IN BRIEF

INNATE IMMUNITY

Plexin-A4–semaphorin 3A signaling is required for Toll-like receptor- and sepsis-induced cytokine storm

Wen, H. *et al. J. Exp. Med.* 22 Nov 2010 (doi:10.1084/jem.20101138)

This study shows that plexin A4 signalling synergizes with Toll-like receptor (TLR) signalling to promote pro-inflammatory cytokine responses. In the absence of plexin A4, macrophages showed defective production of interleukin-6 and tumour necrosis factor in response to various TLR agonists and bacteria. Activation of TLR signalling components was also defective in plexin A4-deficient macrophages. Physiological relevance for plexin A4-enhanced TLR responses was confirmed by the findings that plexin A4-deficient mice showed a reduced cytokine storm after lipopolysaccharide (LPS) treatment compared with wild-type mice and were protected from lethal challenge with LPS. Plexin A4-deficient mice were also resistant to septic inflammation induced by caecal ligation and puncture. Finally, administration of the plexin A4 ligand semaphorin 3A enhanced LPS-induced cytokine production, suggesting that this pathway could be a target in the treatment of sepsis.

INFLAMMATION

Gene from a psoriasis susceptibility locus primes the skin for inflammation

Wolf, R. *et al. Sci. Transl. Med.* **2**, 61ra90 (2010)

The chronic skin inflammation of psoriasis could result from an abnormality of epidermal keratinocytes or from a dysregulated immune response. A combination of these factors is probably responsible for the disease, and a new study supports this idea by showing that S100 proteins expressed by keratinocytes activate an inflammatory cascade through the receptor for advanced glycation end products (RAGE). Transgenic mice overexpressing keratinocyte-restricted S100AA — the single mouse orthologue of the human proteins S100A7 and S100A15, which are encoded in psoriasis susceptibility locus 4 (PSORS4) and are highly expressed by keratinocytes from psoriatic lesions — had an exaggerated inflammatory response to wounding of the skin associated with increased levels of T helper 1 (T_H1) and T_H17 cell-associated cytokines. In turn, these cytokines further upregulated S100AA expression, showing the therapeutic potential of targeting the S100A7/A15–RAGE axis in psoriasis.

MUCOSAL IMMUNOLOGY

T helper type 1 memory cells disseminate postoperative ileus over the entire intestinal tract

Engel, D. R. *et al. Nature Med.* **16**, 1407–1413 (2010)

Localized intestinal surgery can disrupt the motility of the entire gastrointestinal tract (a condition termed postoperative ileus); this is thought to result from neuronal dysfunction. Using a mouse model, this study shows that it is not the nervous system but the immune system that drives postoperative ileus. Intestinal manipulation activated local dendritic cells to produce interleukin-12 and induce interferon-γ (IFNγ)-producing T helper 1 (T_H1) cells, which had dual roles in postoperative ileus: they drove the inflammation that disrupted the local environment and promoted the spread of intestinal dysfunction by migrating to other areas of the intestine. T_H1 cells that were induced in manipulated areas expressed the gut-homing receptor CC-chemokine receptor 9 (CCR9), which may have promoted their spread to other regions of the intestine. Interestingly, in patients undergoing abdominal surgery, the number of IFNγ-producing $CCR9^+$ memory T cells in the blood was markedly increased shortly after the operation, but this population remained stable in patients undergoing non-abdominal surgery.