

Researchers identify molecular 'switch' that could save very young lives

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A team of researchers at Children's Hospital of Pittsburgh of UPMC have identified a molecular "switch" that, when blocked, may help reverse necrotizing enterocolitis (NEC), a leading cause of death in premature infants.

Results of the research were presented by principal investigator David J. Hackam, MD, PhD, a pediatric surgeon and scientist at Children's Hospital, this weekend at the 4th Annual Meeting of the American Society for Cell Biology.

NEC is a severe inflammatory disease of the intestine that occurs in about 5 percent of premature births and can be fatal in as many as half of those cases. In extreme cases, NEC leads to perforation of the intestine, a condition that can be fatal if not treated with emergency surgery. NEC is increasing in frequency due to the increased survival of premature infants, according to Dr. Hackam.

Working in the laboratory with an animal model of NEC, Dr. Hackam's team found that when molecular receptor known as Toll-like receptor-4 (TLR4) was blocked, they enabled the repair of damaged intestinal tissue that is the hallmark of NEC.

"This Toll-like receptor is a defense mechanism that normally switches on the intestine's immune response. But in some premature infants, stresses like oxygen deprivation and toxins caused by underdeveloped lungs stimulate the overproduction of TLR4. Like an unstoppable alarm,

this signaling eventually can lead to cell death and prevent enterocytes from migrating to close wounds in the intestine, which can result in intestinal failure,” Dr. Hackam said. “By interfering with the production of another molecule associated with TLR4 known as focal adhesion kinase (FAK), we were able to silence the TLR4 alarm in intestinal cells.”

Blocking the TLR4 signal allowed enterocytes to once again migrate and heal the damaged intestinal tissue. Dr. Hackam’s team is continuing to research the development of treatment strategies that would block the TLR4 switch by influencing its interaction with FAK. Potentially, these novel treatments could be administered as a component of oral feeds for infants, Dr. Hackam said.

Source: Children's Hospital of Pittsburgh

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