Researchers Reveal Lung's Unique Innate Immune System

April 18, 2006 |

For the first time, scientists have documented an organ-specific innate immune system. In research published in the April 18 edition of the journal *Immunity*, scientists at the University of California, San Diego (UCSD) School of Medicine outline the unique mechanism by which the lung shapes its defensive strategies against microbial invasion.

"This innate immune response is specific to the lung, and was probably designed to minimize collateral damage to lung tissue caused by unchecked inflammation," said Eyal Raz, M.D., Professor of Medicine at UCSD School of Medicine.

The body's respiratory tract is constantly exposed to inhaled particles or microorganisms. The alveola – tiny air sacs in the lung where exchanges of gases between the respiratory and circulatory systems takes place – are protected from invading microbes by the alveolar macrophage.

Macrophages are white blood cells involved in the inflammatory response throughout the body, cells normally on the alert for invaders to kill. Alveolar macrophages are unique among macrophages in the body, because their activation is inhibited by TGFb, a compound expressed in the lung by epithelial cells.

"Because the microenvironment of the alveola is a delicate one, it would be damaged if the macrophage immune system was in a constant battle-ready status," said Raz. "This could readily lead to the type of inflammation we see in autoimmune diseases of the lung such as asthma."

Therefore, the alveola possess a complex immune system in which the macrophage is repressed in its steady state, activated when called upon to fight invading microorganisms, and then re-repressed, in a circuit that is unique to this microenvironment.

"Dissecting this immune mechanism provides us with the knowledge of how we might prolong the activation status of alveolar macrophages. This knowledge could prove to be essential in combating any novel microbial agents that could infect the lower airways, such as a new flu strain or bioterrorist agents," said Raz.

The researchers' data outlines a complex circuit in which the alveolar macrophages circumvent the inhibition by TGFb for brief period of time, in order perform their immune task. This is accomplished through regulation of TGFb activity by a set of cell surface receptors, proteins called integrins.

This regulation allows the alveolar macrophages to take on their "killer" function – the ability of macrophages to engulf invading microorganisms – but only for a very limited period of time. The mediating role of TGFb, briefly inactivated by the integrin, is then restored by one of the lung's own enzymes, the MMP9.

"Basically, the macrophages wake up for a while, but the system's own enzymes activate the inhibitor that puts them back to sleep," said Kenji Takabayshi, Ph.D., first author of the study.

Other contributors to this paper include Maripat Corr, Tomoko Hayashi, Vanessa Redecke, Lucinda Beck, and Donald Guiney of the Department of Medicine at UCSD School of Medicine; and Dean Sheppard, Lung Biology Center, University of California, San Francisco.

The work was supported by grants from the National Institutes of Health.

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