The Wiskott-Aldrich syndrome (WAS) is an X-linked inherited defect of platelets and lymphocytes. Affected males exhibit accelerated destruction of their abnormally small platelets and have profound thrombocytopenia. They also have a combined immunodeficiency; they do not respond to linear polysaccharide antigens, such as the capsular material of pneumococci, and respond poorly to protein antigens. Their T cells do not respond normally to the mitogenic effects of anti-CD3. They also have eczema (1). The enigma posed by the involvement of these disparate cell lineages can now be scrutinized as the gene encoding the defective protein (Wiskott-Aldrich syndrome protein [WASp]) has been cloned, and missense and non-sense mutations in this gene as well as deletions and splice site mutations have been identified (2, 3). X-linked thrombocytopenia has been found to result from mutations in this gene (4).

From a study of obligate female heterozygous carriers of the WAS gene defect it has become apparent that all nucleated blood cells and their progenitors, but no other cells, exhibit nonrandom X-chromosome inactivation. This suggested that WASp would be expressed primarily, if not exclusively, in platelets and lymphocytes and their progenitors, but no other cells, except for platelets and lymphocytes of males with WAS. This also implies that a homologous Cdc42-binding protein may be present in cells that are not affected by mutations in the WAS gene. The carboxy-terminal moiety of WASp contains polyproline stretches that are inviting to SH3 domains. In fact, the adaptor protein Nck, which contains SH3 domains, also binds to WASp (9). More WASp binding partners will ultimately be found.

The circulating T cells of males with WAS appear to be activated, and they express on their surface molecules that are characteristic of activated T cells. However, attempts to activate T cells in vitro from these same patients elicit poor responses. These paradoxical observations are not easily explained. The GTPases Cdc42 and Rac1 appear to play a role in the costimulatory pathway in T cells and probably bind to WASp, which binds, in turn, Nck. The entire complex may then move to the cell membrane. In any case, the T cells in WAS have a form of T cell anergy. Clearly much more work is needed to elucidate the role of WASp in the immune response and in cell biology.

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References