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Redox Regulation of NF-κB: From Basic to Clinical Research

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Since its discovery in 1986 by Sen and Baltimore (9), NF-κB has garnered widespread interest in all disciplines of biology. NF-κB is a vital transcription factor that is activated by a wide range of stimuli, including various stresses, growth factors, and cytokines such as tumor necrosis factor-α (TNF). Upon activation, NF-κB regulates the transcription of a broad array of genes, many of which are associated with inflammation and cell survival, and in a few cases with apoptosis. In immune cells, NF-κB is an essential mediator of inflammation and regulates production of various cytokines. On the other hand, the activation of NF-κB in liver and other tissues promotes cell survival through upregulation of proteins that prevent apoptosis and promotes survival (e.g., Mn-SOD, XIAP, bcl-xl, GADD45b, cFLIP, and A20). The importance of NF-κB in cell survival is underscored in the constitutively active NF-κB that many cancer cells evolve for survival and growth (1, 11). The disregulation of NF-κB appears to be an important contributing factor in many diseases, including cancer, atherosclerosis, AIDS, diabetes, and various liver and heart diseases. Consequently, understanding NF-κB regulation has major clinical implications for numerous diseases, and the articles that comprise this forum are designed to discuss the regulation of NF-κB in cells, both at fundamental and clinical levels.

Reactive oxygen species (ROS) such as superoxide ($O_2^{\bullet -}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($HO^{\bullet}$) were initially viewed as toxic by-products of aerobic metabolism that needed to be removed from cells. During the last 20 years, this concept evolved and nowadays ROS are viewed as normal products of metabolism that may fulfill important biological functions. It is now well recognized that ROS, primarily H_2O_2, can alter protein redox status, particularly thiols on cysteine residues through various post-translational redox modifications (*e.g.*, glutathionylation, disufide bond, sulfenic acid), to modulate many signaling pathways including the activation of NF-κB (7). Fours years after NF-κB's discovery, Herzenberg's group first demonstrated that cellular redox status (*e.g.*, thiol levels) regulates NF-κB activation in a T-cell line (12). A year later, Baeuerle's lab showed that H_2O_2 acts as a messenger to help activate NF-κB in a different T-cell line (8). These early NF-κB redox studies have been followed by hundreds of other cell culture studies that have either supported or refuted the role of ROS and redox changes in activating NF-κB in cells. Many later works also have demonstrated that redox changes inhibit NF-κB activation following various stimuli. Consequently, a great deal of controversy has arisen regarding redox regulation of NF-κB in cultured cells, a topic that will be covered by several articles in this forum.

The first two articles in the forum provide a general overview of redox regulation of NF-κB, particularly pathways involved in its activation. The control of post-translational modifications to NF-κB and associated proteins are addressed by Gloire and Piette (3). In particular, the redox control of NF-κB binding to DNA, chromatin remodeling, and recruitment of co-activators are described. A complex picture with a multitude of redox control check points in the nucleus is presented, the result of which may be both active and inhibited expression of NF-κB-dependent genes. This theme is also addressed by Oliveira–Marques *et al.* who provide insights into how H_2O_2 may be a fine tuner of NF-κB signaling, proposing that H_2O_2 acts as a specific regulator at the level of the single gene (5). H_2O_2 is viewed as a modulator of NF-κB activation caused by other agents, such as TNF, rather than as an agent that activates NF-κB per se. This is exemplified with the dual regulation of inflammation by H_2O_2 and a potential involvement of H_2O_2 in the etiology of diseases associated with κB polymorphisms.

ROS and redox changes have been implicated in the pathogenesis of many diseases through mediating oxidative damage (*i.e.*, DNA oxidation, lipid peroxidation, and protein oxidation). However, it is becoming more and more recognized that ROS mediate cell injury by altering vital signaling pathways, through redox changes to proteins involved in signaling. In view of the central role of NF-κB in many biological processes, a major mechanism by which ROS promote pathogenesis in many diseases may be through alteration of NF-κB signaling, particularly those associated with inflammation, a situation where ROS levels are elevated. The four last articles of the forum focus on redox regulation of NF-κB in various pathologies. Han *et al.* review the redox regulation of TNF signaling and how redox inhibition of NF-κB can sensitize cells to TNF-induced cell death, which may be an important factor in many liver diseases (4). TNF is normally well tolerated in hepatocytes and other cells because NF-κB is also activated by

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TNF and helps to transcribe survival genes. However, redox alterations can inhibit NF-κB activity and sensitize hepatocytes to the cytotoxic actions of TNF. Consequently, ROS generated extrinsically (e.g., during inflammation) or intrinsically (e.g., by drugs and toxins) may act in concert with TNF to promote hepatocyte death and liver injury through redox inhibition of NF-κB in many liver diseases. In the following article, Gao and Dudley review the redox regulation of NF-κB in atrial fibrillation, a new and developing field of clinical research (2). Atrial fibrillation is presented as a self-perpetuating process helped by alterations in gene expression. Here, in contrary to liver, it is the redox activation, instead of inhibition, of NF-κB that mediates the pathology. Activation of NF-κB by ROS, which are increased in this pathology, downregulates the cardiac sodium channel SCN5A, an arrhythmogenic event. The inhibition of the sodium channel is mediated by NF-κB binding to a κB site in the promoter region of the gene, and possibly by a NF-κB-dependent defective splicing, constituting yet one more example of the complexity of the NF-κB pathway, which usually is thought to lead to the activation and not the inhibition of target genes.

The last two articles of the series present original data. Oliver *et al.* study the activation of NF-κB during hypoxia in a cellular model (6). Both continuous and intermittent hypoxia activates NF-κB, through the canonical signaling pathway rather than by the noncanonical pathway. Importantly, this was also observed *in vivo* in synovial biopsies obtained by arthroscopy from patients with active inflammatory arthritis, where the canonical NF-κB pathway was activated in those patents with lower joint pO2 values. NF-κB activation may subsequently contribute to the onset of inflammation, which has important clinical implications because hypoxia and inflammation co-exist in many pathological states, including tumor growth, ischemia, and chronic inflammation. Finally, in the last article in the forum, Shimizu *et al.* provide an example how NF-κB can be used as a therapeutic target (10). In beagle dogs, a large animal model, NF-κB inhibition with decoy oligodeoxynucleotides that target κB regions, prevented the progression of bone loss in periodontitis, a subgingival inflammation, and promoted the wound healing in bone defect through the inhibition of osteoclastic bone resorption. The decoy oligodeoxynucleotides were applied locally at the site of the lesion to avoid possible systemic side-effects, suggesting that this approach might be a potential therapy in various bone metabolic diseases.

Overall, there has been a growing recognition of the importance of redox regulation of NF-κB in many pathologies and this area of research will likely continue to grow in the coming years. Because of the complexity of NF-κB activation and its centrality in the cell, the development of therapeutic strategies aimed at NF-κB signaling is a difficult task that needs to be based on strong fundamental knowledge of its regulation. The goal of this forum is to help further perpetuate the discussion, both at the fundamental level and the clinical level, regarding the redox regulation of NF-κB signaling.

References

1. Dey A, Tergaonkar V, and Lane DP. Double-edged swords as cancer therapeutics: Simultaneously targeting p53 and NF-kappaB pathways. *Nat Rev Drug Discov* 7: 1031–1040, 2008.
2. Gao G and Dudley SC Jr. Redox regulation, NF-κB, and atrial fibrillation. *Antioxid Redox Signal* 11: 2265–2277, 2009.
3. Gloire G and Piette J. Redox regulation of nuclear post-translational modifications during NF-κB activation. *Antioxid Redox Signal* 11: 2209–2222, 2009.
4. Han D, Ybanez MD, Ahmadi S, Yeh K, and Kaplowitz N. Redox regulation of tumor necrosis factor signaling. *Antioxid Redox Signal* 11: 2245–2263, 2009.
5. Oliveira-Marques V, Marinho HS, Cyrne L, and Antunes F. Role of hydrogen peroxide in NF-κB activation: from inducer to modulator. *Antioxid Redox Signal* 11: 2223–2243, 2009.
6. Oliver KM, Garvey JF, Ng CT, Veale DJ, Fearon U, Cummins EP, and Taylor CT. Hypoxia activates NF-κB-dependent gene expression through the canonical signaling pathway. *Antioxid Redox Signal* 11: 2057–2064, 2009.
7. Schafer FQ and Buettner GR. Redox environment of the cell as viewed through the redox state of the glutathione disulfide/glutathione couple. *Free Radic Biol Med* 30: 1191–1212, 2001.
8. Schreck R, Rieber P, and Baeuerle PA. Reactive oxygen intermediates as apparently widely used messengers in the activation of the NF-kappa B transcription factor and HIV-1. *EMBO J* 10: 2247–2258, 1991.
9. Sen R and Baltimore D. Multiple nuclear factors interact with the immunoglobulin enhancer sequences. *Cell* 46: 705–716, 1986.
10. Shimizu H, Nakagami H, Morita S, Tsukamoto I, Osako MK, Nakagami F, Shimosato T, Minobe N, and Morishita R. New treatment of periodontal diseases by using NF-κB decoy oligodeoxynucleotides *via* prevention of bone resorption and promotion of wound healing. *Antioxid Redox Signal* 11: 2065–2075, 2009.
11. Shishodia S and Aggarwal BB. Nuclear factor-kappaB: A friend or a foe in cancer? *Biochem Pharmacol* 68: 1071–1080, 2004.
12. Staal FJ, Roederer M, Herzenberg LA, and Herzenberg LA. Intracellular thiols regulate activation of nuclear factor kappa B and transcription of human immunodeficiency virus. *Proc Natl Acad Sci USA* 87: 9943–9947, 1990.

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2. Jifeng Wang, Baobing Zhao, Yuting Yi, Wei Zhang, Xuan Wu, Lianru Zhang, Yuemao Shen. 2012. Mycoepoxydiene, a fungal polyketide inhibits MCF-7 cells through simultaneously targeting p53 and NF-#B pathways. *Biochemical Pharmacology* **84**:7, 891-899. [CrossRef]
3. Liliana Magnago Pedruzzi, Milena Barcza Stockler-Pinto, Maurilo Leite, Denise Mafra. 2012. Nrf2–keap1 system versus NF-#B: The good and the evil in chronic kidney disease?. *Biochimie* . [CrossRef]