Chapter - VI

Summary & Conclusion
The function of NF-kB family members in learning and memory appears to be distinct from possible effects of these transcription factors on apoptosis. Recently, several agents inhibiting the ubiquitin proteasome pathway have been developed. In addition to hindering IκB degradation, proteasome inhibitors induce apoptosis by affecting the levels of a variety of short-lived proteins, such as p53, Bax, and cyclin-dependent kinase inhibitors. Malignant cells appear to be more susceptible to proteasome inhibition than normal cells, making this a promising candidate therapy for the treatment of cancer.

The drug bortezomib (N-pyrazinecarbonyl-L-phenylalanine- L-leucine boronic acid), the first drug targeting the NF-kB pathway to enter clinical trials, is a promising anticancer agent. This substance rapidly inhibits proteasomal degradation in a reversible manner by blocking the enzymatic activity of the 20S proteasome. In a large multicenter phase II clinical trial, approximately one-third of patients with advanced multiple myeloma responded to bortezomib therapy. Common adverse events included gastrointestinal symptoms, fatigue, thrombocytopenia, and sensory neuropathy, most of which could be managed with standard approaches. The United States Food and Drug Administration (FDA) immediately approved this drug for the treatment of multiple myeloma patients who had relapsed after at least two prior treatment regimens and exhibited resistance to their last treatment.
Currently, several clinical trials with NF-kB as target are ongoing, examining its efficacy against a range of haematological and non-hematological malignancies.
Conclusion

It is now clear that NF-κB is a key player in the pathogenesis of rheumatoid arthritis, and is central to the production of proinflammatory mediators in the inflamed synovium. However, whilst much is known about the signalling pathways that result in NF-κB activation in transformed cells and in mice, these events often differ in the cells that are relevant to arthritis, such as primary human myeloid cells and cells in the synovium. These events are only now being fully explored, using new technologies such as adenoviral infection. Cutting edge technologies, such as small inhibiting (si) RNA, will doubtless also give great insights into the functional roles of these proteins in the future. This will be important to help identify new therapeutic targets for the treatment of arthritis and validate those therapies already under development.

The exquisitely specific NF-κB response induced by different stimuli in different cells gives hope that treatments can be developed to specifically target NF-κB activation in the inflamed synovium without detrimental effects on the innate immune system. This could overcome potentially serious problems that may occur as a result of long-term NF-κB inactivation. In addition to their roles in immune and inflammatory responses, NF-kB family members are well known as crucial regulators of cell proliferation, differentiation, apoptosis and oncogenesis. Initially, research in the CNS also focused attention on the function of NF-kB in response to injury and stress. Along with its previously described function in neurological disorders and apoptotic processes within the brain, NF-kB now has a confirmed role in normal physiological function at both cellular and behavioral levels. Many exciting avenues remain to be explored in the
investigation of NF-κB function. There has been very little work done to delineate the signal transduction mechanisms leading to NF-κB activation. Novel modulatory components in the NF-κB signaling pathways are likely to be identified. Further characterization of retrograde transport mechanisms for NF-κB transcription factors could shed light on the general process of communication. It will also be important to examine potential roles of NF-κB family members in development of the inflammation and cancer and to uncover the relationship of these processes to NF-κB function.

As the aberrant activation of NF-κB is associated with the generation of tumors as well as their maintenance and progression of a range of lymphoid malignancies, NF-κB has been expected as an attractive target for therapy. *In vitro* inhibition of NF-κB activity in lymphoma cell lines suggested this approach to be effective. NF-κB is proving to be paramount in the clinical field. Research on NF-κB will surely provide more effective, directed, and sophisticated treatments for malignancies in the future.