NEW TARGETS FOR TREATING CANCER
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BACKGROUND

Apoptosis

A cancer cell emerges from a normal tissue as a result of several inherited and acquired mutations in its genes which release it from normal growth-controlling mechanisms. One such mechanism is the genetically-controlled process of programmed cell death. All cells in the human body are programmed to die unless they receive a survival signal. Loss of this function means that cells with damaged or mutated DNA and the potential for malignant transformation are not eliminated. Moreover, once the cancer phenotype is established, selective clonal expansion of the cancer cell line will follow. The process of programmed cell death, known as apoptosis, is regulated by a number of genes, including Bcl-2 and the tumour-suppressor gene p53, which is found in all normal cells. Interestingly, mutation of the p53 gene is the commonest mutation found in human cancer cells, whilst Bcl-2 translocation is a feature of follicular lymphomas.

The micro-environment

The survival of an uncontrolled population of cancer cells depends on an appropriate remodelling of the surrounding tissue matrix to accommodate the expanding tumour mass and to ensure an adequate supply of nutrients and oxygen. The tissue matrix is made up of proteins which include the fibrillar collagen of bone, skin and interstitial tissue and the non-fibrillar collagens lamina and fibronectin. Passing through this matrix are the blood capillaries. This micro-environment is constantly undergoing change by degradation and remodelling, processes which are made possible by a family of enzymes – the matrix metalloproteinases (MMPs).

Alteration of the micro-environment is necessary for the growth of new blood vessels. New blood vessel formation is known as angiogenesis and is activated by a number of cytokines, notably vascular endothelial growth factor (VEGF) and basic fibroblastic growth factor (bFGF). Thus matrix remodelling and angiogenesis are closely synchronized, each depending on the other for normal growth and repair.

Metalloproteinases and angiogenesis factors are found in abundance in the micro-environment surrounding cancer cells. Normal tissue structures are disrupted, allowing expansion of the tumour mass, and facilitating invasion of blood and lymphatic vessels and metastatic spread. Interestingly, the highest serum levels of MMPs have been found in cancers with the greatest metastatic potential. Similarly, studies of microvessel density in breast and lung tumours show a correlation between vascularity in the primary tumour and the extent of metastatic spread indicating that angiogenesis is an important determinant of prognosis in these patients.

TARGETS FOR TREATMENT

Until now, targets for anti-cancer drugs have been the various components of the cell cycle, maximising the biological differences in growth and reparation rates between cancer cells and normal cells. The toxicity of treatments is high and improvements in survival, with few exceptions, have been disappointingly small. New technologies and molecular biology have given us a new understanding of the malignant process and new opportunities for targeting and monitoring drug treatments.

Apoptosis

A number of chemicals, including retinoids, arsenical compounds, antibiotics such as Clarithromycin and dietary factors including gamma linolenic acid are being screened for apoptotic activity in animal model systems. It is now known that many cytotoxic drugs such as the anthracyclines and taxanes can induce apoptosis which contributes to their cytotoxic effects.

MMPs

Inhibition of MMPs has been evaluated in animal tumour systems. Xenografts of human ovarian and colorectal cancers and melanoma have demonstrated tumouricidal effects and prolonged survival in animals treated with the synthetic oral MMP inhibitor marimastat. Inhibition of invasive tumour growth, metastatic spread and angiogenesis have been observed. Marimastat is being evaluated in Phase I clinical trials in a range of solid cancers, with and without cytotoxic chemotherapy. Phase I studies define safety and tolerability. Information on efficacy (Phase II) is awaited with interest.
Angiogenesis

Tumouricidal effects and inhibition of metastatic spread of xenografts have also been described with angiogenesis inhibition. Potent endogenous inhibitors include angiostatin and endostatin but there is a number of synthetic agents which have similar effects in animal systems. One of these, the drug thalidomide, is currently being evaluated in Phase II clinical trials. In the late 1950s and early 1960s, pregnant women took thalidomide during pregnancy for its anti-emetic and sedative effects and about 10,000 gave birth to infants with missing or stunted limbs. Because of this teratogenic effect it was one of a number of drugs screened many years later for angiogenesis inhibition in a search for new treatments for diabetic retinopathy. It was found to inhibit the angiogenesis induced by bFGF in a rabbit cornea model assay.

Clinical trials of thalidomide in cancer are underway. A Phase II study was reported at the American Society of Clinical Oncology in Los Angeles in May 1998. Forty-eight patients were treated: seventeen ovary cancers, sixteen melanomas, eight renal cancers and seven breast cancers. There were three responders and ten had stable disease on treatment. Responses were reflected in a fall or stability of serum VEGF levels. These results seem unremarkable, but they were found in a heavily pre-treated population of patients with advanced disease. Much greater effects might be predicted in patients with minimal residual disease.

SUMMARY

Drugs and biological agents which target apoptosis and the micro-environment are promising new approaches to the medical treatment of cancer.

NEW PUBLICATION

Title: One Renegade Cell: The Quest for the Origins of Cancer
Author: Robert Weinberg
Publisher: Weidenfeld and Nicholson
Price: £12.99

The author is professor of biology at the Massachusetts Institute of Technology and is also a director of an oncology laboratory specializing in this research in Cambridge, Mass.