Chapter 4
Apoptosis in Colorectal Tumorigenesis and Chemotherapy

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Abstract Colorectal cancer is the second most common cancer in the western world. At least 40% of colorectal cancer patients develop metastases; chemotherapy alone or in combination with radiotherapy is usually used as adjuvant treatment for advanced disease. Unfortunately adjuvant treatments are often ineffective due to the development of resistance. A major contributor to chemo-resistance is the inhibition or avoidance of apoptosis. This chapter reviews the genetic mutations in colorectal tumorigenesis; the alterations of apoptosis in colorectal cancer progression; and the relationship between mutations and apoptotic changes. The factors which affect and regulate apoptosis in colorectal cancer development are evaluated. The dysfunction in different apoptotic pathways through which colorectal cancer cells develop resistance to chemotherapies is discussed. Finally the potential molecular targets and therapeutic strategies designed against these targets are proposed.

Keywords Chemo-resistance · Colorectal cancer · Dysfunction of apoptosis · Genetic mutations

Introduction
Colorectal cancer (CRC) is the second most common cancer in the western world. Despite advances in the management of this condition, including improved surgical technique, the use of chemo or radiotherapy and more recently the use of screening, the mortality has not changed for decades. Colorectal cancer is presently treated by surgical ablation, but many tumours are detected at a late stage when surgery cannot cure the disease. At least 40% of patients with colorectal cancer develop metastases; chemotherapy alone or in combination with radiotherapy can be used as an adjuvant therapy to surgery for more advanced disease (Labianca et al. 1997).
However, these approaches are not highly effective against disseminated colorectal metastases (Magnuson et al. 1995). New therapeutic strategies are needed for treatment of advanced or metastatic colorectal cancer.

**Epidemiology of Colorectal Carcinoma**

Colorectal carcinoma is primarily a disease of the western world, with the highest reported incidence of about 40 cases per 100,000 people occurring in west Europe closely followed by the USA. It is rare in Asia, Africa and parts of South America. Although no age group is immune, it occurs maximally in the 7th decade of life. The sex incidence of colorectal cancer is almost equal but rectal tumours are more common in men and colonic carcinoma more common in women giving male to female ratio for death of 6:5 for rectal and 7:11 for colonic carcinomas respectively.

**Aetiology of Colorectal Carcinoma**

Aetiologically colorectal cancers can be divided into three categories: sporadic (a single case of CRC), familial (two or more first-degree relatives with CRC) and hereditary CRC. Aetiological studies have shown that the incidence of colorectal carcinoma differs between countries and between different cultural groups within a given country. The finding that migrants show the cancer incidence of their adopted country within a generation supports environmental and cultural factors in the aetiology of colorectal cancer. The most strongly implicated environmental and cultural factor is a high fat, high protein, low fibre diet (Willett 1989). A high fat diet stimulates choleresis increase the amount of primary bile acids in the faeces. The bile acid are then metabolised by colonic bacterial enzymes leading to the production of lithochoholic and chenodeoxycholic acid, both known mutagens. Bacterial action on protein breakdown products entering the large bowel may produce known carcinogens such as the N-nitrosamines. Dietary fibre consists of various undigested polysaccharides, mainly celluloses and some resistant starches. Its protective effects result from increasing the bulk of stool, retaining faecal water, diluting and absorbing luminal toxins and reducing colonic transit time hence decreasing exposure of colon to carcinogens.

Apart from environmental and diet factor, inflammatory bowel disease also predisposes to colorectal carcinoma. Ulcerative colitis increases the risk of developing colorectal cancer with tumours starting to appear 5–8 years after the onset of the disease. Following this the risk increase almost exponentially with time, about 5% of patient developing tumours after 10 years of disease, 20% at 20 years and almost 50% at 30 years. The risk for patients with Crohn’s colitis developing colorectal cancer is less than ulcerative colitis, but still is 4–20 times higher than the general population. Some medical treatments including implantation of ureter into colon, cholecystectomy gastric surgery and terminal ileal resection may also be associated