THE BIOLOGY OF NUCLEAR FACTOR KAPPA BETA (NFkB) IN HEALTH AND PATHOLOGY

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ABSTRACT

This paper reviewed the molecular roles of NFkB 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, disease and 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.

Keywords: NFkB, cancer, inflammation, aging, Alzheimer's disease.

Introduction:

As a cellular regulator of many signaling processes, NFkB represents a family structured-related eukaryotic nuclar transcription factor which modulates cell growth, cell survival, development processes, immune and inflammatory responses as well as apoptosis[1-3]. The NFkB was firstly discovered in 1986 as a nuclear factor activated by lipopolyssacharides from bacterial cell wall[4]. In that seminal paper, authors observed that NFkB 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[4]. NFkB is a heterodimer with two basic subunits: the p50 and the RelA or p65. The negative feedback of the NFkB action is represented by the protein activated kinase Ikk which blocks the action and effects of NFkB[5,6].

Inhibition of NFkB: 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 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[6-19].

The ikk inhibitor of the NFkB 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[6].

NFkB In Cell Aging And Death:

Notwithstanding, it should be noted that pathogenic stimuli like excessive production of toxic reactive oxygen and nitrogen species, e.g., the oxidative stress and nitrosative stresses, and many genotoxic factors activate nuclear factor kappa beta (NFκB) signaling pathways which in turn stimulates the activation of aging-related genes[20,21]. The NFκB trigger genes that block the cell death (by apoptosis or necrosis) resulting in aging of the immune system or "immunosenescence", muscle atrophy, and inflammation[22].

It is important to note that NFκB signaling has also positive effects on human health since it is essential in tumor killing[23] and prevention of endoplasmic reticulum damage in neurons after ischemic stroke events[24].

NFkB In Inflammation:

Microbial infections, especially those caused by bacteria are associated with a higher degree of tissue inflammation and subsequent damage.

For example, during chronic stomach *Helicobacter pylori* infection many inflammatory mechanisms are activated, including the NFκB which causes proliferation of gastric tumor cells[25,26]. 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[27].

Inflammatory signals from the tissues and from the environment, stress and bone and joint overload trigger the nuclear activation of the NFkB which in turn induces matrix metalloproteinases-13 which participates in degeneration of the osteocytes in the osteoarthritis[28].

In aging heart there are many processes that converges to chronic myocardium inflammation

and fibrosis, both of them are activated through NFκB molecular patways and the subsequent release of toxic oxygen free radicals[29]. In hemodialysis patients there is an intense myocardial inflammatory damage caused by blood accumulation of ureia (uremia), a process that is triggered by NFκB activation with subsequent activation of mononuclear cells (macrophages and lymphocytes) and neutrophils[30-32].

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 proinflammatory molecules from NFκB activated endothelial cells[33]. Recently, it has been charactherized the molecular roles of NFκB on atherosclerosis pathogenesis[34].

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[35]. 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[36,37]. Beta-amyloid protein induces a mitochondrial dysregulation state in which those organeles beggin to release a higher and sustained level of oxygen and nitrogen reactive species leading to mitochondrial death by apoptosis or necrosis[38-40]. 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[41].

NFκB activation has been observed in other pathologies like autism, polycistic ovary syndrome, hypertension, myocardiopathy, skeletal muscle damage, smoking-induced lung cancer, insulin resistance and type II diabetes, diabetic retinopathy, metabolic syndrome, herpes and HIV related lymphomas, viral hepatitis, pneumococcal meningitis, influenza virus infection and cocaine toxicity[42-54].

The dual role of NFκB in cell survival or aging and disease pathogenesis is represented in figure 1. 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 side of the coin, NFκB could also modulate pathogenic signaling pathways leading to cell degeneration, aging, disease and death. This dual role of NFκB should be considered if researchers are interested in tumor killing in cancer patients, or in the rescue of brain neurons through inhibition of NFκB by Iκκ or sirtuins in Alzheimer's disease.

Conclusion:

Modulating NFκB 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.

References:

[1] Perkins ND (2007). Integrating cell signaling pathways with NFkB and Ikk function. Nature Rev Mol Biol, v.8, pp.40-62.

[2] Saile B, Matthes N, Armouche HE, Neubauer K, Ramadori G (2001). The bcl, NFκB and p53/p21WAF1 systems are involved in spontaneous apoptosis and in the anti-apoptotic effect of TGF-β or TNF-α on activated hepatic stellate cells. Eur J Cell Biol, v.80, pp.554-61.

[3] Gilmore TD(2006). NF-kB: from basic research to human disease. Oncogene, v.51, pp.6679-99.

[4] Sen R, Baltimore D (1986). Multiple nuclear factors Interact with the immunoglobulin enhancer sequences. Cell, v.46, pp.705-16.

[5] Glezer I, Markourakis T, Avellar MCW, Gorenstein C, Scavone C (2000). The role of the

transcription factor NF-kB in the molecular mechanisms of action of psychoative drugs. Rev Bras Psiquiatr, v.22, pp.26-30.

[6] He G, Yu G-Y, Temkin V, Ogata H, Kuntzen C, Sakurai T, Sieghart W, Peck-Radosavljevic M, Leffert HL, Karin M (2010). hepatocyte ikkb/NFkB inhibits tumor promotion and progression by preventing oxidative stress-driven STAT3 activation. Canc Cell, v.17, pp.286-97.

[7] Demchenko YN, Kuehl WM (2010). A critical role for the NFkB pathway in multiple myeloma. Oncotarget, v.1, pp.59-68.

[8] Sun H-Z, Wang T-W, Zang W-J, Wu S-F (2010). Dehydroepiandrosterone induced proliferation of prostatic epithelial cell is mediated by NFKB via PI3K/AKT signaling pathway. J Endocrinol Metab, v.204, pp.311-8.

[9] Galardi S, Mercatelli N, Farace MG, Ciafrè SA(2011). NFkB and c-jun induce the expression of the oncogenic miR-221 and miR-222 in prostate carcinoma and glioblastoma cells. Nucl Acid Res, v.39, pp.3892-902.

[10] Qiao Q, Nozaki Y, Sakoe K, Komatsu N, Kirito K (2010). NF-kB mediates aberrant activation of HIF in malignant lymphoma. Exp Hematol, v.38, pp.1199-1208.

[11] Messa E, Carturan S, Maffè C, Pautasso M, Bracco E, Roetto A, Messa F, Arruga F, Defilippi I, Rosso V, Zanone C, Rotolo A, Greco E, Pellegrino RM, Alberti D, Saglio G, Cilloni D (2010). Deferasirox is a powerful NF-kB inhibitor in myelodysplastic cells and in leukemia cell lines acting independently from cell iron depravation by chelation and reactive oxygen species scavenging. Haematologica, v.95, pp.1308-16.

[12] Woods DC, White YAR, Dau C, Johnson AL (2011). TLR4 activates NF-kB in human ovarian granulosa tumor cells. Biochem Biophys Res Commun, v.409, pp.675-80.

[13] Zhang Y, Lang JY, Liu L, Wang J, Feng G, Jiang Y, Deng YL, Wang XJ, Yang YH, Dai TZ, Xie G, Pu J, Du XB (2010). Association of nuclear factor kB expression with a poor outcome in nasopharyngeal carcinoma. Med Oncol. Doi: 10.1007/s12032-010-9571-7.

[14] Varani K, Maniero S, Vincenzi F, Targa M, Stefanelli A, Maniscalco P, Martini F, Tognon M, Borea PA (2011). A_3 receptors are overexpressed in pleura from mesothelioma patients and reduce cell growth via Akt/NF-kB pathway. Am J Respir Crit Care Med, v.183, pp.522-30.

[15] Santini D, Schiavon G, Vincenzi B, Gaeta L, Pantano F, Russo A, Ortega C, Porta C, Galluzzo S, Armento G, La Verde N, Caroti C, Treilleux I, Ruggiero A, Perrone G, Addeo R, Clezardin P, Muda AO, Tonini G (2011). Receptor activator of the NF-kB (RANK) expression in primary tumors associates with bone metastasis occurrence in breast cancer patients. PLoS One, v.6(4), pp.e19234.

[16] Andersen V, Christensen J, Overvad K, TjØnneland A, Vogel U(2010). Polymorphisms in NFkB, PXR, LXR and risk of colorectal cancer in a prospective study of Danes. BMC Canc, v.10, pp.484.

[17] Costanzo A, Spallone G, Karin M (2011). NF-kB, Ikb kinase and interacting signal networks in squamous cell carcinomas. In: Glick AB, Van Waes C (eds.). Signaling pathways in squamous cancer. Dordrecht, Springer, Chapter 10, pp.201-22.

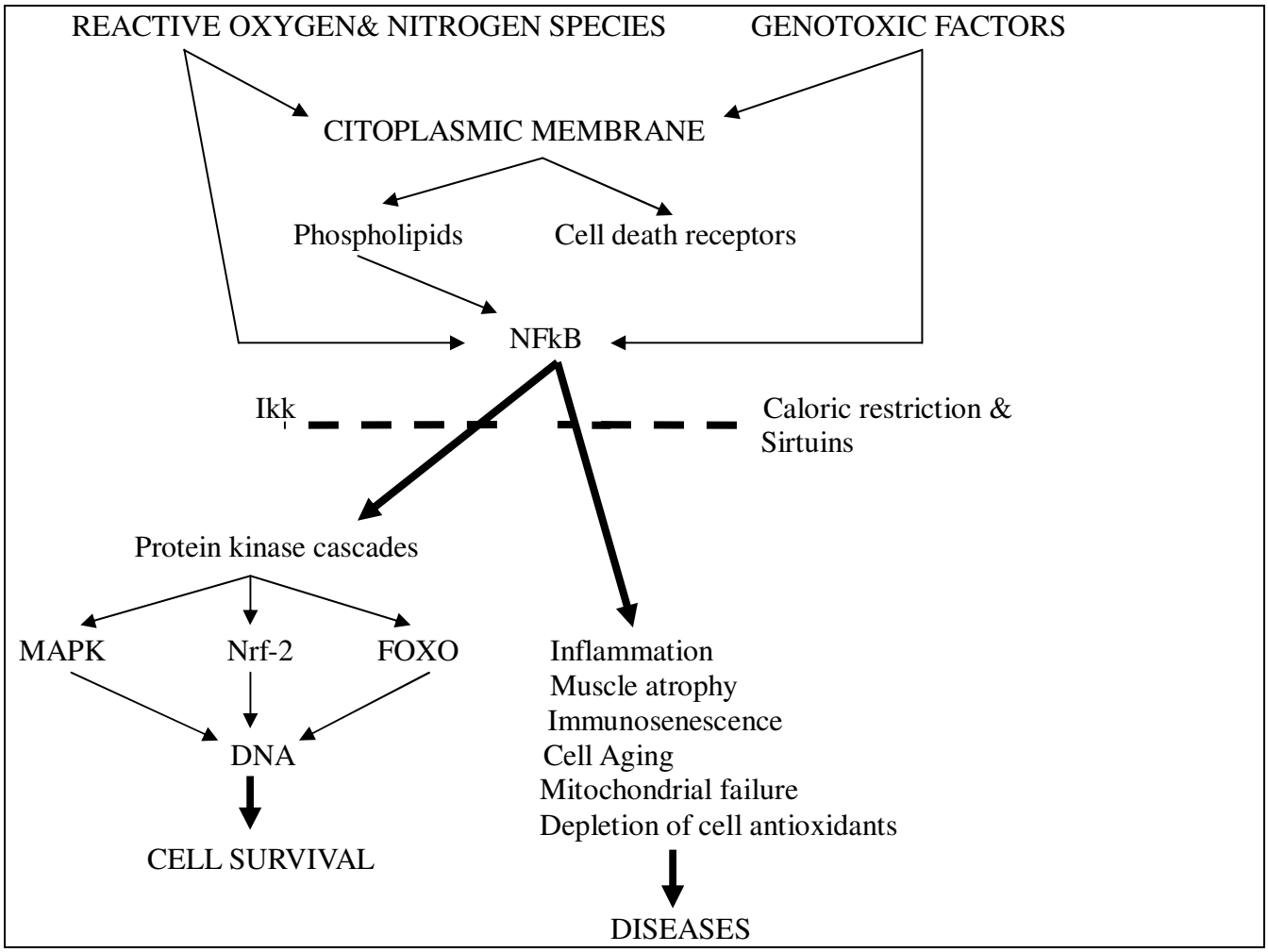
[18] Valkov A, Sorbye SW, Kilvaer TK, Donnem T, Smeland E, Bremnes RM, Busund L-T (2011). The prognostic impact of TGF-β1, fascin, NF-kB and PKC-ζ expression in soft tissue sarcomas. PLoS One, v.6(3), pp.e17507.

[19] Harikumar KB, Kunnumakkara AB, Ochi N, Tong Z, Deorukhkar A, Sung B, Kelland L, Jamieson S, Sutherland R, Raynham T, Charles M, Bagherazadeh A, Foxton C, Boakes A, Farooq M, Maru D, Diagaradjane P, Matsuo Y, Sinnet-Smith J, Gelovani J, Krishnan S, Aggarwal BB, Rozengurt E, Ireson CR, Guha S (2010). A novel small-molecule inhibitor of protein kinase D blocks pancreatic cancer growth *in vitro* and *in vivo*. Mol Canc Ther, v.9, pp.1136-46.

[20] Gutteridge JM, Halliwell B (2010). Antioxidants: molecules, medicines and myths. Biochem Biophys Res Commun, v.393, pp.561-4.
[21] Ferrari CKB, França EL, Honorio-França AC (2009). Nitric oxide, health and disease. J Appl Biomed, v.7, pp.163-73.
[22] Salminem A, Kaarniranta K (2009). NF-kB signaling in the aging process. J Clin Immunol, v.29, pp.397-405.
[23] Ho JQ, Asagiri M, Hoffmann A, Ghosh G (2011). NF-kB potentiates caspase independent hydrogen peroxide induced cell death. PLoS One, v. 6(2), pp.e16815.
[24] Sirabella R, Secondo A, Pannaccione A, Scorziello A, Valsecchi V, Adornetto A, Bilo L, Di Renzo G, Annunziato L (2009). Anoxia-induced NF-kB-dependent upregulation of NCX1 contributes to Ca2+ refilling into endoplasmic reticulum in cortical neurons. Stroke, v.40, pp.922-9.
[25] Lee YS, Sohn SH, Park K-R, Lee SH, Kim HK, Shin SK, Yoon HQ, Kim KH, Lee YC (2010). T1183 activation of Wnt and NF-kB regulated gene CK2 in *Helicobacter pylori*-activated gastric cancer cells. Gastroenterology, v.138(5, Suppl.1), p.S506.
[26] Kim BJ, Kim KS, Oh H-C, Kim JW, Kim JG (2010). T1800 Zinc acexamate inhibits NFKB activation and IL-8 expression induced by *H. pylori* infection. Gastroenterology, v.138(5, suppl.1), p.S581.
[27] Zhong F, Chen H, Han L, Jin Y, Wang W (2011). Curcumin attenuates lipopolyssacharide-induced renal inflammation. Biol Pharm Bull, v.34, pp.226-32.
[28] Goldring MB, Otero M, Plumb DA, Dragomir C, Favero M, Hachem KE, Hashimoto K, Roach HI, Olivotto E, Borzi RM, Marcu KB (2011). Roles of inflammatory and anabolic cytokines in cartilage metabolism: signals and multiple effectors converge upon MMP-13 regulation in osteoarthritis. Eur Cel Mater, v.21, pp.202-20.
[29] Castello L, Froio T, Maina M, Cavallini G, Biasi F, Leonarduzzi G, Donati A, Bergamini E, Poli G, Chiarpotto E (2010). Alternate-day fasting protects the rat heart against age-induced inflammation and fibrosis by inhibiting oxidative damage and NF-kB activation. Free Rad Biol Med, v.48, pp.47-54.
[30] Raff AC, Meyer TW, Hostetter TH (2008). New insights into uremic toxicity. Curr Opin Nephrol Hypertens, v.17, pp.560-5.
[31] Raj DS, Boivin MA, Dominic EA, Boyd A, Roy PK, Rihani T, et al (2007). Hemodialysis induces mitochondrial dysfunction and apoptosis. Eur J Clin Invest, v.37, pp.971-7.
[32] Shah VO, Ferguson J, Hunsaker LA, Deck LM, Vander Jagt DL (2011). Cardiac glycosides inhibit LPS-induced activation of pro-inflammatory cytokines in whole blood through and NF-kB-dependent mechanism. Int J Appl Res Nat Prod, v.4, pp.11-9.
[33] Ferrè S, Baldoli E, Leidi M, Maier JAM (2010). Magnesium deficiency promotes a pro-atherogenic phenotype in cultured human endothelial cells via activation of NFkB. Biochim Biophys Acta, v.1802, pp.952-8.
[34] Dabek J, Kulach A, Gasior Z (2010). Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB): a new potential therapeutic target in atherosclerosis? Pharmacol Rep, v.62, pp.778-83.
[35] Desai A, Singh N, Raghubir R (2010). Neuroprotective potential of the NF-kB inhibitor peptide IKK-NBD in cerebral ischemia-reperfusion injury. Neurochem Int, v.57, pp.876-83.
[36] Jellinger KA (2007). Advances in our understanding of neurodegeneration. In: Qureshi GA, Parvez SH (Ed). Oxidative stress and neurodegenerative disorders. Amsterdam: Elsevier, Chapter 1, pp..1-58.
[37] Smith MA, Harris PLR, Sayre LM, Beckman JS, Perry G (1997). widespread peroxynitrite-mediated damage in Alzheimer's disease. J Neurosci, v.17, pp.2653-7.
[38] Smith MA, Rottkamp CA, Nunomura A, Raina AK, Perry G (2000). Oxidative stress in

Alzheimer´s disease. Biochim Biophys Acta, v.1502, pp.139-44.
[39] Xie Z, Wei M, Morgan TE, Fabrizio P, Han D, Finch CE, Longo VD (2002). Peroxynitrite mediates neurotoxicity of amyloid b-peptide1-42- and lypopolyssacharide-activated microglia. J Neurosci, 22, pp.3484-92.
[40] Keil U, Bonert A, Marques CA, Scherping I, Weyermann J, Strosznajder JB, Müller-Spahn F, Haass C, Czech C, Pradier L, Müller WE, Eckert A (2004). Amyloid-induced changes in nitric oxide production and mitochondrial activity lead to apoptosis. J Biol Chem, v.279, pp.50310-20.
[41] Cai Z, Zhao Y, Yao S, Zhao B (2011). Increases in B-amyloid protein in the hippocampus caused by diabetic metabolic disorder are blocked by minocycline through inhibition of NF-kB pathway activation. Pharmacol Rep, v.63, pp.381-91.
[42] Naik US, Gangadharan C, Abbagani K, Nagalla B, Dasari N, Manna SK (2011). A study of nuclear transcription factor-kappa B in childhood autism. PLoS One, v.6(5), pp.e19488.
[43] Pepene CE, Ilie IR, Marian I, Duncea I (2011). Circulating osteoprotegerin and soluble receptor activator of nuclear factor kB ligand in polycystic ovary syndrome: relationships to insulin resistance and endothelial dysfunction. Eur J Endocrinol, v.164, pp.61-8.
[44] Sorriento D, Iaccarino G, Trimarco B (2010). The role of the transcription factor nuclear factor kappa B in the regulation of cardiac hypertrophy. High Blood Pres Cardiovasc Prev, v.17, pp.209-17.
[45] Hyldahl RD, Ling X, Hubal MJ, Moekel-Cole S, Chipkin S, Clarkson PM (2010). Activation of NF-kB in pericytes of human skeletal muscle following eccentric exercise-induced damage. Med Sci Sport Exerc, v.42, p.96.
[46] Mezzano S, Aros C, Droguett A, Burgos ME, Ardiles L, Flores C, Schneider H, Ruiz-Ortega M, Egido J (2004). NF-kB activation and overexpression of regulated genes in human diabetic nephropathy. Nephrol Dial Transplant, v.19, pp.2505-12.
[47] Kowluru RA, Koppolu P, Chakrabarti S, Shali C (2003). Diabetes-induced activation of nuclear transcriptional factor in retina, and its inhibition by antioxidants. Free Rad Res, v.37, pp.1169-80.
[48] Bierhaus A, Humpert PM, Nawroth PP (2004). NF-kB as a molecular link between psychossocial stress and organ dysfunction. Pediatr Nephrol, v.19, pp.1189-91.
[49] Elks CM, Francis J (2010). Central adiposity, systemic inflammation, and the metabolic syndrome. Curr Hypertens Rep, v.12, pp.99-104.
[50] Harrington Jr WJ (2005). Antiviral targeting of NF-kB: a potential therapy for HIV and herpesvirus associated lymphomas. Braz J Infect Dis, v.9, pp.432-3.
[51] Kumar N, Zhong-Tao X, Liang Y, Hinh L, Liang Y (2008). NF-kB signaling differentially regulates influenza virus RNA synthesis. J Virol, v.82, pp.9880-9.
[52] Koedel U, Bayerlein I, Paul R, Sporer B, Pfister HW (2000). Pharmacologic interference with NF-kB activation attenuates central nervous system complications in experimental pneumococcal meningitis. J Infect Dis, v.182, pp.1437-45.
[53] Kanda T, Yokosuka O, Nagao K, Saisho H (2006). State of hepatitis C viral replication enhances activation of NF-kB and AP-1-signaling induced by hepatitis B virus. Canc Lett, v.234, pp.143-8.
[54] Yao H, Allen JE, Zhu X, Callen S, Buch S (2009). Cocaine and human immunodeficiency virus type 1 gp120 mediate neurotoxicity through overlapping signaling pathways. J Neurovirol, v.15, 164-75.

Figure 1 – The Yin and Yang of the NFkB action mechanisms



MAPK= mitogen-activated protein kinase; Nrf-2= nuclear transcription factor-1
NFkB = fator nuclear kappa beta
▬ ▬ = blocking
⟶ = stimulation

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