Chapter 3

CYTOKINES, NF-κB, MICROENVIRONMENT, INTESTINAL INFLAMMATION AND CANCER

Arndt J. Schottelius\textsuperscript{1} and Harald Dinter\textsuperscript{2}

\textit{Development Sciences, Genentech, Inc., 1 DNA Way, South San Francisco CA 94080\textsuperscript{1} and Research Business Area Dermatology USA and Research Business Area Oncology USA, Berlex Biosciences, 2600 Hilltop Drive, Richmond CA 94806\textsuperscript{2}}

Abstract: Inflammation and cancer have been viewed as closely linked for many years. This link is not merely a loose association but causative. In colorectal cancer (CRC), chronic inflammation as observed in inflammatory bowel (IBD) disease is a key predisposing factor and IBD-associated CRC comprises five percent of all CRCs. Although the molecular mechanisms linking IBD with CRC are not well understood, recent results obtained in preclinical models point to the transcription factor NF-κB as a central player. On the one hand, NF-κB regulates the expression of various cytokines and modulates the inflammatory processes in IBD. On the other, NF-κB stimulates the proliferation of tumor cells and enhances their survival through the regulation of anti-apoptotic genes. Furthermore, it has been clearly established that most carcinogens and tumor promoters activate NF-κB, while chemopreventive agents generally suppress this transcription factor. Actually, several lines of evidence suggest that activation of NF-κB may cause cancer. These include the finding that NF-κB genes can be oncogenes, and that this transcription factor controls apoptosis, cell-cycle progression and proliferation, and possibly also cell differentiation.

Keywords: colorectal cancer; chronic inflammation; NF-κB; macrophages; growth factors
1. INTRODUCTION

Inflammation and cancer have been viewed as closely linked for many years. This link is not merely a loose association but causative. In fact, it is estimated that inflammation-associated processes caused by chronic infections contribute to about one-third of the world’s cancers (Ames et al., 1995). Oxidants produced by leukocytes and other phagocytic cells to fight bacteria and parasites protect the infected individual from death by infection but at the same time cause oxidative damage to the individual’s own DNA. This damage, especially when accumulated over time, may cause multiple mutations ultimately leading to the development of cancer. Furthermore, once the cancer is established, multiple inflammatory processes can contribute to the growth and dissemination of cancer cells. For example, tumor-associated macrophages were shown to produce factors which stimulate tumor angiogenesis, promote metastases and enhance the invasiveness of tumors. Moreover, these macrophages produce mitogens such as epidermal growth factor (EGF), which can directly affect the proliferation of tumor cells (Bingle et al., 2002; Leek and Harris, 2002). Thus, it is not surprising that increased density of tumor-associated macrophages is correlated with poor prognosis in some tumor types or in certain tumor stages (Lin and Pollard, 2004; Miyagawa et al., 2002; Toomey et al., 1999; Lackner et al., 2004).

In colorectal cancer (CRC), chronic inflammation as observed in inflammatory bowel diseases (IBD) is a key predisposing factor. Five to ten percent of IBD patients develop colon cancer after 20 years and 12-20% after 30 years with the disease (Munkholm, 2003). IBD-associated CRC comprises five percent of all CRCs. Furthermore, ulcerative colitis, a subtype of IBD, besides Familial Adenomatous Polyposis and Hereditary Nonpolyposis Colorectal Cancer, is the most common condition predisposing to CRC (Itzkowitz and Yio, 2004). The importance of inflammatory processes in CRC is highlighted by a large number of studies demonstrating the efficacy of anti-inflammatory drugs in CRC. Nonselective, nonsteroidal, anti-inflammatory drugs (NSAIDs) were shown to decrease the mortality in CRC, and aspirin as well as cyclooxygenase-2 inhibitors reduced the risk of CRC (Thun et al., 1993; Giovannucci et al., 1994; Collet et al., 1999; Langman et al., 2001; Jolly et al., 2002; Chan, 2003; Koehne and Dubois, 2004). Although the molecular mechanisms linking IBD with CRC are not well understood, recent results obtained in