CDB SEMINAR

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Monday, June 2, 2008

16:00~17:00 C1F CDB Auditorium

The Role of Transcription Factor Six3 in Forebrain Development

Summary

Members of the Six3 family of transcription factors function during eye and forebrain development. In humans, mutations in Six3 can cause Holoprosencephaly (HPE), a congenital malformation of the forebrain. In mice and medaka, loss of Six3 function results in deficiency of eyes and forebrain tissue, defects that are already evident during early somitogenesis. Whereas Six3 expression role in eye development is well established, its additional roles are less well understood.

By TILLING we isolated a nonsense mutation in *six3b*, one of three zebrafish *six3*-related genes (*six3a*, *six3b* and *six7*). Embryos homozygous for this mutation, or wild-type embryos in which *six7* function was inhibited using morpholino oligonucleotides, appeared normal. However, inhibition of *six7* function in *six3b* mutant embryos resulted in strong reduction or lack of eyes, due to impaired proliferation of prospective eye tissue during early somitogenesis. I will discuss our studies of these Six3 deficient embryos that uncover a new role of Six3 in left-right brain asymmetry.

I will also present our ongoing studies in zebrafish on the role of Six3 in dorsoventral patterning of the telencephalon. We find that the transcription factor Six3 is required for the generation of ventral telencephalic cell fates, and reduced Six3 function results in expansion of dorsal telencephalic cell fates at the expense of ventral ones. Similar phenotypes have been observed when Hedgehog (Hh) pathway activity is lost, and our studies reveal complex interactions between Six3 and Hh signaling in generation of ventral telencephalic cell fates.

Defects in Six3 function and Hh signaling have been associated with HPE, the most common human forebrain malformation. I will present results of our collaborative work with the laboratory of Dr. Guillermo Oliver (St Jude Children Hospital, Memphis, TN). Using luciferase and zebrafish-based assays, we show that HPE-associated Six3-mutant proteins function as hypomorphs. Generated mouse models of Six3-promoted HPE revealed that *Six3* haploinsufficiency causes HPE in a strain-specific manner. Further, *Shh* and *Six3* regulate each other in the rostral diencephalon ventral midline. In mice displaying *Six3*-related HPE, this mutual regulation is disrupted, resulting in abnormal apoptosis in the telencephalon, and ultimately HPE.

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