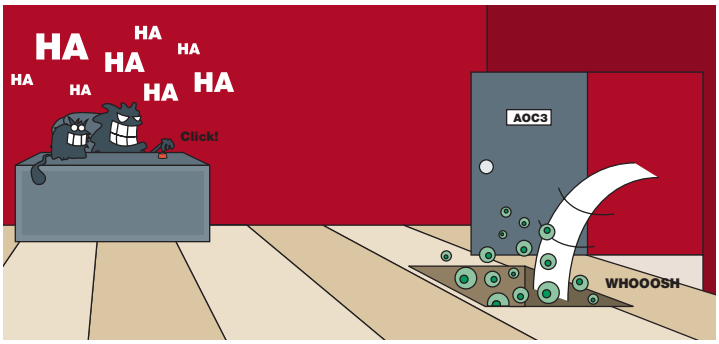
CELL MIGRATION

AOC3 opens doors for leukocytes



Leukocyte trafficking from blood vessels to tissues — a multistep process known as extravasation — is essential for both immune homeostasis and immune responses. Many of the adhesion molecules and activating signals that regulate extravasation have been characterized, but now, a report in *Immunity* defines a role for the ectoenzyme amine oxidase copper-containing 3 (AOC3) in the regulation of leukocyte migration *in vivo*.

AOC3, a semicarbazide-sensitive amine oxidase expressed at the cell surface of endothelial cells, has previously been implicated in leukocyte–endothelial-cell interactions *in vitro*. To investigate the role of AOC3 in leukocyte trafficking *in vivo*, Stolen *et al.* generated AOC3-deficient mice. In a specific-pathogen-free environment, the number of leukocytes in the lymphoid organs of AOC3-deficient mice was normal. However, in the absence of AOC3, intravital video microscopy revealed that the rolling velocity of polymorphonuclear leukocytes (PMNs) on the endothelium of inflamed tissues was greater than in wild-type mice, and the number of PMNs firmly adhering to the endothelium was markedly diminished. Increased rolling velocity and decreased firm adhesion of PMNs were also observed when AOC3-deficient mice were challenged with a stronger inflammatory stimulus, and in this situation, decreased transmigration efficiency was also observed. Consistent with a role for AOC3 in slow rolling and firm adhesion, administration of AOC3-specific antibodies to wild-type mice led to an increase in the rolling velocity of PMNs under inflammatory conditions.

In AOC3-deficient mice, intravital video microscopy also showed that lymphocytes interacting with the high endothelial cells of the Peyer's Patches had an increased rolling velocity, and fewer were firmly attached. By analysing the migration of fluorescently labelled wild-type lymphocytes after transfer to AOC3-deficient mice, it was further shown that AOC3 is required for efficient homing of lymphocytes to lymphoid organs.

Interestingly, AOC3-deficient mice and wild-type control animals generated similar immune responses when immunized with either a T-cell-dependent or -independent antigen, and they showed a similar course of disease after infection with *Yersinia enterocolitica*. By contrast, in a mouse model of autoimmune diabetes, markedly fewer AOC3-deficient mice succumbed to disease, and this correlated with a decreased number of lymphocytes infiltrating the pancreatic islets. Together with the observation that, in the absence of AOC3, the peritoneal infiltration of leukocytes was decreased after intraperitoneal injection of cytokines, these data indicate that AOC3 is required to mount inflammatory responses to non-microbial stimuli *in vivo*.

This study shows that AOC3 is required for leukocyte migration *in vivo*. Further studies will be required to determine the mechanism by which AOC3 regulates leukocyte trafficking; does it function as an adhesion molecule, or does it enzymatically modify other molecules that are crucial for extravasation? Moreover, the authors suggest that AOC3 might provide a new target for anti-inflammatory therapies.

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References and links

ORIGINAL RESEARCH PAPER Stolen, C. M. *et al.* Absence of the endothelial oxidase AOC3 leads to abnormal leukocyte traffic *in vivo*. *Immunity* **22**, 105–115 (2005).