WHEN CELLS TURN ROGUE

Ageing and cancer

Cancer rates increase with age, but is this a function of time or of the ageing processes themselves? Arguably both: as we age, we accumulate more molecular damage, which underpins ageing and cancer. By Richard Twyman.

Cancer can strike at any time, but it is clear that the incidence of the disease increases significantly in later life. At age 65, 30 per cent of deaths in developed countries are cancer-related, and most of these are carcinomas – cancers of rapidly dividing cells that line the skin and internal organs. There is evidence to suggest that both cancer and ageing are underpinned by the body's response to the accumulation of cellular damage, particularly damage to DNA.

The cells in our bodies usually divide only when they receive appropriate instructions, helping to renew our tissues in a controlled and regulated manner. Cancer occurs when cells break loose from this regulation and begin to divide without any external control. However, cells do not lose control all at once. Cancer is a progressive disease, often beginning with the appearance of a group of cells that proliferate slightly faster than normal (dysplasia), followed by the formation of a benign tumour in which most of the cells appear fairly normal. At later stages, the cells gradually become more abnormal and aggressive; they break away from the primary tumour to seed secondary tumours elsewhere in the body (metastasis). At this stage the tumour is described as malignant. In certain well-studied tumours, each stage of progression has been linked to a particular genetic event such as the malfunction of particular sets of genes.

This process is driven by DNA mutations that disable key genes, or that lead to the production of malfunctioning proteins. Several different control circuits have to be disabled, and the chances of these failing simultaneously are very small, a bit like throwing six dice and getting six sixes. Unfortunately, not all the hits have to happen at the same time. A cell can take one mutation in a crucial gene and carry on much as normal, but each successive hit in a different critical gene causes a greater degree of deregulation. The most deregulated cells proliferate more than their neighbours, giving a larger population of target cells for the third hit, and so on. At the same time, an important component of cancer progression is the acquisition of mutations that make DNA more unstable – mutations that encourage further mutations. As these processes stack up, the genome becomes increasingly unstable, gene expression patterns change and the cells themselves become more and more abnormal.

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When cells turn rogue, our bodies are not defenceless: they have a selection of mechanisms that minimise the chances of cancer. These include specialised immune cells that target tumours, and specific processes that either cause cancer cells to commit suicide (apoptosis), or force them into a straitjacket so they can no longer divide (senescence). As both apoptosis and senescence are involved in the process of ageing (see page 18), is there a link between cancer and ageing?

Recent research suggests this may indeed be the case. One reason that cancer is more prevalent in elderly people is simply that it takes time to accumulate the necessary mutations to trigger uncontrolled proliferation. However, it may also be possible that the very defence systems that keep us safe from cancer when we are young betray us in later life.

"When we are young, our bodies usually protect us efficiently from cancer by forcing cells into the apoptotic or senescent pathways when they start to misbehave," says Professor Judith Campisi, Senior Scientist at the Lawrence Berkeley National

Laboratory, USA. “Senescence is a kind of forced retirement, where pre-cancerous cells are prevented from proliferating: the unruly are made to become good citizens. However, once senescent cells accumulate in tissues, they begin to affect the cells around them, and one consequence is that other nearby cells become more likely to form tumours.”

As time goes by, both pre-cancerous cells and senescent cells accumulate, particularly in the epithelial tissues that are most exposed to the environment, and the chances of them occurring in close proximity also increase. “The good citizens become bad neighbours later in life,” says Professor Campisi.

Senescent cells retire from the cell division cycle and enter a permanent non-dividing state; cancer ensues when the signals establishing senescence are overcome. A potential therapeutic approach might therefore be to re-establish these signals, and force uncooperative cells back into senescence. This has already been achieved in cultured cells by expressing inhibitors of cyclin-dependent kinases (proteins that help to promote cell division) or by reactivating the regulator protein p53 (which blocks cell division and induces senescence or apoptosis). However, the possibility that senescent cells may actually encourage cancer means that such approaches, even if practical in the short term, could be storing up trouble for later. There is hope, however. “It should be possible to establish what senescent cells do to encourage tumours, and then develop drugs specifically to target that process,” says Professor Campisi. This might be sufficient to divert pre-cancerous cells from their fate, thereby helping to protect us from cancer.

Dr Richard Twyman is a science writer based in York.

Further reading

Campisi J. Suppressing cancer: the importance of being senescent. Science 2005;309(5736):886–7.