

5-7. The Integrity of the Retinal Pigment Epithelium ©

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OTX2 activates the molecular network underlying retina pigment epithelium differentiation.

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The retina pigment epithelium (RPE) is fundamental for the development and function of the vertebrate eye. Molecularly, the presumptive RPE can be identified by the early expression of two transcription factors, Mitf and Otx. In mice deficient for either gene, RPE development is impaired with loss of melanogenic gene expression, raising the possibility that in the eye OTX proteins operate either in a feedback loop or in cooperation with MITF for the control of RPE-specific gene expression. Here we show that Otx2 induces a pigmented phenotype when overexpressed in avian neural retina cells. In addition, OTX2 binds specifically to a bicoid motif present in the promoter regions of three Mitf target genes, QNR71, TRP-1, and tyrosinase, leading to their transactivation. OTX2 and MITF co-localize in the nuclei of RPE cells and physically interact, and their co-expression results in a cooperative activation of QNR71 and tyrosinase promoters. Collectively, these data suggest that both transcription factors operate at the same hierarchical level to establish the identity of the RPE.

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Specific Pax-6/microphthalmia transcription factor interactions involve their DNA-binding domains and inhibit transcriptional properties of both proteins.

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Pax-6 and microphthalmia transcription factor (Mitf) are required for proper eye development. Pax-6, expressed in both the neuroretina and pigmented retina, has two DNA-binding domains: the paired domain and the homeodomain. Mice homozygous for Pax-6 mutations are anophthalmic. Mitf, a basic helix-loop-helix leucine zipper (b-HLH-LZ) transcription factor associated with the onset and maintenance of pigmentation, identifies the retinal pigmented epithelium during eye development. Loss of Mitf function results in the formation of an ectopic neuroretina at the expense of the dorsal retinal pigmented epithelium. In the present study, we investigated the interaction between Pax-6 and Mitf. In transient transfection-expression experiments, we found that transactivating effects of Pax-6 and Mitf on their respective target promoters were strongly inhibited by co-transfection of both transcription factors. This repression was due to direct protein/protein interactions involving both Pax-6 DNA-binding domains and the Mitf b-HLH-LZ domain. These results suggest that Pax-6/Mitf interactions may be critical for retinal pigmented epithelium development.

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Functional analysis of microphthalmia-associated transcription factor in pigment cell-specific transcription of the human tyrosinase family genes.

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Tyrosinase, tyrosinase-related protein-1 (TRP-1), and TRP-2 are the enzymes involved in melanin biosynthesis and are preferentially expressed in pigment cells. Their human gene promoters share the 11-base pair M box containing a CATGTG motif, which was shown here to be bound in vitro by microphthalmia-associated transcription factor (MITF). Transient cotransfection analysis showed that MITF overexpression increased the expression of a reporter gene under the control of the human tyrosinase or TRP-1 gene promoter but not the TRP-2 promoter. The promoter activation caused by MITF is dependent on each CATGTG motif of the distal enhancer element, the M box, and the initiator E box of the tyrosinase gene and the TRP-1 M box. Furthermore, a truncated MITF lacking the carboxyl-terminal 125 amino acid residues transactivated the tyrosinase promoter less efficiently than did MITF, suggesting that MITF's carboxyl terminus contains a transcriptional activation domain, but unexpectedly such a truncated MITF remarkably transactivated the TRP-2 gene promoter. These results suggest that MITF is sufficient to direct pigment cell-specific transcription of the tyrosinase and TRP-1 genes but not the TRP-2 gene.

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The microphthalmia transcription factor (Mitf) controls expression of the ocular albinism type 1 gene: link between melanin synthesis and melanosome biogenesis.

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Melanogenesis is the process that regulates skin and eye pigmentation. Albinism, a genetic disease causing pigmentation defects and visual disorders, is caused by mutations in genes controlling either melanin synthesis or melanosome biogenesis. Here we show that a common transcriptional control regulates both of these processes. We performed an analysis of the regulatory region of Oa1, the murine homolog of the gene that is mutated in the X-linked form of ocular albinism, as Oa1's function affects melanosome biogenesis. We demonstrated that Oa1 is a target of Mitf and that this regulatory mechanism is conserved in the human gene. Tissue-specific control of Oa1 transcription lies within a region of 617 bp that contains the E-box bound by Mitf. Finally, we took advantage of a virus-based system to assess tissue specificity *in vivo*. To this end, a small fragment of the Oa1 promoter was cloned in front of a reporter gene in an adeno-associated virus. After we injected this virus into the subretinal space, we observed reporter gene expression specifically in the retinal pigment epithelium, confirming the cell-specific expression of the Oa1 promoter in the eye. The results obtained with this viral system are a preamble to the development of new gene delivery approaches for the treatment of retinal pigment epithelium defects.

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