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Study uncovers new explanation for infection susceptibility in newborns

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Cells that allow helpful bacteria to safely colonize the intestines of newborn infants also suppress their immune systems to make them more vulnerable to infections, according to new research in *Nature*.

Published online Nov. 6, the study could prompt a major shift in how medicine views the threat of neonatal infections – and how researchers go about looking for new strategies to stop it, said scientists at Cincinnati Children's Hospital Medical Center who conducted the research. Leading up to this study, the prevailing view has been that newborn infants are susceptible to infection because their immune system cells are immature or underdeveloped.

"The first few days after birth represent a critical developmental period when a baby's immune system must adapt to many new stimulants. This includes environmental microbes that are not present in the womb, but immediately colonize tissues such as the intestine and skin," said Sing Sing Way, MD, senior investigator and a physician in the Division of Infectious Diseases at Cincinnati Children's. "Our findings fundamentally change how we look at neonatal susceptibility to infection by suggesting it is caused by active immune suppression during this developmental period, as opposed to the immaturity of immune cells."

The suppressive cells in this case are CD71+ precursors of mature red blood cells. The researchers found CD71+ precursor cells are enriched in newborn mice (and in human umbilical cord blood) to prevent an over reactive immune response as infants adapt to their new microbe-filled

world. CD71+ cells express an enzyme called arginase-2 that is essential to suppress immune cells. Researchers said this process plays a vital role in infants' developing intestines by preventing an onslaught of inflammation in response to colonizing bacteria that help digestion and related functions.

Researchers used a series of laboratory tests in human blood cells and mouse models to show temporary immune suppression in newborns extends beyond the intestines to also affect other parts of the body. Although newborn vulnerability to infection is well known, Way and his colleagues began their study because earlier research has shown the extent of compromised immunity in infant mice varies significantly depending on specific experimental conditions. This led the authors to hypothesize that there must be a better explanation for compromised immunity in neonates besides pointing to immature immune cells.

The scientists transferred adult immune system cells in bulk from adult mice into newborn mice to see if this would boost neonatal immunity during exposure to infection. Instead of enhancing immunity, researchers said the production of protective immune system cytokines in the adult cells remained blunted in the newborn mice. Similar results were observed when adult immune cells were mixed with neonatal cells in laboratory cultures.

In a complementary experiment, researchers transferred newborn immune system cells into adult mice exposed to infection. In the adult mice, the neonatal immune cells produced the protective cytokine TNF-alpha, which helps ramp up the immune system's protective response against infection.

Way and his colleagues said the benefits of CD71+ immune suppression to allow healthy bacterial colonization of intestines are essential, and this outweighs the threat of systemic infant infections. But the researchers

stressed the importance of follow up studies to develop new strategies for protecting newborns from systemic infections. The goal would be to offer this protection while still allowing CD71+ cells to do their job in helping develop healthy intestines.

One strategy being explored by investigators in their ongoing research is possible modulation or control of immune suppression by CD71+ cells. The authors were careful to emphasize that far more follow up study is needed before direct application of their findings to human infants.

More information: dx.doi.org/10.1038/nature12675

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