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An overview of apoptosis and the prevention of colorectal cancer

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Abstract

Colorectal cancer arises as a result of the accumulation of genetic errors many of which affect the control of apoptosis. Effective chemoprevention strategies for colorectal cancer must rectify these genetic defects. Mutation of *apc* is often the initiating genetic lesion in colorectal cancers that develop along the chromosomal instability pathway. Depending on the cellular context, loss of *apc* activates the Wnt signalling pathway causing immediate widespread apoptosis of colorectal epithelial cells and defects in differentiation and cell migration. Only cells that are inherently resistant to apoptosis survive this initial wave of apoptosis. These surviving cells constitute the epithelial population that develop into adenomas. Two gene targets of the Wnt signalling pathway are of particular relevance to apoptosis. Although controversial, *survivin* may function to inhibit apoptosis. MYC has two outputs in normal cells, the induction of apoptosis and proliferation. These opposing functions work so that MYC can only induce cell proliferation in cells if apoptosis is disabled. *p53* couples apoptosis to mitogenic signals and survival pathways. Under some circumstances, NF-κB can act as an inhibitor of apoptosis possibly through increased expression of bcl-x_L. Tumours that evolve by the microsatellite instability pathway often have mutations in the proapoptotic gene *bax*. Colonic adenomas express cyclo-oxygenase-2 (COX-2) and may be targets of chemoprevention before the development of malignancy. However, the recent discovery that coxibs increase the risk of serious cardiovascular events limits their use as chemopreventive agents. Nevertheless, aspirin remains a drug of great interest as it is already known to reduce the risk of colorectal cancer by up to 50%. The balance of evidence shows that high vegetable fibre diets can prevent colorectal cancer, probably via the fermentation of butyrate enhancing the apoptotic response to DNA damage.

Introduction

On a global scale, colorectal cancer is the fourth commonest malignant neoplasm after lung, breast and prostate [1]. As will be discussed below, approximately 90% of colorectal cancers are derived from benign adenomatous lesions which are estimated to take 5–15 years to evolve into invasive cancer (for review, see [2], [3]). A wealth of epidemiological and clinical trial data suggests that if these premalignant lesions are identified and removed, the subsequent development of colorectal cancer is aborted [4], [5], [6]. Unfortunately, adenomas are largely asymptomatic and so require population-based screening programmes for their detection. Colorectal cancer develops through a number of well characterized stages based on the degree of invasion. When the cancer is confined to the wall of the bowel (Stage 1, $T_1N_0M_0$), resection is essentially curative with 5 year survival rates of 90% or more. However, in Stage IV disease where distant metastases are present, the 5 year survival drops to 15% [7]. Overall, the 5 year survival rate of colorectal cancer is 50%.

These diagnostic challenges have led investigators to attempt to prevent adenoma formation with the minimum of risk. The long natural history of adenomas, their accessibility to biopsy and the existence of two inherited forms of colorectal cancer whose genetic changes mirror those of sporadic cancer have enabled investigation of molecular pathogenesis of sporadic colorectal cancer in great detail, perhaps more than any other neoplasm [8]. These investigations have shown that numerous errors in pathways controlling apoptosis (programmed cell death) occur during the development of colorectal cancer. These abnormalities render cells with clinically significant mutations resistant to elimination through apoptosis (programmed cell death). Abnormalities in core apoptosis mechanisms go hand in hand with inherent resistance to chemotherapy and radiotherapy. Clinical evidence is emerging that defective apoptosis is of pathogenic significance [9]. Apoptosis rates in rectal mucosa are inversely related to the presence of adenomas, while the clinical response of adenomas to treatment with the COX-2 inhibitor celecoxib correlates positively with apoptosis [10], [11]. Thus, a full understanding of molecular abnormalities in apoptosis and its relationship to other molecular pathogenic mechanisms is essential for the rational development of prevention strategies against colorectal cancer.

Section snippets

Molecular pathogenesis of colorectal cancer

Hahn and Weinberg have argued that a normal cell has only to acquire six phenotypes in order to behave as a fully transformed malignant cell. These phenotypes are resistance to growth inhibition, immortalization, independence from mitogenic stimulation, the ability to acquire their own blood supply, the ability to invade and metastasize and the ability to suppress or evade apoptosis [12]. These characteristics are acquired through the mutation of key genes regulating these functions. The…

Vegetable products

A number of dietary components have been reported to cause apoptosis with the implication that mutant cells will, in this way, be eliminated thereby preventing cancer. Such inferences are fraught

with difficulty as modulation of cell death may not necessarily be responsible for cancer protection in the complex environment of the human gut [110]. Diets high in fibre (non-starch polysaccharides) have been recommended to prevent colorectal cancer [111], [112]. Epidemiological studies and…

Conclusions

The majority of genes that are functionally important in the pathogenesis of colorectal cancer in some way inactivate or raise the threshold for induction of apoptosis, giving a growth advantage to neoplastic and malignant clones. Clinical data are emerging that apoptosis in human colonic epithelium is inversely related to cancer development. Studies of mouse models are starting to illustrate how apoptosis fits in and interacts with the other important phenotypes required by cancer cells as…

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