50 Years Ago

Outline of Human Genetics. By Prof. L. S. Penrose — Throughout, Prof. Penrose deals with just those points which are of general interest and particularly topics about which people ignorant of genetics are always asking, for example, Is natural selection still operating in spite of civilization and medical advances? ... In "Commentary" he explains in more detail how common chromosomal abnormalities, such as those causing mongolism and intersexes, are produced; mentions theories dealing with the possibility of inherited cancer; touches on pharmacogenetics; and outlines the vast amount of genetic variability which is being shown up by the complicated polymorphisms of the blood proteins. Finally, he makes the very good point that while geneticists are continually worrying about the quality of the human race we shall have doubled our numbers in the next 50 years and that birth control is far more important than the fruitless task of planning the superman.
From *Nature* 24 August 1963.

100 Years Ago

An exhibit illustrating the damage caused to biscuits sent out in soldered tins for the use of the troops in South Africa—especially during the Boer war—Gibraltar, Malta, Ceylon, &c., has just been placed in the central hall of the British Museum (Natural History), where it will be kept open about a month. The larvae of certain minute moths and beetles were the active agents; and it appears that since these cannot, in all probability, withstand the high temperature to which the biscuits are subjected in baking, the eggs must be laid by the moths during the period when the biscuits are being cooled before tinning.
From *Nature* 21 August 1913.

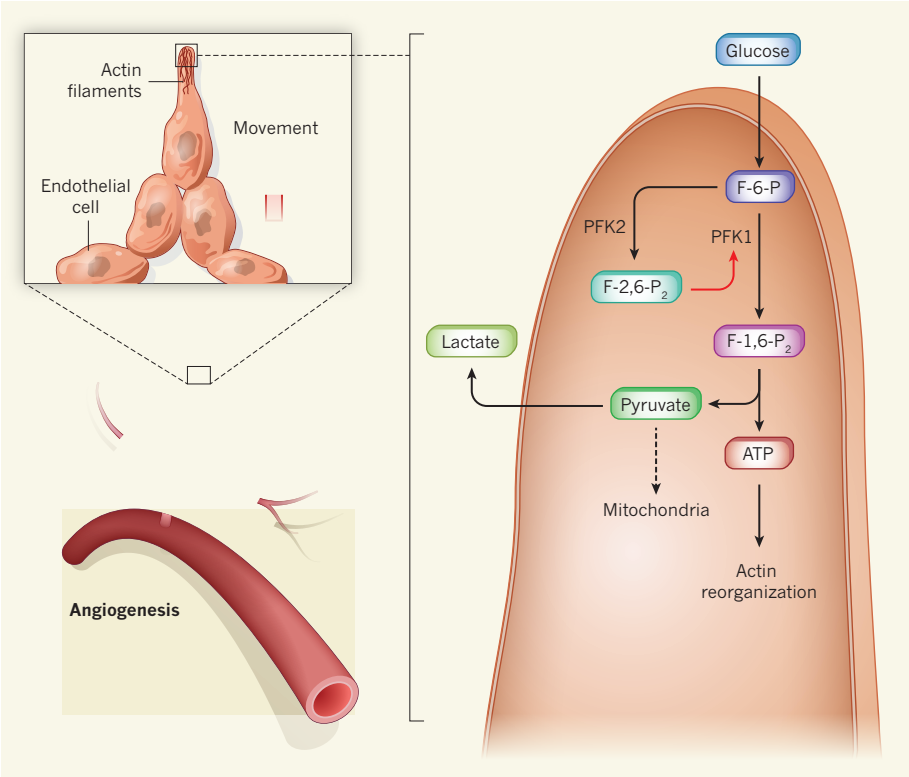

Figure 1 | Glycolysis regulates angiogenesis. The formation of new blood vessels involves the outward movement of endothelial cells from the lining of existing blood vessels, a process that relies on the rapid reorganization of actin-protein filaments in cellular structures called filopodia and lamellipodia (not shown). The energy for this (in the form of ATP) is provided by the breakdown of glucose, but endothelial cells are unusual in that the pyruvate produced by glycolysis is converted to lactate, rather than being channelled into mitochondria for further oxidation, as occurs in most cells. De Bock *et al.*[1] show that both angiogenesis and glycolysis are accelerated by the activity of the enzyme PFK2 in endothelial-cell lamellipodia and filopodia. PFK2 converts the glycolytic intermediate fructose-6-phosphate (F-6-P) into fructose-2,6-bisphosphate (F-2,6-P_2), which, in turn, enhances the activity of the glycolytic enzyme PFK1, thereby accelerating glycolysis at these sites. Pyruvate then leaves the cell as lactate, probably because filopodia and lamellipodia are too small to accommodate mitochondria.

affects their function.

De Bock *et al.* began their study by confirming a previous report[4] that endothelial cells are highly glycolytic but perform little pyruvate oxidation. The authors then asked the interesting question: could modulation of glycolytic activity have an effect on angiogenesis? To assess this, they altered the amount of phosphofructokinase 2 (PFK2) in endothelial cells. PFK2 is a glycolysis-regulating enzyme that was discovered only in the 1980s, long after all key enzymes of the glycolytic pathway were thought to be known[5]. The related enzyme PFK1, identified decades before PFK2, catalyses the crucial committing step of glycolysis: the conversion of fructose-6-phosphate to fructose-1,6-bisphosphate. PFK2, by contrast, converts fructose-6-phosphate to fructose-2,6-bisphosphate, which is a potent allosteric activator of PFK1 (ref. 6). Activation of PFK2 thus drastically accelerates glycolytic flux through PFK1.

De Bock *et al.* show that reducing PFK2 levels in endothelial cells not only lowers glycolytic flux, as expected, but also impairs angiogenesis, by reducing the ability of the cells to form tip cells, migrate and form blood-vessel 'sprouts'. Conversely, and importantly, increasing PFK2 levels has the opposite effect: angiogenesis is increased. The authors also show that PFK2 lies downstream of VEGF and Notch, two proteins that are dominant determinants of endothelial-cell characteristics during angiogenesis.

How does PFK2 achieve these effects? Perhaps most interestingly, the authors demonstrate that PFK2 localizes to structures at the margins of endothelial cells called lamellipodia and filopodia. These cellular projections, which contain meshes and filaments of the protein actin, mediate endothelial-cell movement and sprout formation during angiogenesis (Fig. 1). PFK2 activity at this site probably coincides with the cellular position of large complexes of glycolytic enzymes, known as metabolons, which facilitate the channelling of metabolic products from one enzyme to the next[7]. Thus, it seems that PFK2 alters angiogenic capacity by altering glycolytic flux at the site of primary cell motion.

The study is important for several reasons. The findings imply that glucose metabolism can 'steer' the angiogenic process, in addition to simply being its 'engine'. This unveils