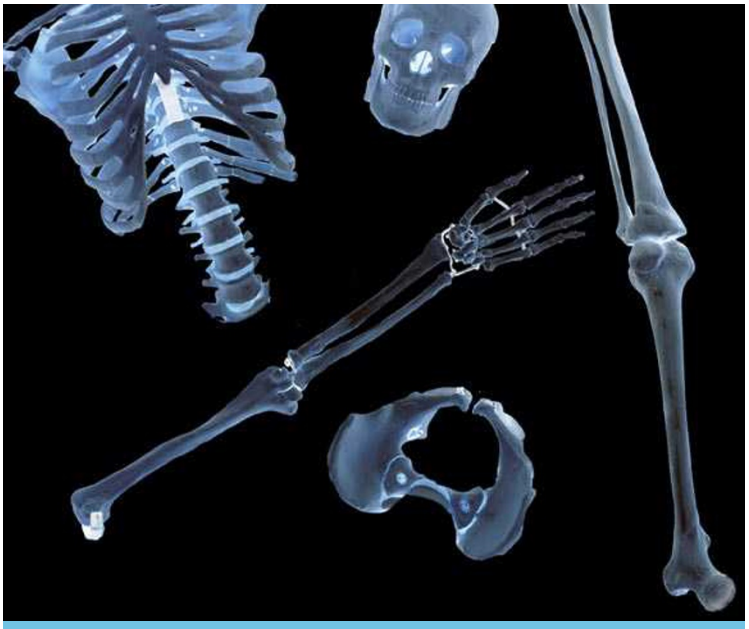
Nature Reviews Immunology | AOP, published online 12 December 2008; doi:10.1038/nri2477



IMMUNE RESPONSES

Rearranging the cytoskeleton

A study published in the *Journal of Experimental Medicine* has identified a role for haematopoietic protein 1 (HEM1) in the regulation of the actin cytoskeleton. HEM1 is an adaptor protein expressed by haematopoietic tissues, and its orthologues in lower organisms are known to mediate cytoskeletal rearrangements in response to RHO GTPases, such as RAC1. Now, Park *et al.* describe a mouse pedigree that was generated using *N*-ethyl-*N*-nitrosourea (ENU) mutagenesis, which has a nonsense mutation that maps to the *Hem1* gene and provides information on the role of HEM1 in mammalian tissues *in vivo*.

Compared with wild-type mice, HEM1-deficient mice had increased numbers of neutrophils, which showed defects in both chemotaxis and phagocytosis; decreased phagocytosis by the macrophages of these mice was also observed. Both migration and phagocytosis require actin polymerization, and unsurprisingly, HEM1-deficient neutrophils showed decreased actin polymerization and a diffuse distribution of F-actin. As transfection with *Hem1* restored the defective phenotype of HEM1-deficient neutrophils, the authors concluded that HEM1 is required for actin polymerization in innate immune cells.

The authors then examined the phenotype of lymphocytes from HEM1-deficient mice and identified a decrease in the numbers of both B cells and T cells. In addition, T-cell development was impaired, with a defect in the transition from the double-negative to the double-positive stage in both αβ and γδ T-cell development. Similarly to mice that lack other regulators of the cytoskeleton, HEM1-deficient T cells showed decreased activation and proliferation compared with wild-type T cells. Surprisingly, some T-cell functions were normal, including the production of interleukin-2 (IL-2) and interferon-γ, and the capacity to differentiate to T helper 1 (T_H1) cells. By contrast, others were enhanced, such as the secretion of tumour-necrosis factor, IL-6 and IL-17, and the capacity to differentiate to T_H17 cells. In addition, HEM1-deficient thymocytes and T cells displayed defective actin polymerization and capping, and decreased integrin-mediated adhesion to fibronectin, which indicates that HEM1 has an integral role in the rearrangement of the cytoskeleton of adaptive immune cells. The defect in actin polymerization was found to be due to an absence of the WAVE complex proteins, which are also thought to be targets of RHO GTPases. As the HEM1-deficient T cells had normal levels of mRNA that encodes WAVE proteins, it was suggested that HEM1 is involved in either stabilization or translation of these proteins.

This study highlights the importance of proteins that are involved in the regulation of the actin cytoskeleton, revealing fundamental roles for HEM1 in both innate and adaptive immune cells. The authors propose that HEM1 could be a valuable drug target for the treatment of inflammatory diseases, as it is specifically expressed by cells of haematopoietic and urogenital tissues.

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ORIGINAL RESEARCH PAPER Park, H. *et al.* A point mutation in the murine *Hem1* gene reveals an essential role for hematopoietic protein 1 in lymphopoiesis and innate immunity. *J. Exp. Med.* **205**, 2899–2913 (2008)