IN BRIEF

TUMOUR BIOLOGY

IRF4 addiction in multiple myeloma.

Shaffer, A. L. *et al. Nature* **454**, 226–231 (2008)

Using a recently developed screening method to identify therapeutic targets in cancer, Shaffer ***et al.*** describe interferon-regulatory factor 4 (IRF4) as a master regulator of aberrant gene expression in multiple myeloma — a malignancy of plasma cells — making this factor an 'Achilles' heel' of the disease. The RNA-interference-based screen revealed that knockdown of *IRF4* expression was toxic to all myeloma cell lines tested, regardless of their oncogenic mutations. Gene-expression analysis showed that indeed IRF4 directs a broad gene-expression programme in myeloma cells that is distinct to that of plasma cells and activated B cells. *MYC* was a key IRF4 target gene and established a positive regulatory loop by upregulating the expression of *IRF4*. The dependency of myeloma cells on IRF4 was described as "non-oncogene addiction", as this normal cellular protein seems to carry out an aberrant function to cause cancer-cell proliferation or survival.

B-CELL RESPONSES

APRIL secreted by neutrophils binds to heparin sulfate proteoglycans to create plasma cell niches in human mucosa.

Huard, B. *et al. J. Clin. Invest.* 10 July 2008 (doi:10.1172/JCI33760)

Long-lived plasma cells reside in the bone marrow, where their survival factors have been characterized, or in mucosa-associated lymphoid tissue (MALT). It has now been shown that niches in which APRIL (a proliferating ligand) is concentrated promote plasma-cell survival in human MALT through the upregulation of anti-apoptotic factors. Interestingly, infiltrating neutrophils were found to be the main source of APRIL, although tonsillar epithelial cells could also produce this factor. Secreted APRIL accumulated in niches by binding to heparin sulphate proteoglycans expressed on the surface of epithelial cells. It is thought that by promoting plasma-cell accumulation and survival, these APRIL-rich niches maintain plasma cells in close contact with invading pathogens, enabling a long-lasting humoral response in mucosal tissues.

HIV

Evidence for HIV-associated B cell exhaustion in a dysfunctional memory B cell compartment in HIV-infected viremic individuals.

Moir, S. *et al. J. Exp. Med.* 14 July 2008 (doi:10.1084/jem.20072683)

In this study, Moir ***et al.*** describe a population of $CD20^{hi}CD21^{low}CD27^{-}$ B cells (similar to a population found in human tonsillar tissues) that is increased in the blood of HIV-viraemic, but not HIV-aviraemic or control, individuals. These memory B cells express high levels of the inhibitory receptor Fc-receptor-like 4 (FCRL4), other potentially inhibitory receptors and homing receptors for chronically inflamed tissues. This receptor-expression profile was previously shown to be associated with virus-induced T-cell exhaustion. Accordingly, these B cells from the blood of HIV-viraemic individuals had reduced cell division and somatic hypermutation compared with classical memory B cells, and proliferated poorly in response to stimulation *in vitro*, which is consistent with premature exhaustion. In addition, this cell population contained a higher frequency of HIV-specific antibody-secreting cells compared with other populations. So, B-cell exhaustion might explain the ineffectiveness of HIV-specific antibody responses in these individuals.