Student Review

The master regulator: NF-kappa B

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Nuclear factor kappa B (NF-κB) proteins are a family of transcription factors that have a variety of essential roles in eukaryotic organisms and have been found to play a role in many human diseases. NF-κB was identified as a regulator of expression of the κB light chain in B cells more than two decades ago. The NF-κB family of proteins is composed of transcription factors that have been found to play a part in the control of many normal cellular processes, such as immune and inflammatory response, cellular growth, apoptosis, and developmental processes. Today, research into the function of regulation of the NF-κB family continues with the promise of new insight into human disease. Hyperactivation of these transcription factors has been found in many diseases including cancer, chronic inflammation, asthma and arthritis, and mounting research evidence has shown that NF-κB plays a major role in oncogenesis. Immense interest into mechanisms of regulation of NF-κB has arisen of late, which has been further sparked by the continually lengthening list of diseases linked to NF-κB dysfunction.

NF-κB proteins are conserved in a variety of organisms from the fruit fly, to mice, to humans; and have recently been found to occur in simple organisms such as Cnidarians. Various positive and negative regulatory elements exist that are essential for the understanding of NF-κB signaling. Inducing stimuli initiates IKK activation which leads to phosphorylation, ubiquitination, and degradation of IκB proteins. The NF-κB dimers that are released through this process translocate to the nucleus where they bind precise sequences of DNA and upregulate the transcription of target genes.

The NF-κB family of closely related transcription factors consists of five genes which give rise to seven proteins that share a Rel Homology Domain (RHD) in their sequence. The RHD contains sequences required for their dimerization and DNA binding and mediates interaction with their specific inhibitors. There are two classes of NF-κB proteins which differ in that one class is synthesized in its mature form and contains a transactivation domain which interacts with the transcriptional apparatus, while the other class is synthesized in its precursor form.

NF-κB dimers are found in the cytoplasm of most cells due to their interactions with the inhibitors of NF-κB (IκBs), which prevent nuclear localization and DNA binding. IκB proteins are a family of proteins that contain regions that interact with RHD domains of NF-κB. Through these interactions, IκB proteins primarily regulate the activity of NF-κB. When a cell receives one of many extracellular signals, NF-κB rapidly enters the nucleus and activates targeted gene expression. The NF-κB-IκB interaction that is most well known and studied is that of p50-rel A NF-κB dimer. The interaction of IκB with this dimer prevents NF-κB from binding to DNA and therefore results in NF-κB being maintained in the cytoplasm.

Most signals that lead to the activation of NF-κB activate a complex that contains an IκB kinase (IKK), which is serine specific. Once activated, the IKK complex leads to the phosphorylation of two specific serines near the N terminus of

Figure 1. Canonical pathway of NF-κB activation.

IkB, which makes IkB a target for ubiquitination. Additional pathways have been hypothesized but the shown pathway is by far the most understood. NF-kB that is released as a result of ubiquitination of IkB is now able to enter the nucleus and activate gene expression.

Many exogenous factors lead to the activation of NF-kB. It is a misconception that NF-kB is only activated by "negative" factors. NF-kB regulates many genes important for many biological processes and aging. An example of a human disease that results from NF-kB activation deficiency is incontinentia pigmentosa, an x-linked disorder. The disease is a result of a mutation in NEMO (see Figure 1 to see NEMO's position in the canonical pathway), preventing NF-kB from translocating to the nucleus. The disease is lethal in males (because the mutation prevents activation of NF-kB and males only have one copy of the x-linked gene). In females it may cause skin lesions, alopecia, abnormal teeth and many other symptoms.

A great deal of attention has been given to NF-kB due to its role in regulation of apoptosis and its link to various cancers. The role of NF-kB in apoptosis was first established in 1996 by four independent reports that showed that activation of NF-kB promotes cell survival. These four reports also unanimously showed that downregulation of NF-kB sensitizes the cells to apoptosis. It is speculated that NF-kB may activate genes which suppress cell death by various pathways (mitochondrial and death receptor). NF-kB is also known to induce expression of the Inhibitors of Apoptosis (IAPs) and some members of the Bel-2 family, which are involved in preventing apoptosis. Other evidence has shown that NF-kB can inhibit or activate apoptotic cell death, depending on various conditions in the cell, such as levels of RelA and c-Rel, which has further complicated the issue. Research has also shown that NF-kB activation also promotes survival of tumor cells and is involved in tumor cell metastasis.

Abnormal activation of the NF-kB pathway has been shown to be a contributing factor to asthma, atherosclerosis, AIDS, muscular dystrophy, heart disease, Alzheimer's disease, and many other human diseases. In addition, studies have also shown that various carcinogens and tumor promoters activate NF-kB. For example, UV radiation has been shown to cause cutaneous inflammation sunburn reactions (characterized by swelling, leukocyte infiltration, and accumulation of proinflammatory cytokines) leading to premature aging, and skin cancer. Suppression of NF-kB has been shown to block the sunburn-induced damage.

Evidence shows that there is sustained, or constitutive activation of NF-kB in tumor cells and cell lines. This contributes to the progression towards malignancy and resistance to therapeutic intervention in multiple human cancers. Several different tumor cell line types have been reported to express constitutively active NF-kB. These include leukemia, lymphoma, myeloma, melanoma, prostate, colon, breast, pancreas, and head and neck squamous cell carcinoma. Moreover this has also been found in samples obtained from cancer patients. Many research studies are being performed to further understand the cause(s) of this constitutive activation.

The pharmaceutical industry has been working on developing drugs that are targeted towards the NF-kB pathway and effective against cancer. The importance of NF-kB in tumor progression has been highlighted in several studies that utilized NF-kB inhibitors. As a result, many methods have been developed to prevent the activation of NF-kB. NF-kB inhibitors have already shown promise against tumor growth in xenograft models and have spurred clinical trials in some cases. A wide variety of compounds (e.g. IKK inhibitors, inhibitory peptides, antisense RNA, proteasome inhibitors, chemopreventive agents) are being evaluated for their ability to inhibit NF-kB.

Most recently, NF-kB has been the focus of anti-aging studies. Mechanisms of aging, as well as changes in gene expression during aging are not well understood. However, the NF-kB pathway has been implicated in several ageing studies. In one particular study, NF-kB was blocked for two weeks in the epidermis of aged mice. The skin characteristics of these mice reverted to those of young mice, both in terms of appearance and gene expression. Studies have also linked aging phenotypes to constitutive activation of NF-kB. Resveratrol, a compound synthesized by plants when being invaded by pathogens, has been commercially marketed for the past decade as an anti-aging compound. Though researchers are still investigating the claims made by resveratrol marketers, it is generally agreed that there is some validity that resveratrol could be used to modify the phenotypic symptoms of aging because of its ability to inhibit NF-kB.

Research into the function of regulation of the NF-kB family continues to provide us with greater insight into many human diseases. NF-kB shows much promise in helping us understand aging and cancer in humans, both areas that continue to challenge researchers. With the increasing human life span, it will be important to understand the mechanisms that drive aging and its associated diseases. Learning more about NF-kB will potentially improve quality of life and has the chance to have an impact on reducing health care costs associated with cancer and long-term care.

References

Figure 1. Gilmore, T (2006). Introduction to NF-kB: players, pathways, perspectives. Oncogene 25, 6680-6684