50 Years Ago

Recent reports on the occurrence of "pink spot" in the urines of schizophrenics are somewhat conflicting and cast doubt on its chemical identity and its relationship to schizophrenia … The possibility that "pink spot" may be associated with brain damage induced by drugs is supported by the fact that it is also found in high concentration in the urines of patients suffering from Parkinsonism, a disease in which the brain is indisputably damaged. This leaves open the questions of the relationship of "pink spot" to schizophrenia and also its relationship to dopamine metabolism … it would be interesting to know whether any of the patients who have been reported in the literature as "pink spot" excreters also showed clinical signs of brain damage in the form of dyskinesia induced by drugs at the time of investigation or whether they have developed it since the reports were published.

From *Nature* 26 November 1966

100 Years Ago

Whatever difference of opinion may exist in regard to the stimulus which has moved the Government to take control of our food supplies, all are agreed that it has not come about a moment too soon … The provisions outlined will empower the Food Controller to take measures both preventive and regulatory … But Government measures cannot stop with the mere regulation of food supplies. Powers must be taken to compel a greater production of home food and to ensure a larger acreage of wheat … Objection may be raised to the shortage of labour … why should prisoners of war not be utilised to the fullest degree possible in raising the home production of food?

From *Nature* 23 November 1916

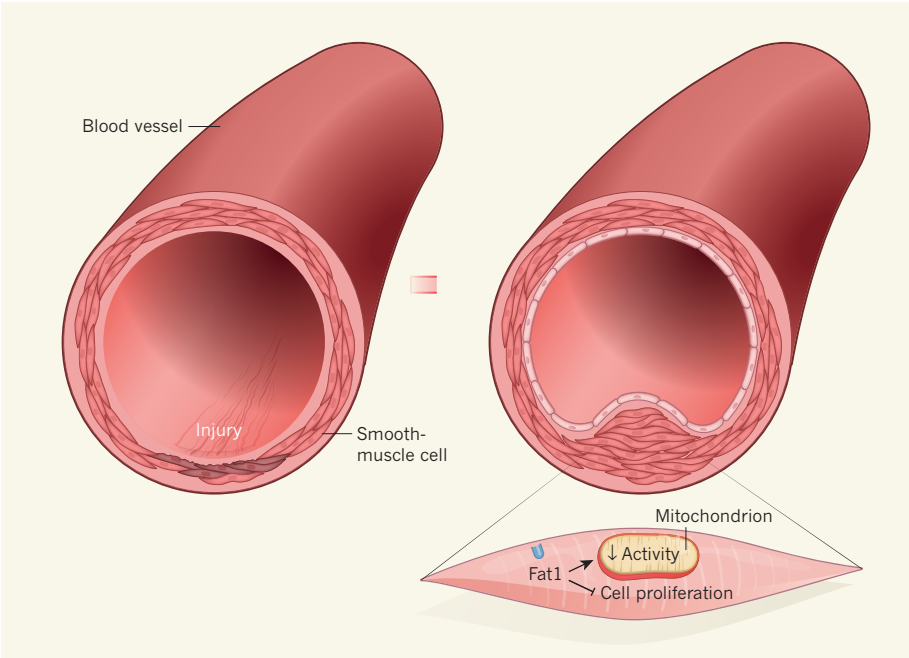

Figure 1 | Fat1 goes with the flow. Injury to the walls of blood vessels can occur through natural causes or surgical interventions. Vascular smooth-muscle cells (VSMCs) migrate to the damaged site and proliferate as part of the healing response. However, this can result in cellular overproliferation, causing vessel-wall thickening and narrowing the blood vessel. The Fat1 receptor protein (blue) limits the proliferation of VSMCs[3]. In studies using mice and human cells, Cao *et al.*[1] report that a portion of Fat1 interacts with proteins in the mitochondria and inhibits mitochondrial activity in VSMCs.

the inner mitochondrial membrane.

Many biochemists would be cautious about further investigating any such interactions with mitochondrial proteins because non-specific interactions with these proteins are common. Nonetheless, Cao *et al.* tested and validated their findings using a variety of techniques. The authors observed that Fat1 is present inside the mitochondria of VSMCs. They also found that non-full-length portions of Fat1 are enriched in mitochondria, and that these portions interact directly with proteins of the mitochondrial respiratory machinery that generate the energy-carrying nucleotide ATP. Subsequent analyses revealed that mouse VSMCs lacking Fat1 had enhanced mitochondrial respiration in the absence of other alterations to mitochondrial structure or mass that might be responsible for such enhancement. Cao and colleagues conclude that Fat1 dampens mitochondrial respiration to suppress VSMC proliferation (Fig. 1).

The importance of mitochondrial function to the proliferative capacity of VSMCs was already known[4]. But how central is Fat1 signalling to the mitochondrial regulation needed to enable VSMC repair of vascular damage? Cao *et al.* established the relevance of this pathway in human tissue through *in vitro* studies demonstrating that human FAT1 can regulate mitochondrial respiration and proliferation in human VSMCs from arterial blood vessels. The authors also observed FAT1 expression in human VSMCs in an artery-repair context, when they tested post-mortem artery samples from people who had undergone surgical insertion of a stent device to correct atherosclerosis, an artery-narrowing condition.

Cao and colleagues investigated a model of arterial injury using mice whose smooth-muscle cells lacked the *Fat1* gene. Injured arteries in these mice became significantly narrower than did those of control mice, establishing that the presence of Fat1 normally limits the potential of VSMCs to contribute to vascular blockage. However, although this model system might be relevant to many aspects of vascular-cell proliferation and remodelling, it does not reflect all the processes involved in vascular disease. Nevertheless, this work establishes a framework with which to further investigate the Fat1 and mitochondrial signalling pathway — for example, by testing whether this mitochondrial-control pathway is evolutionarily conserved in other members of the Fat protein family.

Vascular biology is not the only relevant setting for Fat1 investigation. Roles for Fat1 have been proposed in a surprisingly diverse range of disease states[1,2]. Cancer is of particular interest, given that studies[5] in the fruit fly *Drosophila melanogaster* indicate that *Ft*, a fly version of *Fat1,* is a tumour-suppressor gene. A tumour-suppressor function is consistent with reports of repression or inactivation of FAT1 in certain human cancers[2,6] — for example, loss of FAT1 can result in tumour-promoting Wnt-protein signalling[6].

However, FAT1 is overexpressed in some types of cancer[7], creating a conundrum about