cate that approximately 45% of adults express Th2-dependent reactivity against aero-allergens, and yet only a small minority of these develop asthma/AHR. Likewise, most adults experience multiple episodes of respiratory infection without developing asthma symptoms. Clearly, additional factor(s) must function to determine whether a person develops airway inflammation and asthma/AHR.

Current interest in this question focuses mainly on the endogenous control mechanisms that regulate the intensity and duration of airway mucosal T-cell responses, including those targeted at antigen presenting cells or at Th2 themselves[4]. γδ T cells have previously been implicated in this context in regulation of αβ T cell responses to allergen in both the respiratory and gastrointestinal tracts[5]. However, the current report from the Lahn *et al*. suggests a potential role for γδ T cells that is independent of αβ T cells. $\delta^{-/-}$ mice developed higher levels of AHR in response to antigen challenge than intact control mice, despite showing lower levels of inflammation in the lungs. This indicates that the target for the regulatory effects of γδ T cells is not the inflammatory process itself but one of the downstream sequelae in the pathway linking inflammation to AHR development.

Although the precise mucosal target for regulatory γδ T cells remains to be defined, the most attractive candidate based on current knowledge would seem to be AECs, which provide the link between Th2-mediated inflammation and local tissue remodeling (Fig. 1). Mucosal γδ T cells have been demonstrated to control the growth and differentiation of epithelial cells in the gastrointestinal[6] and respiratory[7] tracts, and may be essential in facilitating post-inflammatory repair by regulating the removal of necrotic epithelial cells[7,8].

In humans, recognition of necrotic cells may be a chief function of a large subset of γδ T cells with Vγ9/Vδ2, which cross-reacts with a range of phosphorylated non-peptidic metabolites released from epithelial cells after lysis[9]. Moreover, recent studies indicate that although γδ T cells are infrequent in resting human airway mucosa, they are a substantial feature of inflammatory infiltrates in atopics[10]. Of additional interest is the growing epidemiological literature suggesting protective effects of mucosal microbial exposure on asthma/AHR development, through modulation of the Th1/Th2 balance[11]. The postnatal establishment of functional mucosal γδ populations is equally reliant on these microbial stimuli, suggesting a further avenue for environmental modification of AHR development independent of effects on Th1/Th2 functions.

Thus, the discovery of a previously unknown role for these enigmatic mucosal-dwelling T cells has a range of theoretical implications for ongoing research in the asthma/AHR area, particularly in relation to the subtle interactions between inflammatory and repair mechanisms in disease pathogenesis.

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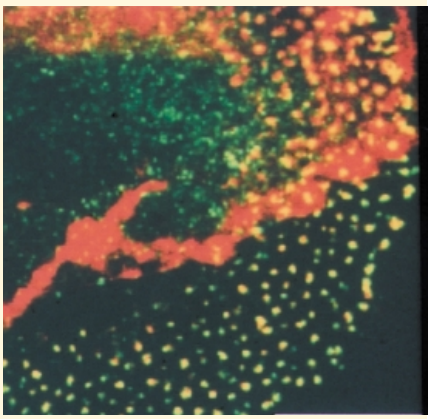
[1]TVW Telethon Institute for Child Health Research Perth, Western Australia; the Departments of [2]Microbiology and [3]Pediatrics University of Western Australia Division of Cell Biology, O Box 855West Perth Western Australia 6872 Australia

E-mail: patrick@ichr.uwa.edu.au

Mutant WASp stops cells in their tracks



Wiskott–Aldrich Syndrome (WAS) is a recessive disorder characterized by severe immunodeficiency. The gene responsible for WAS encodes a hematopoietic cell-specific protein, WASp, which has several binding sites for different actin regulatory molecules. How mutations in a potential actin-regulatory protein could affect immune function has been debated until recently. In the 17 August issue of *Proceedings of the National Academy of Sciences*, Linder *et al*. reported that WASp localizes to podosomes, the dynamic actin-containing adhesion structures formed by macrophages, monocytes, platelets, neutrophils, B cells and T cells that are necessary for chemotaxis. The figure shows part of a podosome structure formed by a primary human macrophage, localizing actin (red) and WASp (green), and areas of overlap (yellow). "Patients with WAS express very low levels of WASp," explained David Nelson, co-author on the study. The authors reported that macrophages taken from WAS patients could not assemble podosomes or respond normally to a bacterial chemoattractant. "Inability to form podosomes in hematopoietic cells probably causes defects in substrate adhesion and crawling, leading to immunodeficiency," said Nelson. The authors proposed that WASp functions by interacting with CDC42Hs, a member of the Rho family of GTPase-binding proteins, to control the formation of podosomes and other actin-based structures. Nelson added that this is one of the first known diseases caused by defects in cytoskeletal organization.

KRISTINE NOVAK