mechanism involves tumours expressing Fas, which enables them to delete (by apoptosis) antitumour lymphocytes. This phenomenon is known as the "tumour counterattack."[10] There is also increasing evidence that systemic stimuli such as insulin-like growth factor I (anti-apoptotic) and insulin-like growth factor binding protein 3 (pro-apoptotic) may influence the development and progression of many common cancers.[11]

Potential treatments

This brief review has shown that many human diseases may result when cells die that shouldn't or others live that should die. Modulation of apoptotic processes may thus offer valuable methods of treatment. It is now known that many existing drugs (for example, non-steroidal anti-inflammatories) act by altering the levels of apoptosis. Virtually all cytotoxic drugs and radiotherapy programmes induce apoptosis in tumour cells, and resistance to apoptosis is associated with treatment failure. These therapies also induce apoptosis in normal cells, and side effects on bone marrow, gut, and oral mucosa limit the dose that can be used. Many more new treatment strategies are currently in preclinical trials and show promise (box).[3 12] If future clinical studies are fruitful, this translation from basic science to clinical practice will be unique as it will affect not just one, but a broad range of disorders—and many patients will benefit.

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How apoptosis is regulated, and what goes wrong in cancer

Johanna Sjöström, Jonas Bergh

Departments of Oncology and Pathology, Helsinki University Hospital, PL 180, 00029 HYKS, Finland

Johanna Sjöström *researcher*

Radiumhemmet, Karolinska Institute and Hospital, SE-171 76 Stockholm, Sweden

Jonas Bergh *professor*

Correspondence to: J Sjöström johanna.sjostrom@hus.fi

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Programmed cell death (apoptosis) is an evolutionarily conserved pathway needed for embryonic development and tissue homoeostasis.[1] Apoptosis is the normal physiological response to many stimuli, including irreparable DNA damage. Various diseases evolve because of hyperactivation (neurodegenerative diseases, immunodeficiency, ischaemia-reperfusion injury) or suppression of programmed cell death (cancer, autoimmune disorders).[2]

In cancer, the balance between proliferation and programmed cell death is disturbed, and defects in apoptotic pathways allow cells with genetic abnormalities to survive. Most cytotoxic and hormonal treatments, as well as radiation, ultimately kill cancer cells by causing irreparable cellular damage that triggers apoptosis. Consequently, the efficacy of cancer treatments depends not only on the cellular damage they cause but also on the cell's ability to respond to the damage by inducing apoptotic machinery. Accordingly, mutations in apoptotic pathways may result in resistance to drugs and radiation. Such mutations might serve as predictors of chemoresistance and, most importantly, as new treatment targets.

Mitochondria and cell surface receptors mediate the two main pathways of apoptosis.[1] The mitochondrial pathway is thought to be important in response to cancer treatment and is mediated by bcl-2 family proteins. The final execution of cell death is performed by the caspase cascade, which is triggered by release of cytochrome C from mitochondria.

Apoptotic genes

The most studied genes related to apoptosis are the tumour suppressor gene p53, the anti-apoptotic gene bcl-2, and the pro-apoptotic gene bax. Normal wild type p53 can limit cell proliferation after DNA damage by two mechanisms: arresting the cell cycle or activating apoptosis.[3] p53 has a dual and complex role in chemosensitivity; it can either increase apoptosis or arrest growth and thereby increase drug resistance. This may explain why promising preclinical data indicating that presence of wild type p53 would predict chemosensitivity have translated into more conflicting clinical data.[4 5] Moreover, drugs that do not cause DNA damage, for instance taxanes and vinca alkaloids, may induce apoptosis through pathways that are independent of p53. Heterogeneous clinical data may also have resulted from use of different protein and molecular based methods to determine the p53 status. Sequencing gives the most complete picture of the p53 status,[6] but even functional p53 does not exclude defects somewhere downstream in the apoptotic pathway. The importance of p53 for chemosensitivity, however, is supported by the fact that, currently, the most curable cancers are among the minority of tumours in which p53 is not mutated—that is, some haematopoietic and germ cell tumours.

Overexpression of bcl-2 was first associated with follicular B cell lymphomas. Theoretically, overexpression of bcl-2 could provide a survival advantage for cancer cells, but in vivo, bcl-2 expression has been

associated with a more favourable prognosis in many malignant diseases. Indeed, in breast cancer, tumours positive for bcl-2 often have oestrogen receptors and a more favourable prognosis. Oestrogen has been shown to be a positive regulator of bcl-2 gene expression in breast cancer cell lines.[7]

The pro-apoptotic protein bax is the most studied member of the bcl-2 family in cancer. Loss of bax function seems to be important in the pathogenesis of colorectal cancers.[8] In preclinical studies, induction of bax has been reported to restore sensitivity to drug and radiation induced apoptosis, whereas overexpression of bcl-2 has been shown to suppress apoptosis. However, the few clinical studies on the predictive value of bcl-2 family proteins in treatment of haematological malignancies or solid tumours have produced conflicting results.[5 9]

Inducing apoptosis

Several strategies have been tried to induce the apoptotic programme. The first approach was gene directed therapy to restore normal p53. Although the results have been interesting, refinement of the vectors and delivery concepts is needed. The first phase I pharmacokinetic study with bcl-2 antisense oligonucleotide (which effectively degrades messenger RNA) in patients with non-Hodgkin's lymphoma shows that the treatment is well tolerated.[10] However, only one patient showed objective response while 11 patients had stable disease, and in nine patients the cancer progressed.[10] These types of therapies, however, are likely to be more efficient when combined with chemotherapy or radiation, which triggers apoptosis. It might also be beneficial to combine pro-apoptotic treatment with anti-angiogenesis treatments as hypoxia has been shown to promote apoptosis.[11]

Tumour heterogeneity and clonal variability will provide an extra challenge for future investigations and successful treatments based on apoptosis. The factors in apoptotic pathways have opened a new exciting dimension in our understanding of how and when cancer treatments succeed or fail—this holds promise for better therapeutic strategies in the future.

Competing interests: JS has received fees for speaking, organising education, and consulting from Aventis Pharma. She also works as a medical adviser at Aventis Pharma, Finland. The Karolinska Institute has a formal research collaboration with Bristol Myers Squibb on pharmacogenomics, from which JB's research group benefit. JB has received reimbursement for attending and speaking at scientific meetings and symposiums from many pharmaceutical companies active in oncology. He has received fees for consulting from Pharmacia.

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Does apoptosis have a role in neurodegeneration?

Rosemary M Gibson

School of Biological Sciences, University of Manchester, Manchester M13 9PT

Rosemary M Gibson
research fellow

r.m.gibson@man.ac.uk

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Cells within the central nervous system die during both acute and chronic neurodegenerative disorders. Since the morphological and biochemical features of apoptosis were first described, neuroscientists have been asking whether this cell death is due to apoptosis and whether elucidating the mechanisms of apoptosis can provide new treatment strategies for intractable diseases such as stroke, Alzheimer's disease, and Huntington's disease.

Detecting apoptosis

Much debate has ensued. Firstly, cell death in the central nervous system may not fit perfectly with our current classification of apoptosis and necrosis, which was defined using peripheral cells. Some of the methods used may not distinguish conclusively between apoptosis and necrosis. For example, transferase-mediated dUTP nick end labelling (TUNEL), a staining method that detects the broken ends of DNA within cells, is used to provide evidence of apoptosis. However, DNA can be fragmented in necrosis too.

Secondly, clinical symptoms may result from loss of neuronal function rather than apoptotic cell death. Many chronic neurodegenerative diseases are associated with intracellular aggregates of mutated proteins that cannot readily be disrupted, even by aggressive laboratory procedures. Such deposits may compromise neuronal function—for example, by blocking transport of nutrients along axons. A study of Huntington's disease in mice has shown that if generation of the mutant protein is halted, the aggregates are dissolved by the proteasome (the cellular machinery for removing unwanted proteins) and the neurological scores of the mice improve.[1] This suggests that, initially at least, symptoms may result from compromised neuronal function, with cell death having a subsequent role.

Supporting evidence

Evidence supporting a role for apoptosis in neurodegenerative diseases has come from studying rodent brain cells and by manipulation in animal models of