New Target Identified for Potential Treatment of Retinopathy in Premature Babies

May 5, 2009

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Results of a study in mice by researchers at the University of California, San Diego strongly suggest that the protein kinase JNK1 plays a key role in the development of retinopathy in premature infants. Their findings, reported online the week of May 4-9 in advance of print in the *P* r *oceedings of the National Academy of Sciences (PNAS),* may lead to an effective way to treat the leading cause of childhood blindness in industrialized countries using JNK1 inhibitors.

Retinopathy, damage to the thin layer of cells at the back of the eyeball where light is converted into neural signals sent to the brain, is often caused by the growth of abnormal blood vessels and can lead to loss of vision. Retinopathy of prematurity (ROP) affects infants exposed to high oxygen concentrations as a part of the essential treatment they receive to allow their lungs and other organs to develop after premature birth.

"Paradoxically, it isn't high oxygen levels that damage the retina," explained first author Monica Guma, MD, PhD, of the departments of pharmacology and pathology at the UC San Diego School of Medicine. "Rather, the premature retina is first exposed to a high-oxygen environment and becomes accustomed to it. When the infant is more mature and is returned to a 'normal' oxygen environment, the retina reacts to this hypoxia - or decrease in oxygen availability - as a stress."

The JNK group of protein kinases - discovered in the lab of principal investigator Michael Karin in 1993 - responds to the stress of hypoxia by inducing the over-production of vascular endothelial growth factor (VEGF), which promotes the growth of blood cells. In ROP, as well as in diabetic retinopathy or age-related macular degeneration, this results in vision loss due to aberrant angiogenesis, or unregulated growth of new capillaries from pre-existing blood vessels.

Using a mouse model of ROP, the UC San Diego researchers showed that mice lacking JNK1 exhibited lower levels of VEGF in the retina, so angiogenesis and normal retinal function were barely disrupted.

"We found that injection of a highly specific and cell-permeable JNK peptide inhibitor, D-JNKi, into the mouse retina decreased VEGF expression, thus reducing the abnormal growth of blood vessels that can lead to loss of vision," said UC San Diego investigator Jordi Rius, PhD.

The researchers explained that using some of the currently available anti-VEGF drugs could be a concern in newborn infants, since the growth factor is also essential for neuronal development. Therefore, development of future therapies would need to keep suppression of VEGF in balance.

"Using the JNK1 inhibitor, we were able to decrease VEGF production in half," said Guma. "Cells were still able to secrete some VEGF, but not enough to induce overgrowth of blood vessels in the retina."

This study showed that D-JNKi reduced abnormal VEGF expression and abnormal formation of blood vessels in the mouse retina, without retinal damage or impaired retinal development - thus identifying an important new

pharmacological target for treating ROP in humans. Such therapies are becoming more critical because of the increased survival rate of premature infants and because the prevailing current treatment, laser ablation of the retina, is destructive and only partially effective.

One Australian hospital reported ROP in nearly 50 percent of infants born between 27 and 28 weeks gestation; this level rose to 65 percent in infants born at 23 to 26 weeks gestation (102 out of 157 babies examined for the disease.) This retinopathy induces irreversible damage to the immature retinal vessels, which often regresses but which can lead to vision loss if the abnormal blood vessel formation leads to detachment of the retina.

This study was conducted in the Laboratory of Gene Regulation and Signal Transduction at UC San Diego, under the direction of Michael Karin, PhD, Distinguished Professor of Pharmacology and Pathology and American Cancer Society Research Professor.

Additional contributors include Karen X. Duong-Polk and James D. Lindsey of UC San Diego's Hamilton Glaucoma Center, and Gabriel G. Haddad, chair of the UCSD department of pediatrics.

Support for this study was provided in part by grants from the National Institutes of Health, and by postdoctoral fellowships from the Spanish Ministry of Education and Science and support from the Spanish Society of Rheumatology. Karin, Guma and Rius have filed a patent application regarding the use of JNK inhibitors in the treatment of retinopathies.

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