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Revisiting the Pathology of the Nuclear Factor Kappa Beta

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ABSTRACT

This study reviewed the molecular roles of NFκB in cell survival, disease and death. By activating FOXO, nuclear transcription factor-2 (Nrf-2) and Mitogen-Activated Protein Kinase (MAPK) signaling mechanisms, NFκB mediates cell survival mechanisms which guarantee cell viability against pathogenic stimuli. On the other hand, NFκB could also modulate pathogenic signaling pathways leading to cell degeneration, aging, many types of diseases and cell death. This dual role of NFκB should be considered into development of novel strategies for tumor killing in cancer patients, or for the preservation of brain neurons in Alzheimer's disease. Further, the pleiotropic roles of NFκB in many disease processes are discussed and presented.

Key words: NFκB, cardiovascular disease, cancer, inflammation, infection, Alzheimer's disease

INTRODUCTION

NFκB comprises a family of structured-related eukaryotic nuclear transcription factor which modulates cell growth, cell survival, development processes, immune and inflammatory responses as well as apoptosis (Saile *et al*., 2001; Gilmore, 2006; Perkins, 2007). It was firstly discovered in 1986 as a nuclear factor activated by lipopolyssacharides from bacterial cell wall (Sen and Baltimore, 1986). In that seminal paper, authors observed that NFκB was linked to a sequence of 10 pair of DNA bases in the promoter region associated with the light chain (kappa) of the B-cell-derived immunoglobulins (Sen and Baltimore, 1986). NFκB is a heterodimer with two basic subunits: the p50 and the RelA or p65. The negative feedback of the NFκB action is represented by the protein activated kinase Ikk which blocks the action and effects of NFκB (Glezer *et al*., 2000; He *et al*., 2010).

NFκB: the key of cell survival and death: NFκB is important to control normal B cell development and proliferation (Feng *et al*., 2004).

One of the molecular linking of the cell survival pathways, NFκB rescue neuronal cells from death in ischemic stroke damage (Koulich *et al*., 2001; Sirabella *et al*., 2009) and it also helps cell survival against sub-acute pathogenic stimuli such as the massive release of reactive oxygen, chlorine and nitrogen species, e.g., the oxidative and nitrosative stresses and the role of genotoxic factors which trigger the nuclear factor kappa beta (NFκB) signaling pathways activating aging-related genes (Ferrari *et al*., 2009; Gutteridge and Halliwell, 2010). The NFκB triggers genes that block the cell death (by apoptosis or necrosis) resulting in aging of the immune system or immunosenescence, muscle atrophy and inflammation (Salminen and Kaarniranta, 2009). It is important to note that NFκB signaling has also positive effects on human health since it is also important in tumor killing (Ho *et al*., 2011).

NFκB and infection: As NFκB can increase cell survival it has been suggested that its activation is crucial for herpesvirus survival and latency (Jellinger, 2007; Kumar *et al*., 2008). Although NFκB has been implicated in successful influenza virus replication, excessive triggering of the NFκB activates phagocyte NADPH oxidases which in turn lead to massive release of oxygen free radical increasing the lethality of this viral infection. In the same context, it has been suggested that inhibition of NFκB is useful in the treatment of herpesvirus and HIV-associated lymphomas (Harrington, 2005).

Microbial infections, especially those caused by bacteria are associated with a higher degree of tissue inflammation and subsequent damage. Aggravation of pneumococcal meningitis is associated with activation of NFκB once its pharmacological blocking alleviated the symptoms (Koedel *et al*., 2000). Another example is represented by chronic stomach *Helicobacter pylori* infection on which many inflammatory mechanisms are activated, including the NFκB which causes proliferation of gastric tumor cells (Lee *et al*., 2010; Kim *et al*., 2010). Bacterial lipopolyssacharides can trigger massive inflammation via NFκB molecular pathways and release of interleukin-8 (IL-8) and monocyte-chemoattractant protein-1 (MCP-1) from activated lymphocytes of the immune system (Zhong *et al*., 2011).

NFκB and inflammation in cardiovascular diseases and metabolic syndrome: In aging heart there are many processes that converge to chronic myocardium inflammation and fibrosis, both of them are activated through NFκB molecular pathways and the subsequent release of toxic oxygen free radicals (Castello *et al*., 2010). Moreover, hypertension causes inflammatory reactions on the heart left ventricule via NFκB (Miguel-Carrasco *et al*., 2010). During the course of cardiac hypertrophy there is also a huge expression of the NFκB with subsequent higher grade of myocardial inflammation (Sorriento *et al*., 2010).

In hemodialysis patients there is an intense myocardial inflammatory damage caused by blood accumulation of urea (uremia), a process that is triggered by NFκB activation with subsequent activation of mononuclear cells (macrophages and lymphocytes) and neutrophils (Raff *et al*., 2008; Raj *et al*., 2007; Shah *et al*., 2011).

One of the most important consequences of magnesium deficiency is the increased risk of atherosclerosis. Magnesium deficiency-induced atherosclerosis is associated with increased release of pro-inflammatory molecules from NFκB activated endothelial cells (Ferre *et al*., 2010). Recently, it has been characterized the molecular roles of NFκB on atherosclerosis pathogenesis (Dabek *et al*., 2010). Rabbits with congestive heart failure experienced augmentation of NFκB expression which was involved in the pathogenesis of aortic atherosclerosis (Feng *et al*., 2010). The massive production of the NFκB has been associated with induction of P selection and intracellular accumulation of lipids into macrophages or foam cells (Wang *et al*., 2011). Farther, it is well recognized that obese, insulin resistance syndrome and metabolic syndrome patients suffer from chronic inflammation (Kriketos *et al*., 2004; Arkan *et al*., 2005; Ferrari, 2007; Ferrari, 2008). This could be due to visfatin (and possible by other adipokines) which has been implicated in endothelial oxidative stress and markedly vascular inflammation both activated by upregulation of NFκB (Arkan *et al*., 2005; Kim *et al*., 2008; Elks and Francis, 2010; Baker *et al*., 2011). In patients with both polycystic ovary syndrome and insulin resistance amelioration of symptoms has been achieved due to abrogation of the NFκB synthesis (Pepene *et al*., 2010).

NFκB, brain injury and alzheimer's disease: Very interesting studies have pointed out that brain exposition to toxic insults such as smoking, alcohol or cocaine has been associated with activation of NFκB mechanisms leading to strongest induction of proteases, inflammatory cytokines (TNF-α, IL-1β, IL-6), monocyte chemotactic protein-1, cell adhesion molecules, inducible isoform of nitric oxide synthase (μNOS), activation of microglial cells and massive production of oxygen and nitrogen reactive species via activation of both NADPH oxidase and mitochondrial systems (Csiszar *et al*., 2008; Yao *et al*., 2010; Muriach *et al*., 2010; Zou and Crews, 2010; Lim *et al*., 2011).

Ischemic-reperfusion cerebral damage the most common type of brain injury is characterized by massive release of oxygen and nitrogen reactive species. NFκB participates in this process and its inhibition by Iκκ sucessfully protects brain neurons against damage (Desai *et al*., 2010). Another important neurodegenerative inflammatory brain disease is represented by Alzheimer,s Disease (AD). The characteristic neurodegeneration of AD is caused by massive release in brain neurons of beta-amyloid protein (Jellinger, 2007; Smith *et al*., 1997). Beta-amyloid protein induces a mitochondrial abnormal regulation state in which those organelles begin to release a higher and sustained level of oxygen and nitrogen reactive species leading to mitochondrial death by apoptosis or necrosis (Smith *et al*., 2000; Xie *et al*., 2002; Keil *et al*., 2004). The release of both beta-amyloid and the toxic reactive oxygen/nitrogen species is mediated via NFκBκ mechanisms, once NFκB inhibition rescue neurons and attenuate AD cognitive impairment (Cai *et al*., 2011).

NFκB in diabetes mellitus and pancreas damage: In acute pancreatitis NFκB induces NADPH oxidases with subsequent formation of free radicals and expression of inflammatory adhesion molecules (Chan and Leung, 2007).

Insulin resistance has been associated with TNF-α and NFκB activation (Sun *et al*., 2011). In diabetic nephropathy there is induction of both RANTES and monocyte-chemotactic protein-1 (mcp-1) due to the stimulatory role of NFκB (Mezzano *et al*., 2004).

In diabetes mellitus patients with left ventricular dysfunction, it has been found that NFκB overexpression impairs mitochondrial function contributing to disease progression (Mariappan *et al*., 2010). The pathogenesis of diabetic retinopathy had been related with increased free radical production and inflammation due to massive expression of the NFκB (Kowluru *et al*., 2003).

In a very interesting Alzheimer's disease model, the diabetic metabolic decompensation induced neuronal formation of the amyloid β neuron deposits as well as release of cycloxigenase-2, interleukin-1β, TNF-α and inducible isoform of nitric oxide synthase (μNOS) both of which triggered by NFκB activation (Cai *et al*., 2011).

Inflammatory signals from the tissues and from the environment, stress and bone and joint overload trigger the nuclear activation of the NFκB which in turn induces matrix metalloproteinases-13 which participates in degeneration of the osteocytes in the osteoarthritis (Goldring *et al*., 2011). In muscles, the excessive overload during eccentric exercising had led to NFκB activation and subsequent inflammatory damage (Hyldahl *et al*., 2010).

NfκB activation and its harmful effects have also been observed in children suffering from like autism and psychosocial stress (Bierhaus *et al*., 2004; Naik *et al*., 2011).

The multiple roles of NFκB in disease pathogenesis are represented in Fig. 1.

Inhibition of NFκB: an important molecular pathway against cancer: Activation of the nuclear factor kappa beta has been related to a great number of benign and malignant tumors. For

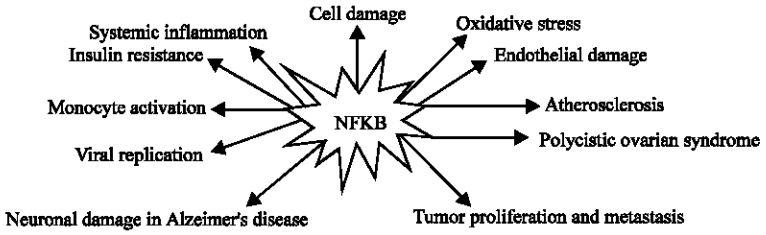

Fig. 1: Pleiotropic pathogenetic roles of the NfκB

example, hormonal-associated prostate cancer, lung carcinoma, hepatocellular carcinoma, hepatoma, multiple myeloma, melanoma, glioblastoma, ovarian tumor, malignant lymphoma, leukemia, breast cancer, colorectal cancer, pancreatic cancer, squamous cell carcinomas, mesothelioma, nasopharyngeal carcinoma, biliary cancer cells, soft tissue sarcomas, mesothelioma and other tumors (Andersen *et al*., 2010; He *et al*., 2010; Demchenko and Kuehl, 2010; Harikumar *et al*., 2010; Messa *et al*., 2010; Qiao *et al*., 2010; Sun *et al*., 2009; Zhang *et al*., 2011; Costanzo *et al*., 2011; Galardi *et al*., 2011; Santini *et al*., 2011; Valkov *et al*., 2011; Varani *et al*., 2011; Woodsa *et al*., 2011). Overexpression of the NFκB had also been found in patients with aggressive forms of cervical cancer and nasopharyngeal carcinoma predicting poor prognosis as well massive expression of NFκB was associated with metastatic behavior of ovarian carcinoma and hepatocellular carcinoma (Li *et al*., 2009; Zhang *et al*., 2011; Kleinberg *et al*., 2009; Li *et al*., 2011). Notwithstanding, with an overact expression of NFκB in tumor cells there was also the activation and expression of other oncogenes such as miR-221 and miR222 that were found in glioblastoma and prostate carcinoma (Galardi *et al*., 2011).

The ikk inhibitor of the NFκB plays an important role in cancer cell death. In this respect, it has been demonstrated that ikk triggers the activation of mitochondria and other reactive oxygen releasing organeles (peroxissomes) which in turn induces the activation of both the JUNK signaling pathway and the STAT3 proteins blocking the progression of the hepatocellular carcinoma, a very aggressive malignant tumor (He *et al*., 2010).

Upregulation of the NFκB has been associated with strongest stimulation of the antiapoptotic genes (Bcl-2/Bcl-x) and chemotherapy resistance in metastatic melanoma cells (Jazirehi *et al*., 2011).

CONCLUSION

Modulating NFkB cell pathways is essential to control cancer growth, aging process and improve cell survival of important target tissues and organs. Future therapies should explore the multiple pathways triggered by NFκB in cell proliferation and death.

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