IN BRIEF

MACROPHAGES

Arteriogenic macrophages protect against ischaemia

This study showed that a lower level of expression of the oxygen-sensing molecule PHD2 (also known as EGLN1) by macrophages (in *Phd2*$^{+/-}$ mice) can protect against ischaemic damage to heart and skeletal muscle by increasing the number of collateral arterial vessels at baseline and by 'preconditioning' these vessels for remodelling (arteriogenesis). *Phd2*$^{+/-}$ macrophages have a gene expression signature similar to that of M2 macrophages (which promote wound healing and angiogenesis) and produce soluble factors that increase the migration and proliferation of smooth muscle cells. This skewing of *Phd2*$^{+/-}$ macrophages was shown to depend on activation of the canonical nuclear factor-κB pathway, which is negatively regulated by PHD2 at high oxygen concentrations. Therefore, therapeutic inhibition of PHD2 might be used to promote macrophage-mediated collateral vascularization in patients at risk of ischaemia.

ORIGINAL RESEARCH PAPER Takeda, Y. *et al.* Macrophage skewing by *Phd2* haplodeficiency prevents ischaemia by inducing arteriogenesis. *Nature* 9 Oct 2011 (doi:10.1038/nature10507)

MONOCYTES

How a high-fat diet results in monocytosis

Many studies have described an association between monocytosis and cardiovascular disease. This paper reports a mechanistic link between hypercholesterolaemia and monocytosis that helps to explain their combined effects on atherosclerosis. In the apolipoprotein E-deficient (*Apoe*$^{-/-}$) mouse model of atherosclerosis, feeding a high-cholesterol diet results in increased proliferation of haematopoietic stem and multipotential progenitor cells (HSPCs), monocytosis and the increased entry of monocytes into atherosclerotic lesions, thereby enlarging the lesions. In wild-type mice, the authors observed high levels of APOE bound to proteoglycans on the surface of HSPCs, and this suppressed the proliferation of HSPCs in a cell-autonomous manner — probably by promoting cholesterol efflux from HSPCs. The results indicate that, in mice on a high-fat diet, a lack of cholesterol efflux from *Apoe*$^{-/-}$ HSPCs leads to membrane cholesterol accumulation and cell proliferation; this could be suppressed by the addition of the potent cholesterol acceptor high-density lipoprotein.

ORIGINAL RESEARCH PAPER Murphy, A. J. *et al.* ApoE regulates hematopoietic stem cell proliferation, monocytosis, and monocyte accumulation in atherosclerotic lesions in mice. *J. Clin. Invest.* **121**, 4138–4149 (2011)

TECHNIQUE

Recapitulating human TB *in vitro*

Studies of human tuberculosis have been hampered by the lack of an *in vitro* model that recapitulates all the features of a natural infection with *Mycobacterium tuberculosis*. This paper describes a unique combination of *in vitro* culture conditions that enables the generation of human monocyte-derived macrophages (MDMs) that can survive infection with *M. tuberculosis* and control its replication for more than 2 weeks. The new protocol involves monocyte culture for 2 weeks at 10% oxygen in 40% human plasma containing the cytokines GM-CSF and TNF, with the medium replaced every 3–4 days, followed by 'activation' with interferon-γ for 2 days prior to infection. The authors showed that culture in fetal bovine serum or with M-CSF (two additives that are commonly used for the culture of human monocytes) led to the generation of MDMs that were unable to control *M. tuberculosis* replication and died.

ORIGINAL RESEARCH PAPER Vogt, G. & Nathan, C. *In vitro* differentiation of human macrophages with enhanced antimycobacterial activity. *J. Clin. Invest.* **121**, 3889–3901 (2011)