Is Alzheimer's disease a form of cancer?

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Researchers have discovered that nerve cell death in Alzheimer's disease (AD) is preceded by a failed attempt at cell division. Inappropriately controlled cell division such as this is characteristic of cancer, and researchers are now considering the possibility that aberrant regulation of the cell cycle could be a determining factor in other diseases.

AD is characterized clinically by memory impairment followed by increasing cognitive, and eventually global, deficits leaving end-stage patients bedridden, incontinent and dependent on custodial care. The most consistent pathological correlates of the clinical manifestation of AD are the presence of neuritic plaques and neurofibrillary tangles, as well as synaptic and neuronal loss. The plaques are caused by the deposition of β-amyloid (Aβ) peptides in the extracellular space, whereas the tangles are formed by aggregates of hyperphosphorylated and conformationally abnormal tau protein within the neurons.

There is no universally accepted theory of how AD develops[1]. However, many AD researchers view Aβ as a toxic agent that causes the pathogenic process, although it is unclear how plaque and tangle formation are biochemically linked, and some would argue that the lesions are compensatory responses to the disease.

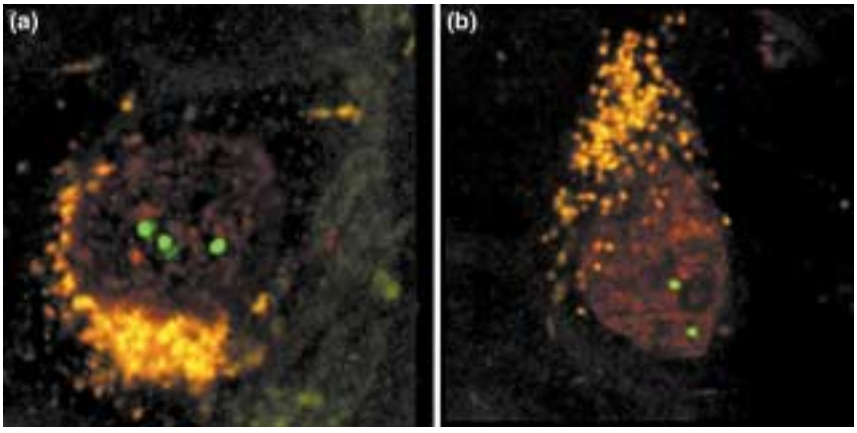

Figure 1. Fluorescent *in situ* hybridization of neurons in brain areas affected by AD and control neurons. **(a)** Three bright spots of fluorescence (one additional spot is out of focus) in the nucleus, suggesting a doubling of the number of chromosomes in this cell. **(b)** Controls show normal diploid chromosomal complement. Kindly provided by Karl Herrup.

Involvement of the cell cycle

In the past few years, evidence has accumulated that suggests an involvement of cell-cycle mechanisms in the development of AD. Since then, immunocytochemical studies have consistently shown that cell-cycle proteins are activated in neurons that are at risk of death[2]. However, the activation of cell-cycle proteins alone does not constitute firm evidence that a co-ordinated cell cycle is initiated. Peter Davies (Albert Einstein College of Medicine, New York, NY, USA), one of the scientists investigating the role of the cell cycle in AD, says: 'People in this field proposed that cell death in neurodegenerative conditions may be mediated by a utilization of various pieces of the cell-cycle machinery.' Furthermore, Karl Herrup (University Hospitals of Cleveland and Case Western Reserve University School of Medicine, Cleveland, OH, USA) wondered whether neurons in the AD brain are simply using parts of the cell-cycle machinery, or whether they are actually attempting to divide. Therefore, he started looking for evidence of DNA duplication in autopsy material from AD patients and non-AD controls.

Using fluorescent *in situ* hybridization, Herrup investigated four separate genetic loci on three different chromosomes[2]. Although cells in unaffected regions of the AD brain or in the hippocampus of controls showed no abnormalities, hippocampal neurons from AD patients had four, rather than two, copies of the genetic material under investigation (Fig. 1).

Davies is fascinated by these findings: 'The results are crystal clear, there is some DNA duplication. It is very hard to imagine how you could arrive at that result if the cell has not actually entered the cell cycle.'

AD – cancer of the brain?

Although inappropriately regulated cell division is characteristic of cancer, this might not be relevant to AD because adult nerve cells are unable to divide. Herrup says, 'The cells seem to be trapped in this tetraploid state. It is the resulting genetic imbalance between nucleus and cytoplasm that underlies what I believe is a protracted cell death. It probably culminates in an active suicide programme, but only after all kinds of protective mechanisms have failed.' Davies adds: 'We have always been intrigued by the fact that neuroblastomas

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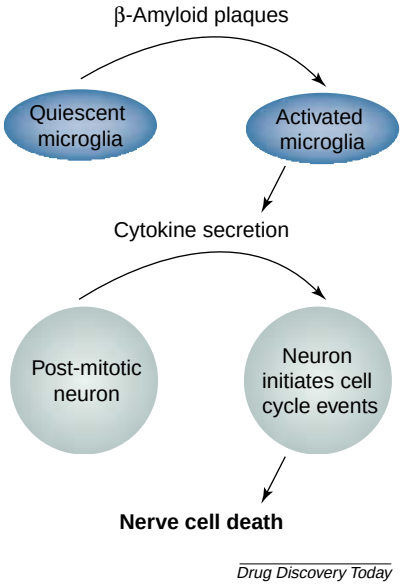

Figure 2. Proposed model for the progression of Alzheimer's disease[3].

– tumours originating from nerve cell division – are unknown in the adult, whereas you find tumours of almost every other tissue. Maybe the answer is that, in a way, you do find neuroblastoma in the adult, but we call it AD. The condition may be some kind of early cancer of the brain.'

New opportunities for AD therapy

This hypothesis enables new potential strategies for the treatment of AD. For example, one approach would be to block the signal that is responsible for initiating mitosis, either by reducing its concentration or by interfering with the neurons' response to it. Herrup says, 'We have ideas of what the signal might be, but there is no direct evidence for it yet. I am very partial myself to the inflammatory theory of AD, which says that a lot of the progression of AD, not the initiation, is due to chronic brain inflammation and activation of microglial cells. The cytokines that are released by these cells may actually be the source of the mitotic pressure that the nerve cells ultimately succumb to' (Fig. 2).

Another approach explored by Herrup and his team is to prevent the cells from re-entering the cell cycle, independent of what triggers them to do so. He concludes, 'Disregulation of the cell cycle may underlie more diseases than just cancer. Certainly, in terms of where we are looking in our attempt to block the effect of the mitotic pressure on these cells, we are going straight to the cancer literature where the work on the cell cycle has been extraordinary. That work is going to feed directly into what we are doing.'

References

1 Khachaturian, Z.S. and Mesulam M-M. (2000) Alzheimer's disease. a compendium of current theories. *Ann. New York Acad. Sci.* 924
2 Yang, Y. *et al.* (2001) DNA replication precedes neuronal cell death in Alzheimer's disease. *J. Neurosci.* 21, 2661–2668
3 Wu, Q. *et al.* (2000) β-Amyloid-activated microglia induce cell cycling and cell death in cultured cortical neurons. *Neurobiol. Aging* 21, 797–806

Serious infections stunt tumour growth

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Severe infections could have anti-tumour properties that are independent of the specific immune system. Indeed, it has long been recognized that serious infections can slow or even halt tumour growth. Andrei Thomas-Tikhonenko (University of Pennsylvania, Philadelphia, PA, USA) and colleagues propose that infections might induce the upregulation of anti-angiogenic factors, which stunt cancer growth by cutting off the blood supply. Identifying the key factors responsible for this upregulation could, therefore, offer exciting new prospects for cancer therapy.

Historical observation

William B. Coley first observed that infection interferes with tumour growth in 1893. He described how streptococcal infection resulted in the regression of rare soft-tissue sarcomas in ten patients[1]. Subsequent studies showed that infection by several other pathogens also conferred host resistance to tumours and that the pathogens themselves could non-specifically activate macrophages to kill tumour cells *in vitro*. 'Despite the long-held belief that infection somehow stimulates the immune system, causing increased tumour surveillance, no cell-type or factor has ever been found to fully explain this phenomenon,' explains Thomas-Tikhonenko.

Is the immune system involved?

Thomas-Tikhonenko's group investigated the growth of B16F10 melanomas in mice infected by *Toxoplasma gondii*. The B16F10 cell line is only weakly immunogenic and causes rapidly growing tumours when injected subcutaneously in mice. As expected, mice infected by *T. gondii* on the day of tumour implantation developed much smaller tumours. By day 12 after implantation, the tumours

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