

# Leading cause of death in 'preemies' might be controlled by resetting a molecular switch

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Blocking signals from a key molecular receptor that normally switches on the intestine's immune response but instead becomes too intense in the presence of stress and toxins may help reverse necrotizing enterocolitis (NEC), a leading cause of death in premature newborns, according to scientists at the American Society for Cell Biology 47th annual meeting.

David J. Hackam and his laboratory team at the Children's Hospital of Pittsburgh report that neonatal mice with inactivating mutations in the Toll-like receptor 4 (TLR4) are protected from NEC. It's a case of defenders becoming unwitting attackers, says Hackam.

"Toll-like receptors" are key players in the innate immune system. Protruding from enterocytes that form the innermost barrier-like layer of the small and large intestines, TLR4 receptors are primed to recognize pathogenic bacteria and sound the alarm.

But Hackam's group found that the stresses of oxygen deprivation and bombardment by bacterial toxins, conditions that can occur in premature infants with underdeveloped lungs, stimulate too much production of TLR4. Like an unstoppable alarm, the increased numbers of TLR4 blare out signals that eventually tip the cells into cellular suicide. They also stop enterocytes from migrating to close wounds in the intestines.

These events, which do not occur in the TLR4-deficient mice, allow NEC to spread as the fragile lining of the gut gives way, releasing a flood of pathogens into the bloodstream. Even with modern advances in neonatal care, NEC affects 20 percent of premature babies and is fatal in nearly half of all cases, according to Hackam.

Hackam's group discovered another way to switch off the molecular alarm in mice with NEC by interfering with production of a focal adhesion kinase (FAK) that the researchers found associated with TLR4. By shutting down FAK with small interfering RNA, the TLR4 siren was silenced. Under these conditions, the researchers watched enterocytes regain the ability to migrate, a property important for healing the damaged tissue.

Says Hackam, "We hope to develop treatment strategies that allow us to block the TLR4 switch from working?perhaps by influencing its interaction with FAK?using novel treatments that could be administered as a component of oral feeds."

Source: American Society for Cell Biology

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