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NF-κB, a hot topic in biochemical and medical studies in China

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In 1986, nuclear factor (NF)-κB was first discovered in the laboratory of Nobel Prize laureate David Baltimore via its interaction with a sequence (5′-GGGACTTTCC-3′) in the immunoglobulin light-chain enhancer in B cells [1]. As a multifunctional factor, NF-κB is involved in the regulation of many signaling pathways that are related to certain common diseases such as carcinoma, neurodegeneration, diabetes, and immunopathies [2–4]. Currently, much attention is focused on research on NF-κB signaling pathways and related diseases in China.

Pei Gang and colleagues (Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences; Tongji University) investigated the β-arrestins that link receptor signals to transcription [5,6]. Their investigations showed that β-arrestin-2 interacts with IκBα and suppresses UV-induced NF-κB activation, and that β-arrestin prevents TRAD6 autoubiquitination and inhibits downstream NF-κB activation. The research by Pei has provided a new mechanism, designated "IκB kinase complexes: gateways to NF-κB activation and transcription" [7–9].

Zhang XiaoDong *et al*. [10] (Nankai University), Xiao ZhiQiang *et al*. [11], Shen ShouRong *et al*. [12] (Central South University), and their colleagues investigated the roles of NF-κB in carcinogenesis, metastasis, and cell death in hepatoma, nasopharyngeal carcinoma, and colon carcinoma, respectively. For cell apoptosis, Zhang Lan and coworkers (Guangzhou Medical College) studied the mechanism of the JNK/Bim/Bax apoptotic pathway induced by tumor necrosis factor (TNF)-α in differentiated PC12 cells. Their research revealed that NF-κB can inhibit mitochondrial pathway apoptosis through upregulation of Bcl-x_L induced by TNF-α. Bim_L displaces Bcl-x_L in the mitochondria and promotes Bax translocation during TNF-α-induced apoptosis [13]. With a view to discovering new regulators of the NF-κB signaling pathway, Shi TaiPing and colleagues (Chinese National Human Genome Center, Beijing) established a high-throughput cell-based screening model based on a dual luciferase reporters system, and obtained a number of genes that can activate the NF-κB signaling pathway by screening 439 genes with novel functions. Among these genes, TMEM9B can obviously activate the NF-κB signaling pathway and thus cause apoptosis [14].

Infection and immunology investigations carried out by Wu NanPing and coworkers (Zhejiang University) revealed that NF-κBp50 stimulates the expression of dendritic cell-specific intercellular adhesion molecule-3-grabbing nonintegrin (DC-SIGN) in THP-1 cells. Interleukin (IL)-4 upregulates DC-SIGN expression on THP-1 cells as well as NF-κB production [15]. Their data further revealed that NF-κB is associated with IL-4-induced DC-SIGN expression. Cai GuoPing and colleagues (Tsinghua University) found that lipopolysaccharide (LPS) stimulates TNF-α ex-

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pression through activation of NF-κB, and that TNF-α then induces CHI3L1 expression [16]. This is the first study showing that CHI3L1 expression is promoted in osteomyelitis and LPS-treated osteoblasts.

Sepsis is currently one of the most serious problems encountered in modern medicine and improvements to its treatments are urgently needed. Bone marrow-derived stromal cells (BMSCs) have potent immunosuppressive effects in humans *in vivo*. Bi LiangKuan and colleagues (Sun Yat-sen University) showed that systemic delivery of IL-10 by BMSCs may serve as a potential treatment in sepsis therapy [17].

The immune-inflammatory responses mediated by LPS are firmly related to the development of atherosclerosis. ATP-binding cassette A1 protein (ABCA1) has been identified to play a key role in cellular cholesterol efflux, which is regarded as an anti-atherosclerosis process. Tang ChaoKe and coworkers (University of South China) showed that LPS can downregulate the expression of ABCA1, promote the accumulation of lipids, and decrease cellular cholesterol efflux in THP-1 macrophage-derived foam cells, which may be related to the TLR4/NF-κB-dependent and LXRα-independent pathways [18]. Hydrostatic pressure has direct effects on the vascular endothelium. Endothelial lipase (EL) is a newly identified member of the triglyceride lipase family that is only secreted by endothelial cells. Liao DuanFang and colleagues (University of South China) provided new insights into the effects of hydrostatic pressure on EL expression through NF-κB signaling pathways [19]. Pan Jie and colleagues (Shandong University) investigated the sequential expressions of atherosclerosis-related genes in young ApoE gene-deficient mice. Their results suggested that the sequential and differential expressions of genes related to atherosclerosis form a complex regulatory network with NF-κB as the core, and that the genes may interact with one another and play important roles in the early stages of atherosclerosis of young apoE$^{-/-}$ mice [20].

The human embryonic kidney cell line 293FT has been used as a model to investigate the function of Nogo-A in neurons. Jin WeiLin and colleagues (Shanghai Jiao Tong University) used a pathway profiling reporter system to examine the involvement of Nogo-A in regulating the intracellular signaling pathways [21]. They found that overexpression of Nogo-A could specifically activate NF-κB signaling. In subsequent experiments using different Nogo-A alternatively spliced isoforms and serial truncation mutants, they confirmed that the activation of NF-κB by Nogo-A relies on its N-terminal proline-rich domain. This indicates that Nogo-A can significantly activate NF-κB, and that this activation is primarily dependent on its N-terminal proline-rich domain. Several groups have been studying the relationships between NF-κB and neurodegeneration, especially the roles of NF-κB in the chronic inflammation involved in neurodegenerative diseases. Furthermore, Chinese scientists have investigated the NF-κB pathways related to neuroimmunological events.

To analyze the functions of NF-κB, Sun YiMin and coworkers (Tsinghua University) established a reproducible and reliable high-throughput mouse oligonucleotide array-based platform that can simultaneously explore the activities of nearly 200 different transcription factors [22]. The array comprises 240 synthetic probes that contain transcription factor-binding sequences based on 226 PSSMs (position-specific scoring matrices) provided by the TRANSFAC database. Purified NF-κB was used to test the sensitivity and quantitative ability of the microarray. The data revealed that the system can detect as little as 0.5 nmol/L of NF-κB protein. Consequently, they have established a reliable microarray platform for profiling mouse transcription factor activities.

As investigations continue, more pathways related to NF-κB will be found. The gene regulations involved in NF-κB signaling form a complex network with systematic regulation. Will they result in "NF-κBomics"? Here, we must explain that we have not introduced all of the work focused on NF-κB in China, such as the use of NF-κB in clinical and pharmaceutical studies. Some important work in immunology and applied research is also not mentioned here. However, studies on NF-κB are progressing in China, and our Chinese colleagues will, we believe, obtain further fruitful results in the future.

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