IN BRIEF

DENDRITIC CELLS

Alum interaction with dendritic cell membrane lipids is essential for its adjuvanticity

Flach, T. L. *et al. Nature Med.* **17**, 479–487 (2011)

Alum, a term used to refer to trivalent aluminium-containing salts, is the most commonly used adjuvant in human vaccines. However, its mechanism of action remains unclear. This study shows that alum crystals interact with lipids in the plasma membrane of dendritic cells (DCs), but not macrophages or B cells. This interaction results in membrane lipid sorting, activation of the SRC–ITAM–SYK–PI3K signalling pathway for DC activation and non-phagocytic uptake of admixed antigen. Alum-stimulated DCs showed increased adhesion to $CD4^+$ T cells owing to increased ICAM1–LFA1 interactions. Injection of mice with alum-treated DCs and antigen induced an antigen-specific antibody response similar to that induced by injection of antigen and alum. Of note, these alum-mediated effects were independent of the NLRP3 inflammasome pathway. So, this study proposes that alum directly activates DCs by engaging membrane lipids.

CELL MIGRATION

Repulsive guidance molecule-A (RGM-A) inhibits leukocyte migration and mitigates inflammation

Mirakaj, V. *et al. Proc. Natl Acad. Sci. USA* 5 Apr 2011 (doi:10.1073/pnas.1015605108)

Repulsive guidance molecule A (RGMA) is a chemorepulsive factor that regulates neural tube closure during neuronal development. It has also been shown to be selectively expressed in areas of CNS inflammation post development. But, does RGMA have a chemorepulsive role in the periphery? The authors found that RGMA is expressed in various organs, including the lung, spleen and intestine. It is produced by epithelial cells, neutrophils, monocytes and B and T cells and inhibits neutrophil migration (induced by FMLP) *in vitro*. Using a model of zymosan A-induced peritonitis, the authors showed that administration of RGMA reduced leukocyte migration and histological signs of inflammation, such as oedema formation. This chemorepulsive effect of RGMA was dependent on the expression of its receptor neogenin *in vitro* and *in vivo*. So, RGMA is an endogenous inhibitor of leukocyte chemotaxis.

IMMUNOTHERAPY

CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans

Beatty, G. L. *et al. Science* **331**, 1612–1616 (2011)

Pancreatic ductal adenocarcinoma (PDAC) tumours are infiltrated by leukocytes, which contribute to the immunosuppressive environment. Patients with metastatic disease who received a combination of a CD40-specific activating monoclonal antibody and the chemotherapeutic agent gemcitabine exhibited increased median overall survival compared with those treated with chemotherapy alone. The tumour lesions of patients with disease regression did not contain any T cells but were infiltrated by macrophages, indicating that, surprisingly, T cells were not involved in the antitumoural effects of the CD40 agonist. Interestingly, studies in a mouse model of spontaneous PDAC showed an essential role for systemic macrophages in tumour regression, and macrophages stimulated with the CD40 agonist displayed increased expression of co-stimulatory molecules, secreted pro-inflammatory cytokines and migrated to the tumour. Treatment with the CD40 agonist resulted in degradation of the tumour stroma, and this was dependent on the pro-inflammatory activity of macrophages.