10  **TNF Blockade: An Inflammatory Issue**


Abstract. Tumor necrosis factor (TNF), initially discovered as a result of its antitumor activity, has now been shown to mediate tumor initiation, promotion, and metastasis. In addition, dysregulation of TNF has been implicated in a wide variety of inflammatory diseases including rheumatoid arthritis, Crohn’s disease, multiple sclerosis, psoriasis, scleroderma, atopic dermatitis, systemic lupus erythematosus, type II diabetes, atherosclerosis, myocardial infarction,
osteoporosis, and autoimmune deficiency disease. TNF, however, is a critical component of effective immune surveillance and is required for proper proliferation and function of NK cells, T cells, B cells, macrophages, and dendritic cells. TNF activity can be blocked, either by using antibodies (Remicade and Humira) or soluble TNF receptor (Enbrel), for the symptoms of arthritis and Crohn’s disease to be alleviated, but at the same time, such treatment increases the risk of infections, certain type of cancers, and cardiotoxicity. Thus blockers of TNF that are safe and yet efficacious are urgently needed. Some evidence suggests that while the transmembrane form of TNF has beneficial effects, soluble TNF mediates toxicity. In most cells, TNF mediates its effects through activation of caspases, NF-κB, AP-1, c-jun N-terminal kinase, p38 MAPK, and p44/p42 MAPK. Agents that can differentially regulate TNF expression or TNF signaling can be pharmacologically safe and effective therapeutics. Our laboratory has identified numerous such agents from natural sources. These are discussed further in detail.

10.1 Introduction

Tumor necrosis factor (TNF)-α and TNF-β, produced primarily by monocytes and lymphocytes, respectively, were first isolated in 1984, as cytokines that kill tumor cells in culture and induce tumor regression in vivo (Aggarwal et al. 1984). Intravenous administration of TNF to cancer patients produced numerous toxic reactions, including fever (Kurzrock et al. 1985). In animal studies, TNF has been shown to mediate endotoxin-mediated septic shock (Beutler et al. 1985). Other reports have indicated that dysregulation of TNF synthesis mediates a wide variety of diseases, including rheumatoid arthritis and inflammatory bowel disease (also called Crohn’s disease) (Fig. 1).

10.2 TNF Cell Signaling

TNF is a transmembrane protein with a molecular mass of 26 kDa that was originally found to be expressed in macrophages and has now been found to be expressed by a wide variety of cells. In response to various stimuli, TNF is secreted by the cells as a 17-kDa protein through a highly regulated process that involves an enzyme: TNF-activating converting enzyme (TACE).