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Plant Derived Polyphenols, Other Drugs Targeting NF- κ B and its Therapeutic Implications

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ABSTRACT

Nuclear factor - kappa B (NF- κ B) consists of family transcription factors that play critical roles in inflammation, immunity, cell proliferation, differentiation and survival. The transcription factor NF- κ B was discovered over 15 years ago, yet owing to its wide range of important cellular roles it remains an area of interest and current research. Discovered in the “B cell” white blood cell type, NF- κ B is the nuclear factor for the κ immunoglobulin light chain in B cells. Since it was first observed, NF- κ B has been found to play an active role in inflammatory responses, cellular growth and apoptosis as well as being present in diseases such as cancer, arthritis, asthma, chronic inflammation, neurodegenerative diseases and heart diseases. The extensive involvement of Rel/NF- κ B transcription factors in human inflammation and disease establishes them as targets for therapeutics. There are over 800 compounds that have been shown to inhibit NF- κ B signaling and thus, the physiological or the pharmacological utility of using any single compound for inhibition of NF- κ B acting is a bit muddled. Nevertheless, knowledge of the molecular details of the pathway is enabling the development of more specific and potent inhibitors of NF- κ B signaling, and indeed, some NF- κ B signaling inhibitors are entering clinical trials.

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Introduction

NF- κ B (nuclear factor Kappa light chain enhancer of activated B cells) is a protein complex that controls transcription of DNA. NF- κ B is found in almost all animal cell types and is involved in cellular responses to a stimulus such as stress, cytokines, free radicals, ultraviolet irradiation, oxidized LDL and bacterial or viral antigens¹⁻⁵. Incorrect regulation of NF- κ B has been linked to cancer, inflammatory and autoimmune diseases, septic shock, viral infection, and improper immune development. NF- κ B has also been implicated in places of synaptic plasticity and memory⁶⁻¹⁰. NF- κ B was discovered by Dr. Ranjan Sen in the laboratory of Nobel Prize laureate David Baltimore via its interaction with a TTTT sequence in the immunoglobulin light chain enhancer in B cells¹¹. All proteins of the NF- κ B family share a Rel homology domain in their N-terminus. A subfamily of NF- κ B proteins, including Rel A, Rel B and C-Rel, have a transactivation domain in their C-termini. In contrast, the NF- κ B1 and NF- κ B2 protein are synthesized as large precursors, p105 and p100, which undergo processing to generate the mature NF- κ B subunits, p50 and p52 respectively. The processing of p105 and p100 is mediated by the ubiquitin/proteasome pathway and involves selective degradation of their C-terminal region containing ankyrin repeats whereas the generation of p52 from p100 is a tightly regulated process, p50 is produced from constitutive processing of p105^{12,13}. The p50 and p52 proteins have no intrinsic ability to activate transcription and thus have been proposed to act as transcriptional repressors when binding κ B elements and homodimers^{14,15}.

Distribution and Signaling

In addition to mammals, NF- κ B is found in a number of simple animals as

well¹⁶. NF- κ B heterodimerizes with Rel B to form a ternary complex with DNA that promotes gene transcription¹⁷. NF- κ B is important in regulating cellular responses because it belongs to the category of “rapid-acting” primary transcription factors and thus is the first responder to harmful cellular stimuli. Known inducers of NF- κ B activity are highly variable and include reactive oxygen species (ROS), tumour necrosis factor alpha (TNF α), interleukin 1-beta (IL-1B) bacterial lipopolysaccharides (LPS), isoproterenol, cocaine and ionizing radiation¹⁸. In unstimulated cells, the NF- κ B dimers are sequestered in the cytoplasm by a family of inhibitors, called I κ Bs (inhibitor NF- κ B), which are proteins that contain multiple copies of a sequence called ankyrin repeats¹⁹.

Role and Involvement of NF- κ B in Various Diseases

The ubiquitously expressed transcription factor NF- κ B is involved in a wide spectrum of cellular responses, including cell cycle control, apoptosis and stress adaptation. Among the many diseases linked in recent years to aberrant NF- κ B activation, cancer has been the major focus because of NF- κ Bs role as central regulator of the inflammatory response, its regulation of genes involved in cellular survival (Bcl-2, Bcl-XL, CIAP, XIAP and SOD) and tumour progression (ICAM-1, VCAM-1, ELAM-2, COX-2, iNOS, & MMP-9), and its constitutive activity in many types of tumours, including leukemia, lymphoma, prostate cancer, breast cancer, colon cancer, melanoma and head and neck cancer²⁰.

Defects in NF- κ B results in increased susceptibility to apoptosis leading to increased cell death. This is because NF- κ B regulates anti-apoptotic genes, especially the TRAF1 and TRAF2 and therefore, checks the activities of the caspase family of enzymes, which are central to most

apoptotic processes²¹. In a recent study of four tumor cell lines, each treated with different chemotherapeutic regimens (doxorubicin, 5 FU, cisplatin and paclitaxel), cell survival correlated with the level of NF- κ B activity induced by the drugs²². In another study, NF- κ B binding activity decreased in breast cancer cells treated with anti-Her-2/neu antibody (trastuzumab, Herceptin), suggesting a role of NF- κ B in the therapeutic efficacy of this antibody combined with chemotherapy for patients with Her-2/neu positive breast cancer²³. In tumor cells, NF- κ B is active either due to mutations in genes encoding the NF- κ B transcription factors themselves or in genes that control NF- κ B activity (such as I κ B genes), in addition, some tumor cells secrete factors that cause NF- κ B to become active. Blocking NF- κ B can cause tumour cells to stop proliferating, to die, or to become more sensitive to the action of anti-tumour agents. Thus, NF- κ B is the subject of much active research among pharmaceutical companies as a target for anti-cancer therapy²⁴.

Polyphenols Targeting NF- κ B

Many plants derived polyphenols lead to NF- κ B inhibition, therapy blocking tumor initiation, progression and metastasis like, resveratrol, curcumin, green tea, flavopiridol, genistein, silymarin and ginger, capsaicin, eugenol, emodin and diosgenin.

Resveratrol

(Trans-3, 5, 4' trihydroxystilbene) found in various plants, including grapes, berries and peanuts and research in recent years has focused on its anticancer properties, as suggested by its ability to suppress the proliferation of lymphoid and myeloid cancers, multiple myeloma, breast cancers, prostate, colon, pancreatic cancers, melanoma, head and neck squamous cell

carcinoma, ovarian and cervical carcinoma²⁵⁻²⁷.

Curcumin

A diferuloylmethane derived from turmeric (*curcuma longa*) has been the subject of intense study as a chemopreventive agent and as a complement to chemotherapy and radiotherapy²⁸⁻³⁰. Studies have demonstrated that curcumin inhibits NF- κ B activation induced by various inflammatory stimuli, the I κ k activation needed for NF- κ B activation and NF- κ B induced osteoclastogenesis³¹. An epidemiological study suggested that the low incidence of gastrointestinal malignancies in India may be attributable to the presence of natural additives, including curcumin in the Indian diet³².

Green Tea

Mounting evidence has suggested that the amino acid theanine, a component of green tea plus chemotherapy has a major synergistic effect for a variety of cancers. An investigation of the combined effects of theanine, and glutamate transport inhibitors on the antitumor activity of doxorubicin in ovarian sarcoma bearing mice revealed that compared to the doxorubicin-alone group, theanine significantly enhanced the inhibitory effect of doxorubicin on tumor growth and increased the drug concentration in the tumors³³.

Flavopiridol

Potentiate the effects of chemotherapy in several types of cancer. For example, flavopiridol potentiate the cytotoxic effects of mitomycin C by promoting drug induced apoptosis in breast and gastric cancer cells³⁴. The mechanism accounting for the sensitizing effects of flavopiridol may involve its inhibition of NF- κ B. Indeed, in one study, flavopiridol

inhibited NF- κ B, which in turn, down regulated cyclin D₁, COX-2 and MMP-9³⁵.

Genisterin

Several reports have highlighted the enhanced efficacy of chemotherapy when it is combined with several plant polyphenols. Genisterin has been shown to potentiate the effects of chemotherapy for numerous tumor types. In the pancreatic cancer cell line, treatment with genistein before docetaxel or cisplatin administration etc. enhanced tumor cell death compared with treatment with either chemo-therapeutic drug alone. This effect may have been mediated by the inhibition of NF- κ B by genisterin, causing increasing apoptosis³³.

Silymarin

Silymarin may potentiate the effects of chemotherapy on cancer. Silymarin appears to protect rat cardiomyocytes against anthracycline induced oxidative stress, perhaps through its effects on cell membrane stabilization³⁶. In MDR breast cancer cells, it potentiated doxorubicin cytotoxicity by inhibiting P-glycoprotein ATPase activity, which is responsible for cellular efflux of cytotoxic substances³⁷.

Ginger

Ginger may prevent chemotherapy and radiotherapy induced nausea. In shrews, rats and dogs, ginger inhibited chemotherapy induced gastric emptying and showed comparable results to standard antiemetic compounds³⁸⁻⁴⁰. Furthermore ginger reduced radiation – related sickness and free radical production in mice⁴¹.

Other actions of NF- κ B and drugs utilizing this pathway

Because NF- κ B controls many genes involved in inflammation, it is not surprising that NF- κ B is found to be chemically active in many inflammatory diseases, such as

inflammatory bowel diseases, arthritis, sepsis, gastritis, asthma, atherosclerosis⁴² and others. It is important to note though that elevation of some NF- κ B inhibitors, such as osteoprotegerin (OPG) are associated with elevated mortality, especially from cardiovascular disease^{43, 44}. Elevated NF- κ B has also been associated with schizophrenia⁴⁵. Recently, NF- κ B activation has been suggested as a possible molecular mechanism for the catabolic effects of cigarette smoke in skeletal muscle and sarcopenia⁴⁶.

There is a search for corticosteroids that are metabolized rapidly in the circulation after absorption from the lungs to reduce systemic effects. It has been possible to develop corticosteroids that dissociate the DNA binding effects of corticosteroids (which mediates most of the adverse effects) from the inhibitory effect of transcription factors such as NF- κ B (which mediates much of the anti-inflammatory effects). Such "dissociated steroids" or selective glucocorticoid receptor agonists (SEGRAs) should, theoretically, retain anti-inflammatory activity but have a reduced risk of adverse effects, achieving this separation of desired and adverse effects is difficult *in vivo*⁴⁷.

The circumsporozoite protein of plasmodium falciparum has been shown to be an inhibitor of NF- κ B⁴⁸. Disulfiram, olmesartan and carbamates can inhibit the nuclear factor $\kappa\beta$ (NF- κ B) signaling cascade⁴⁹. Thalidomide and lenalidomide, the immunomodulation analogs (IMiDs) which find use in erythema nodosum laparosum (ENL), multiple myeloma utilize at least four distinct, but potentially a complementary mechanism and one of them is direct anti-proliferative/pro apoptic effects by inhibiting anti-apoptic effects of NF- κ B and the anti apoptotic BCL-2 family member A1/Bfl-1⁵⁰.

Bortezomib, an inhibitor of proteasome mediated protein degradation, which has earned a central role in the treatment of multiple myeloma has its effect on NF- κ B. Most NF- κ B is found in the cytosol bound to I κ B and cannot enter to the nucleus to regulate transcription. In response to stress signals, I κ B becomes ubiquitinated, releases NF- κ B which enters the nucleus, where it transcriptionally activates a host of genes involved in cell survival (e.g. Cell adhesion proteins E-selectin, ICAM-1 and VCAM-1) as well as proliferative (e.g. cyclin D₁) or anti-apoptotic molecules (e.g. cIAPs, BCL-2)⁵¹. A proposed mechanism for the immune suppressive effects of the morphine of neutrophils is through a nitric oxide dependent inhibition of NF- κ B activation⁵². Theophylline prevents the translocation of the pro-inflammatory transcription factor NF- κ B into the nucleus, potentially reducing the expression of inflammatory genes in asthma and COPD. Inhibition of NF- κ B appears to be due to a protective effect against the degradation of the inhibitory protein I- κ B α ⁵³. NSAIDs like aspirin and salicylate have recently been shown to suppress NF- κ B activation by specifically inhibiting an upstream kinase, I- κ B kinase (I- κ BK), thus preventing the release of NF- κ B from its inhibitor I- κ B⁵⁴.

Conclusion

As aberrant NF- κ B activation underlies various disease states, precise activation and termination of NF- κ B is ensured by multiple regulatory processes. Tremendous progress has been made in understanding the regulatory mechanisms shaping the NF- κ B response, yet it is striking how much still remains to be discovered. Because of the well characterized links between NF- κ B and diseases like cancer or arthritis, unraveling

the complexity of NF- κ B regulation remains a major goal to help act on specific steps of the NF- κ B pathway, thereby avoiding the risk of harmful side effects that could result from general inhibition of NF- κ B. Some of the evidence that has come from studies using superphysiological doses of plant polyphenols must be confirmed in clinical trials before the agents can be recommended as safe adjunct treatment.

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