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 blood cells. Stewart et al. in this issue of *The Journal* report use of the first monoclonal antibody to WASp to find its abundant expression in platelets, T cells, monocytes, and transformed B cell lines. Their failure to find WASp in K562 cells and little of it in MOLT-4 cells is discrepant with the findings of others (1), but this matters less than the fact that they find WASp exclusively in the cytoplasm and not in the nucleus of these cells. It appears not to be a transcription factor, as was suggested earlier. Further work is needed to ascertain the subcellular localization of WASp for reasons that will soon be clear.

WAS appears to have joined the league of cytoskeletal diseases such as spherocytosis, Duchenne muscular dystrophy, etc. The platelets and lymphocytes of males with WAS exhibit bizarre morphology and disorganization of the actin cytoskeleton (1). Recently three groups have independently discovered that WASp binds the small GTPase, Cdc42 in the GTP, but not in the GDP form (5–7). This protein is known to play a role in the regulation of cytoskeletal reorganization to form lamellopodia and filopodia. It is also critical for the polarization of T cells when they contact an antigen-presenting B cell (8). This may now explain why males with WAS respond poorly or not at all to highly T-dependent antigens.

These findings are early intimations that WASp plays an important role in signal transduction in affected cells. It 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

1. Remold-O'Donnell, E., F.S. Rosen, and D.M. Kenney. 1996. Defects in Wiskott-Aldrich syndrome blood cells. *Blood*. 87:2621–2631.

2. Derry, J.M., H.D. Ochs, and U. Francke. 1994. Identification of a novel gene mutated in Wiskott-Aldrich syndrome. *Cell*. 78:635–644.

3. Kwan, S-P., T.L. Hagemann, B.E. Radtke, R.M. Blaese, and F.S. Rosen. 1995. Identification of mutations in the Wiskott-Aldrich syndrome gene and characterization of a polymorphic dinucleotide repeat at DXS6940 adjacent to the disease gene. *Proc. Natl. Acad. Sci. USA*. 92:4706–4710.

4. Villa, A., L. Notarangelo, P. Macchi, E. Mantuano, G. Cavagni, D. Brugnoni, D. Strina, M.C. Patrosso, U. Ramenghi, M.G. Sacco, et al. 1995. X-linked thrombocytopenia and Wiskott-Aldrich syndrome are allelic diseases with mutations in the WASP gene. *Nature Genet*. 9:414–417.

5. Aspenstrom, P., U. Lindberg, and A. Hall. 1996. The two GTPases, Cdc42 and Rac, bind directly to a protein implicated in the immunodeficiency disorder Wiskott-Aldrich syndrome. *Curr. Biol*. 6:70–75.

6. Symons, M., J.M. J. Derry, B. Karlak, S. Jiang, V. Lemahieu, F. McCormack, U. Francke, and A. Abo. 1996. Wiskott-Aldrich syndrome protein, a novel effector for the GTPase Cdc42Hs, is implicated in actin polymerization. *Cell*. 84:723–734.

7. Kolluri, R., K. Fuchs Tolias, C.L. Carpenter, F.S. Rosen, and T. Kirchhausen. 1996. Direct interaction of the Wiskott-Aldrich syndrome protein with the GTPase Cdc42. *Proc. Natl. Acad. Sci. USA*. 93:5615–5618.

8. Stowers, L., D. Yelon, L.J. Berg, and J. Chant. 1995. Regulation of the polarization of T cells toward antigen-presenting cells by Ras-related GTPase Cdc42. *PNAS*. 92:5027–5031.

9. Rivero-Lezcano, O.M., A. Marcilla, J.H. Meshima, and K.C. Robbins. 1995. Wiskott-Aldrich syndrome protein physically associates with Nck through Src homology 3 domains. *Mol. Cell Biol.* 15:5725–5731.

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