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Innate immune system targets asthma-linked fungus for destruction

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A new study shows that the innate immune system of humans is capable of killing a fungus linked to airway inflammation, chronic rhinosinusitis and bronchial asthma. Researchers at Mayo Clinic and the Virginia Bioinformatics Institute (VBI) have revealed that eosinophils, a particular type of white blood cell, exert a strong immune response against the environmental fungus *Alternaria alternata*. The groundbreaking findings, which shed light on some of the early events involved in the recognition of *A. alternata* by the human immune system, were published recently in the *Journal of Immunology*.

Eosinophils typically combat parasitic invaders of the human body larger than bacteria or viruses, such as flukes or parasitic worms (collectively known as helminths). Evidence from different experimental approaches suggests that asthma and chronic sinusitis can arise when the body perceives that it has encountered a disease-causing organism. Environmental fungi such as Alternaria do not typically cause invasive infections like parasites but for some reason, in certain people, the body responds as if it is being attacked and chronic inflammation can result from the ensuing cascade of immune-related events.

Principal Investigator Hirohito Kita, M.D., from Mayo Clinic, remarked: "Our results strongly demonstrate that eosinophils have the capacity to recognize and exert immunological responses to certain fungi such as Alternaria. We have shown that CD11b receptors on the surface of eosinophils recognize and adhere to beta-glucan, a major cell wall component of the fungus. This in turn sets in motion the release of toxic

granule proteins by the white blood cells, leading to extensive damage and ultimate destruction of the fungus. To the best of our knowledge, this is the first time that live eosinophils and not just the intracellular components have been shown to target and destroy a fungus."

The researchers used fluorescence microscopy to determine the outcome of the interaction between eosinophils and *A. alternata*. The contact of fungus with eosinophils resulted in bright red fluorescence due to the damaged fungal cell wall and subsequent death of Alternaria. Immunohistochemistry confirmed the release of toxic granular proteins by eosinophils due to contact with the fungus.

Dr. Chris Lawrence, Associate Professor at VBI and the Department of Biological Sciences at Virginia Tech, remarked: "T helper 2 (Th2) cells in the immune system typically produce cytokine signaling molecules or interleukins that lead to the recruitment of eosinophils for the dysregulated immune response commonly associated with airway inflammatory disorders. Continual exposure of sensitized individuals to common environmental fungi like Alternaria may result in Th2 cells being constantly activated to recruit eosinophils and this sustained defense mechanism results in chronic inflammation. It has been shown previously that degranulation of eosinophils causes damage of airway mucosa and enhances inflammation. The next step in our transdisciplinary research collaboration will be to use recombinant fungal proteins and fungal knockout mutants for specific genes to dissect the different molecular steps involved in the development and progression of this acute immune response."

Hirohito Kita added: "We have taken an important step in showing that the innate immune system of eosinophils is capable of targeting an asthma-associated fungus for destruction. The biological significance of these results will need to be verified further in animal models and in humans and our collaborative efforts with Dr. Lawrence's research group

for proteomics and functional genomics will be invaluable in this respect. We suspect that the dysregulated immune responses to Alternaria, other filamentous fungi, and perhaps chitin-encased insects, such as mites and cockroaches, may play a pivotal role in chronic inflammation and the subsequent development of bronchial airway disease."

Citation: Juhan Yoon, Jens U. Ponikau, Christopher B. Lawrence, Hirohito Kita (2008)
Innate Antifungal Immunity of Human Eosinophils Mediated by a â2 Integrin, CD11b. *J. Immunol.* 181: 2907-2915.

Source: Virginia Tech