unc-62* in *C. elegans* as well as *Meis1-3* and *Prep1-2* (also known as *Pknox1-2*) in vertebrates, and the PBC-family with vertebrate *Pbx1-4*, *extradenticle (exd)* and *ceh-20* in *D. melanogaster* and *C. elegans* respectively, were early on recognized as components of multimeric transcriptional complexes.¹⁻³ First insights into the biology of MEIS- and PBC-family proteins came from studies of their invertebrate orthologs *hth* and *exd*. Mutation of either gene leads to homeotic transformations without disturbing HOX gene expression itself, indicating that these transcription factors control patterning of the body axis by modulating HOX protein activity rather than by controlling HOX gene activation.⁴⁻⁸ In fact as subsequently observed in numerous physiological and pathophysiological contexts, MEIS- and PBX-proteins function as cofactors of homeodomain proteins of the HOX clusters.^{3,9,10} Direct association of PBX with HOX enables cooperative binding of both proteins to DNA binding sites in the regulatory regions of downstream genes that extend over the known consensus binding motive bound by each factor alone. As a consequence, dimerization with PBX increases the specificity and affinity of the HOX protein for distinct target sites in the genome, thereby fine-tuning the activity of a particular HOX-protein toward specific physiological needs. MEIS proteins can also associate with HOX proteins, either directly with members of the Abd-B / paralog group 9–13 or indirectly via association with PBX, and thereby add an additional level of complexity to the system.¹¹⁻¹³ In fact,

HOX, MEIS and PBX contact each other in multiple ways and through different domains within their polypeptide chains, which ultimately allows for the formation of dimeric or trimeric HOX-TALE containing complexes of varying composition on a relatively broad range of binding sites in the genome. Depending on the composition of the complex and the cellular context in which the complex forms, transcriptional co-activators or co-repressors and proteins with enzymatic activities toward DNA or histones are then recruited, eventually leading to transcriptional activation or

-repression at the respective gene loci.^{2,3}

MEIS-PAX Co-Expression in the Vertebrate Brain

Yet, MEIS and PBX expression is not restricted to HOX-expressing cells and tissues. In fact, whereas PBX and PREP are rather broadly expressed in vertebrate embryos, MEIS expression is spatially and temporally highly dynamic and includes many regions in the embryo that lie outside of the classic HOX gene expression domains. This is particularly evident in

the embryonic neural tube, where the anterior border of HOX gene expression coincides with the rhombomere (r) 1/2 boundary, whereas Meis1 and Meis2 expression extends into the mes-, di- and telencephalon (Fig. 1A).¹⁴ Both Meis-family members are, for instance, highly expressed in the embryonic neural retina and loss-of-function studies performed in fish, chick and mice showed that both genes control progenitor cell proliferation in the early eye anlage and the specification of these cells toward a retinal cell fate.¹⁵⁻¹⁹ Strong Meis2 expression further marks the dorsal mesencephalic vesicle, the anlage of the optic tectum, and Meis2 is both necessary and sufficient for tectum development.²⁰ Meis1 and Meis2 also participate in the developmental regulation of striatal neuron- and cortical interneuron generation, in part through direct control over expression of *Dlx* (distalless-) homeodomain proteins.²¹ Other examples for apparent HOX-independent functions of MEIS-family proteins in the central nervous system (CNS) include the production of hormones that are important for reproductive functions in the hypothalamus and pituitary gland of the adult brain.^{22,23} In each of these cases, MEIS protein expression does not correlate with HOX expression, suggesting that here MEIS may partner with other proteins. Indeed, MEIS-family members can directly interact and cooperate with non-HOX homeodomain proteins, such as PDX1 in the embryonic pancreas, or with myogenic bHLH proteins during skeletal muscle differentiation.^{24,25} In the embryonic and adult anterior brain, paired-type homeodomain (PAX) transcription factors emerge as major TALE interacting partners.

Similar to HOX proteins, PAX proteins have critical functions in animal development and oncogenesis and control biological processes as diverse as cell proliferation, compartmentalization and pattern formation, lineage restriction, execution of differentiation programs, or cell migration.²⁶ The PAX protein family comprises 9 members, all of which but PAX1 and PAX9 are expressed in the neural tube. In a manner quite similar to HOX genes, members of the PAX2/5/8, PAX3/7 and PAX4/6 subgroups are

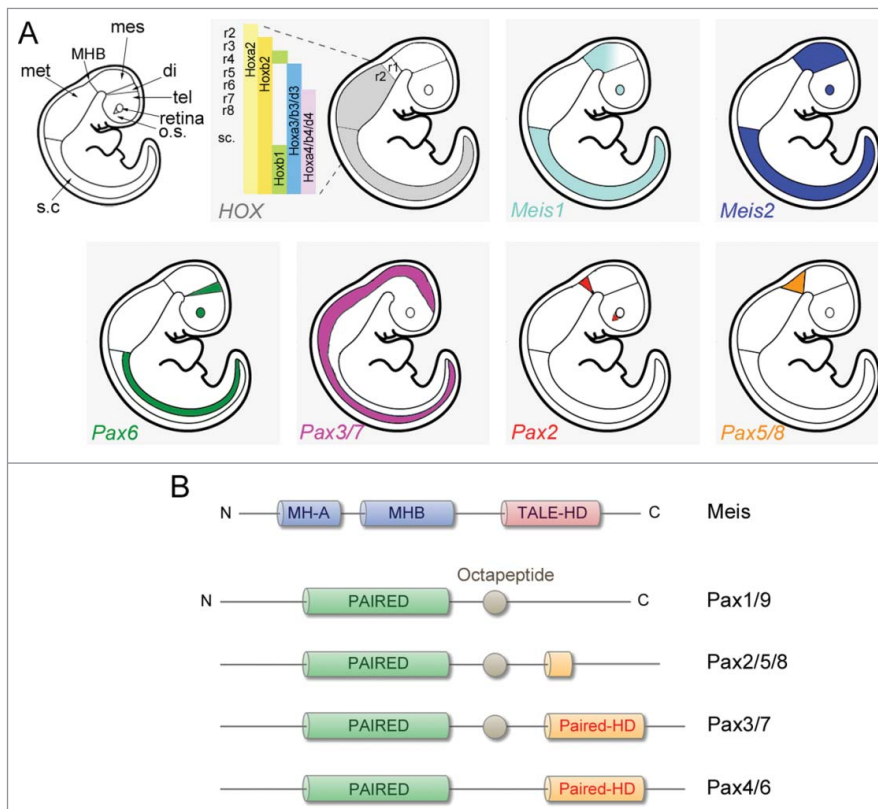


Figure 1. (A) Overlapping expression of Meis1 and Meis2 in relation to expression of HOX genes and members of the Pax4/6, Pax3/7 and Pax2/5/8 families in the mouse neural tube. Schematic views of mouse embryos at E11 are shown; the expression domains of the respective HOX genes is given without indicating any rhombomere-specific differences in gene expression levels. In the CNS anterior of the rhombomere 1–2 boundary, Meis1 and Meis2 are co-expressed with Pax3/7 in the mesencephalon, with Pax2/5/8 in the rostral mid-hindbrain boundary region and with Pax6 in the eye anlage. [di: diencephalic vesicle; mes: mesencephalic vesicle; met: metencephalic vesicle; o. s.: optic stalk; r: rhombomere; s.c.: spinal cord; tel: telencephalic vesicle.] **(B)** Schematic drawing of the major protein domains found in Meis-family members and different PAX proteins. Protein domains are not drawn to scale. MEIS family proteins contact members of the PBC-family of TALE-homeodomain proteins through MH-B, the C-terminal half of the bipartite MEIS-homology domain. [MH-A / MH-B: MEIS-homology domain A / B; TALE-HD: 3 amino acid loop extension homeodomain; paired: paired-domain; HD: homeodomain.]

expressed in nested and overlapping domains in the developing CNS (Fig. 1A). Unlike HOX, however, their expression extends into the anterior most parts of the neural tube: Pax6 transcripts are present in the telecephalon, diencephalon and neural retina, Pax3/7 transcripts extend through the spinal cord into the mesencephalon and posterior diencephalon and Pax2/5/8 expression surround the mid-hindbrain boundary (MHB).²⁷ Still, although expression of individual Pax genes demarcates defined territories within the developing CNS, these domains rarely correspond to a single functional unit that gives rise to an anatomically and functionally defined brain structure. PAX-protein function thus needs to be fine-tuned to fulfill specific physiological requirements. One way by which this may be achieved is through cooperation with other transcriptional co-regulators.

MEIS-PAX Cooperation in the Regulation of Neurogenic Programs

A first example for how the activity of broadly expressed PAX proteins may be tailored to particular developmental programs is evident in the development of the optic tectum, an important center for sensory information processing that develops from the dorsal mesencephalic vesicle. Pax3- and Pax7-expression is not specific for the tectal anlage, yet either gene can trigger development of ectopic tectal structures when misexpressed.²⁸ Meis2 expression, by contrast, faithfully demarcates the future optic tectum at mid-to-late somite stages and is pivotal for tectal development.²⁰ As we recently reported, MEIS2 directly binds PAX3 and PAX7 in the embryonic midbrain.²⁹ Association with MEIS2 may therefore confer tectal specificity to the more widely expressed PAX3 and PAX7. Hence in this developmental context, spatially and temporally restricted complex formation with a MEIS-cofactor may modulate the developmental function of the otherwise broadly expressed PAX partner. A second example for MEIS-PAX cooperation concerns the adult subventricular zone (SVZ) / olfactory bulb neurogenic niche. Here, adult neural stem cells

residing in the lateral walls of the SVZ generate immediate progenitor cells, most of which mature into young neurons, termed neuroblasts. Neuroblasts leave the SVZ, migrate along the rostral migratory stream (RMS) toward the olfactory bulb, where they disperse radially, differentiate into a limited number of neuronal cell types and integrate into existing neuronal networks.^{30,31} The paired-type transcription factor PAX6 plays a dual role in this neurogenic system, being crucial for the general neuronal fate specification of adult progenitors in the SVZ and the subsequent differentiation toward the dopaminergic neuro-transmitter phenotype of some of the SVZ-derived progeny.³²⁻³⁴ MEIS2 is co-expressed and forms heteromeric complexes with PAX6 in neuroblasts of the SVZ and RMS as well as in dopaminergic neurons of the olfactory bulb.³⁵ MEIS2 cooperation with PAX6 is an essential requirement for the pro-neurogenic function of PAX6 in adult SVZ neurogenesis, as siRNA-mediated knock-down of MEIS2 abrogated the neuron-inducing activity normally observed after PAX6 overexpression in adult SVZ progenitors. In addition, MEIS2 and PAX6 bind to closely located or partially overlapping sites in the promoter/enhancer and cooperate in the transcriptional activation of some genes that are relevant for neuronal fate specification and dopaminergic differentiation, such as doublecortin and tyrosine hydroxylase.³⁵ MEIS2 and PAX6 containing protein complexes are also present in the embryonic vertebrate neural retina, another site of extensive co-expression of both proteins.^{17,35} Of note, protein association of the respective ortholog proteins of *D. melanogaster*, *hth* and *eyeless*, also occurs, at least when tested *in vitro*.³⁶ MEIS-family proteins thus emerge as evolutionary conserved cofactors of PAX-proteins in non-HOX expressing cells and tissues.

MEIS-PAX Protein Interaction

The protein domains involved in this interaction are just beginning to be characterized. *In vitro* binding studies identified C-terminal sequences in MEIS2 to be essential for complex formation with PAX3 and PAX7.^{29,35} This is reminiscent

of the Abd-B paralog group HOX protein binding to MEIS, which also preferentially occurs at the C-terminal portion of MEIS^{11,12}. Although the precise domains in PAX3/6/7 that mediate binding to MEIS2 have not yet been mapped, the observation that 3 different splice variants of PAX6, namely the canonical and the PAX6(5a) isoforms, which contain paired- and homeodomain, as well as a paired-less isoform, can all dimerize with MEIS2 implicate that sequences in the homeodomain of PAX engage in complex formation. The paired-type homeodomain, unlike the paired-domain, is only partially conserved within the PAX protein family. While PAX3/7 and PAX4/6 possess a full homeodomain containing the 3 helices characteristic of this motive, the homeodomain of PAX2/5/8 is truncated to comprise only the first helix, and PAX1/9 lack the homeodomain all together (Fig. 1B). Pull-down experiments with recombinant proteins indicated that MEIS2 is formally capable of binding to PAX2/5/8, at least in solution, although we did not observe *in vivo* association of MEIS2 with any of these 3 PAX proteins in cells of the embryonic MHB or in a panel of cell lines (K. Jost and D. Schulte, unpublished results). Nevertheless, the observed association of MEIS2 with recombinant PAX2/5/8 suggests that the N-terminal helix 1 of the paired-type homeodomain mediates contact between PAX and the MEIS partner protein. This model agrees well with the overall structure of PAX proteins, as it is the paired-domain that serves as primary DNA-binding motive in all PAX family members, leaving the homeodomain available for protein-protein interaction. Yet, MEIS cofactor binding to helix 1 of the paired-type homeodomain is also possible when PAX binds DNA through its homeodomain, as helix 1 faces away from the DNA in the crystal structure of the isolated paired-type homeodomain bound to DNA and is thus free to engage in protein-protein interaction.³⁷ Direct association of the paired-domain with the paired-type homeodomain was in fact reported for vertebrate and invertebrate PAX family members and can occur both, intramolecularly and intermolecularly.^{38,39} In agreement with this notion, several structurally diverse

homeodomains, including those of the TALE-family proteins PBX1 and PREP1 co-precipitate with PAX6 when tested as GST-fusion proteins *in vitro*.³⁹

Concluding Remarks

What purpose may PAX heterodimerization with TALE-proteins serve? Likely a very similar one as that already described for HOX-TALE protein interaction. On one hand, cooperative DNA-binding may increase the target-selectivity of the PAX protein, allowing the complex to read additional sequences surrounding the core DNA-binding site. Thereby different sets of downstream targets can be activated by a single PAX protein in different subdomains of its overall expression territory. On the other hand, complex formation may aid the recruitment of additional cofactors, which themselves possess no DNA-binding activity or have only very limited sequence specificity. Thereby, altering the composition of the PAX-TALE protein complex may result in the differential recruitment of transcriptional co-activators or co-repressors. In this context it is important to point out that MEIS family proteins not only recruit the histone-acetyl transferase CBP, a transcriptional co-activator, and active RNApolIII to the regulatory regions of downstream genes, but also displace co-repressors like histone deacetylases (HDACs) or members of the Groucho/Tle family from pre-existing transcriptional complexes.^{40,41} Hence, TALE-proteins can modulate the controlled assembly or disassembly of transcription regulator complexes to fine-tune gene expression.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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