IDEAS IN THEORETICAL BIOLOGY

ORIGIN OF CANCEROUS CELLS FROM TUMOURS

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ABSTRACT

With a previous paper (Niu & Wang, 1995), a general, hypothetical outline of the mechanism of carcinogenesis was proposed. With reference to the fact of starvation-induced hypermutation in micro-organisms, we propose that the hypoxia commonly seen in the cells at the centre of solid tumours might also result in hypermutation, and then p53-dependent programmed cell death. Like the apparently adaptive mutations in micro-organisms, only those genes (e.g. p53) that enable the cells to escape from apoptosis may be selected.

At the centre of solid tumours with poor blood supply, low levels of oxygen (hypoxia) often result in cell death. Because cells exposed to hypoxia accumulate wild-type p53 protein, which is an integral part of DNA damage-induced apoptotic pathway, the hypoxia-induced cell death has been assumed to be p53-dependent programmed cell death. And it has been found that mutations of p53 reduce the programmed cell death and give the mutant cells a survival advantage over cells with intact p53 (Graeber *et al.*, 1996). Based on these points, Graeber *et al.* (1996) proposed that the physiological selective pressure in tumours resulting from hypoxia offers an explanation for why p53 is one of the most commonly mutated genes in human cancers.

But as Kinzler and Vogelstein (1996) questioned, essential links have been missed in the model of Graeber *et al.* What is the molecular messenger carrying the hypoxic signal to p53? Is the increased expression of wild-type p53 protein due to direct effect of an altered redox environment, or an indirect effect mediated by the metabolic consequences of hypoxia (Kinzler & Vogelstein, 1996)? And how to explain the origin of so many other mutations in the oncogenes of cancerous cells.

When a population of micro-organisms is unable to grow because nutrients they can use are not available, while others that they cannot use exist, useful mutations (that enable the cell to use other nutrients and hence survive) arise in unexpected rates (Cairns *et al.*, 1988). There are two possibilities: Hypermutation that gives high rate of mutations for any genes to various directions and mutation directed to the genes and type needed. Hypermutation has obtained more support than directed mutation from two recent papers (Foster, 1997; Torkelson *et al.*, 1997). In 1992, Strauss pointed out that the origin of point mutations in tumour cells might be similar to that in starved micro-organisms. Torkelson *et al.* (1997) also suggested that genome-wide hypermutation may account for the somatic mutations that give rise to cancers in multicellular organisms. Richards *et al.* (1997) found that human tumour cell lines

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deficient in the key mismatch repair protein hMSH2 showed little or no increase in mutation rate when the cells were maintained in culture conditions allowing rapid growth. However, mutations accumulated at a high rate in these cells when they were maintained at high density. As the authors suggested, the conditions in high density cultures resemble the cell-growth-arrested conditions at the centres of solid tumours. Perhaps, the time has now arrived for us to make the assumption of Strauss (1992) more detailed.

Low levels of oxygen (and maybe glucose, too) exert a starved state to the cells at the centre of tumours, which, by some unknown mechanisms, results in hypermutation. The high mutation rates will disguise the cells as a DNA damaged state, which in consequence, activates the DNA damage-induced apoptotic pathway. As p53 is an integral link of the DNA damage-induced apoptotic pathway, it is thus reasonable for cells exposed to hypoxia accumulate wild-type p53 protein. In micro-organisms, hypermutation manifests as adaptive mutations that enable the cells to use new resources. Similarly for the case of tumours, only mutations that enable the cells to escape from programmed cell death and get more nutrients (oxygen and maybe glucose, etc.) can be selected and be detected in malignant cells. This may account for the mutations occurred in p53 and other genes that control cell-cycle or angiogenesis.

As tumour cells progress towards malignancy, they must switch to an angiogenic phenotype for their growth and metastasis. Angiogenesis is controlled by the local balance between stimulating factors and inhibitory factors. It has been found that wild-type p53 inhibits angiogenesis (Dameron *et al.*, 1994). While metabolic demands are thought to regulate the angiogenesis of tissues and tumours. Hypoxia can upregulate vascular endothelial growth factor (Shweiki *et al.*, 1992; Plate *et al.*, 1992). Therefore, if p53 mutated in the process of hypermutation (resulting from hypoxia), hypoxia would initiating angiogenesis without any resistance.

This does not mean that all cells at the centre of solid tumours should become malignant and metastasize? Starvation is a nonlethal selection for both *E. coli* and cells at the center of solid tumours, but it is not the only suffering that those tumour cells faced. If 'adaptive' mutation does not arise in the course of hypermutation, a bacterial cell can still survive (but not grow). By contrast, if p53 (and maybe some other genes, the same below) does not mutate in the course of genome wide hypermutation, the tumour cell will die of DNA-damage induced apoptosis. Even if p53 involved in hypermutation, it is not absolute for the cell to escape from apoptosis. Only when p53 happens to mutate before DNA-damages in hypermutation accumulate to such a level that is enough to trigger p53-mediated apoptosis, may the cell with p53 mutation escape from programmed cell death and become malignant.

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