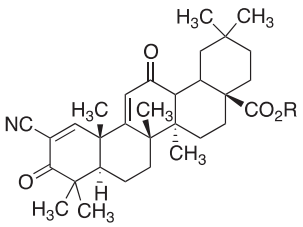
8.1.6 Inhibitors of NK-κB and TNF-α

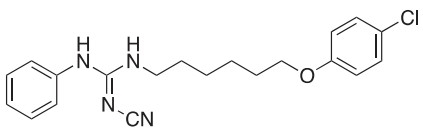
NF-κB is a family of heterodimeric transcription factors that control hundreds of genes and are present in many, if not all, cell types of the body. These factors can be activated by various physiological agents and stress situations, such as those produced in cancer cells due to the higher levels of ROS originated by their high rate of metabolism and inefficient respiration. The chronic activation of NF-κB, which is characteristic of many cancers, is a critical adaptation to these higher levels of oxidative stress that allows cancer cell survival by preventing activation of the pro-apoptotic c-Jun N-terminal kinases (JNKs; see Chapter 10, Section 6.5.4) through an increased expression of JNK–MAPK phosphatase 1 (MKP1).[211] NF-κB also induces inhibition of Smad expression, leading to subsequent inhibition of the transforming growth factor-β (TGF-β) signaling (see Chapter 10, Section 7). However, in certain tumors in which other oncogenes provide pro-survival signals, NF-κB enhances instead the sensitivity to cytotoxic chemotherapy, thereby exerting a tumor-suppressor function.[212]

Some synthetic triterpenoids, especially CDDO and CDDO-Me, inhibit NF-κB activity, leading to sustained activation of JNKs and triggering caspase-mediated apoptosis. These compounds have shown potent activity in multiple cancer animal models and in treatment-resistant cancer cell samples. CDDO-Me was able to prevent the progression of pre-neoplastic lesions to the adenocarcinoma of the prostate in a mouse model.[213]

NF-κB activity can also be inhibited by interference with its activation processes, which depends on a group of proteins known as IκB (inhibitory proteins of κB family, also known as IKK). For instance, the anticancer activity of CHS-828 (a compound evaluated in clinical trials without notorious results in solid tumors)[214] is due to inhibition of the IKK activity leading to apoptosis promotion.[215] In unstimulated cells, IKK proteins sequester NF-κB in the cytoplasm, but when cytokines such as TNF-α and IL-1β are triggered, they induce IκB degradation, thus permitting the translocation of NF-κB to the nucleus (see Figure 11.5).[216]



R = H CDDO (RTA-401)
R = CH_3 CDDO-Me (RTA-402)



CHS-828

On the other hand, TNF-α is a multifunctional cytokine highly expressed in tumors, in which it is thought to be proangiogenic. Paradoxically, it is a potent antivascular cytokine at higher doses, which may be clinically used to destroy tumor vasculature. TNF-α is also able to initiate cellular apoptosis, but this apoptotic pathway is deactivated in tumor cells. Due to its very toxic systemic side effects, administration of TNF-α has limited uses, and to target TNF-α specifically to tumors, the human recombinant hTNF-α gene (rhTNF-α) has been tested. Its success was limited to the regional treatment of locally advanced solid tumors. More complex treatments to overcome these limitations include the hybrid adeno-associated virus phage vector AAVP-TNF-α that induces the tumor endothelium to express TNF-α[217] and also the use of a conjugate protein obtained by fusion of a recombinant mutant human TNF-α with the peptide GX-1, which binds selectively to the human gastric cancer vasculature.[218] Both strategies have been studied in human melanoma and gastric tumor models.