Scientists show Six3 gene essential for retinal development

September 20 2010

New research led by St. Jude Children's Research Hospital investigators adds to evidence that the Six3 gene functions like a doorman in the developing brain and visual system, safeguarding the future retina by keeping the region where the eye is forming free of a signaling protein capable of disrupting the process.

The findings underscore the pivotal role Six3 plays in the developing nervous system as a key regulator of the Wnt family of signaling proteins and expands on earlier work from the laboratory of Guillermo Oliver, Ph.D., member of the St. Jude Department of Genetics. Oliver is senior author of research being published in the September 20 advance online edition of the Journal of Clinical Investigation.

"Our work suggests that Six3 evolved as a direct regulator of different members of the critical Wnt signaling pathway," Oliver said. The family of Wnt proteins influences the fate of different cell types by binding to receptors on the cell surface.

"A few years ago we determined that very early in development Six3 is required for repressing one member of the Wnt family, a gene called Wnt1, to allow proper development of the forebrain. With this new research, we show that a few hours later Six3 is called on again, this time to repress a different Wnt family member, Wnt8b, so formation of the retina can begin."

The retina is the multilayered structure lining the back of the eye. It

includes light-sensing cells and the lens, both required for vision. Unlike some animals, humans cannot make new cells to replace those in the retina that are lost to age or illnesses like macular degeneration or glaucoma.

Oliver said realizing the potential of stem cells or other cell-based replacement therapies to correct vision or treat blindness requires a more detailed understanding of the genes and molecular mechanisms involved in normal retinal development.

In this study, investigators showed that when Six3 was switched off at a key point in mouse embryonic development the retina did not form. The association between Six3 and the retina was further strengthened when researchers found that the retinal pigmented epithelium, a cell layer outside the retina that normally nourished the retina cells, was largely unaffected by the gene's absence.

The scientists went on to directly link the lack of a retina to the abnormal expansion of Wnt8b expression into a region where the forebrain normally develops. That region of the developing anterior brain is where cells undergo a process called specification, followed by differentiation to become the highly specialized cells of the retina and eye.

Further analysis showed that the Six3 protein binds directly to regulatory regions of Wnt8b. "Our results conclusively demonstrated that for retinal formation to begin, the embryonic forebrain must be Wnt8b free. So the first step in the process is for Six3 to bind to and repress Wnt8b so its expression remains restricted inside its normal boundaries," Oliver explained. "Our findings provide a molecular framework to the developmental program leading to retina differentiation. The work may also be relevant for devising novel strategies aimed at characterizing and eventually treating different abnormalities in eye formation.

Researchers are now working to understand the pathway activated when Six3 blocks Wnt8b. "We are focused on a very narrow window of time when specification takes place. We need to identify the critical genes that appear in that timeframe," Oliver said.

Provided by St. Jude Children's Research Hospital