Team shows how childhood viral infection leads to increased risk for allergic asthma as adult

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(Medical Xpress)—Researchers in the Division of Pulmonary, Allergy and Critical Care Medicine at the University of Pittsburgh School of Medicine have shown in an animal model that a common childhood virus disables the normal immune tolerance transferred from the mother to child through breast milk, leading to increased susceptibility for allergic asthma later in life. Their findings were reported in the online version of *Nature Medicine*.

Early in life, regulatory T cells, or Treg, play an important role in the establishment of immune tolerance, which can prevent the immune system from triggering an allergic reaction to antigens such as pollen and dust, explained senior authors Anuradha Ray, Ph.D., and Prabir Ray, Ph.D., both professors of medicine and immunology, Pitt School of Medicine.

"We know that recurrent infections by respiratory syncytial virus (RSV) that require hospitalization in early life increase the risk for asthma in adult life," noted Dr. Anuradha Ray. "But, until now, it hasn't been clear why this happens."

Allergens and biologic molecules that suppress the immune system are transferred from mothers to infants via breast milk, which induces protective regulatory Tregs in the infants to help block the development of allergic diseases later in life, such as asthma.

"So we went from 'bedside to bench' to better understand the immunological impact of early, repeated RSV infection and to see if it affects Tregs," explained lead author, Nandini Krishnamoorthy, Ph.D., postdoctoral associate, Division of Pulmonary, Allergy and Critical Care Medicine, Pitt School of Medicine.

First, the research team fed newborn mice with breast milk from their mothers, who in turn had been exposed to the egg-white protein ovalbumin every other day for 10 days, to see if the babies would become tolerant to the protein. The newborn mice were weaned after 21 days, and then some of them were infected with RSV several times for the next three weeks to mimic human infection. In the sixth week, the young mice were challenged with ovalbumin.

Mice that had not been infected with RSV did not have an immune response to the ovalbumin, to which they had been exposed through their mothers' milk, indicating they had developed tolerance for it. Those that had been repeatedly infected with RSV, however, had increased immune cell infiltration in their airways and increased mucus production when challenged with the egg protein.

In another experiment, Treg cells were isolated from either the RSV-infected or uninfected mice and transferred into ovalbumin-exposed animals, which were then challenged with the protein. The cells from the uninfected mice, but not those from the infected ones, potently prevented airway inflammation and other markers of allergic reaction, the researchers found. They also noted that RSV promoted the production of regulatory proteins called cytokines that foster inflammation, as well as triggered other changes in the cellular microenvironment altering the function of Treg cells.

"So without the suppressive function of the Tregs, the mice developed inflammatory immune responses to the ovalbumin allergen and developed asthma-like symptoms," said Dr. Prabir Ray, who initiated the study. "If the memory Tregs are crippled early in life, an important protective mechanism against allergens is lost, which

increases susceptibility to asthma."

"These studies suggest a link between early RSV viral infection and the development of adult allergy via direct effects of the virus infection on the very important regulatory T cell," said Mark T. Gladwin, M.D., chief of the Division of Pulmonary, Allergy and Critical Care Medicine, Pitt School of Medicine and UPMC. "From a clinical standpoint, efforts to control RSV infection or to enhance activation of regulatory T cells with breastfeeding and other strategies appear to be a promising approach to reducing our current asthma and allergy epidemic."

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