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Editorial

20 years of NF-κB

We are celebrating this year 20 years of research dedicated to the transcription factor NF-κB. From 1986, the year of its initial identification as a DNA-binding activity for the enhancer of the immunoglobulin κ light-chain in activated B cells by Sen and Baltimore [1] to 2006, almost 20,000 papers related to this transcription factor were published, which means three reports per day. This amazing amount of data generated over the years and throughout the world reflects the critical roles played by NF-κB in biology. It is indeed increasingly difficult to find circumstances where NF-κB is not involved at one point. One reason is due to the amazing amount of signals that can activate NF-κB. They include bacterial, viral and fungal products but also inflammatory cytokines, oxidative stress and therapeutically used drugs (as reviewed by Y. Habraken and J. Piette in this issue) and are listed in Tom Gilmore's website (http://www.nf-kb.org) (Boston University). Another reason is due to the functional κB sites found in about 100 genes [2]. These numerous NF-κB target genes play critical roles in cell survival and proliferation, as well as in innate and adaptive immunity, which reflects the essential role of this transcription factor in physiology and diseases.

NF-κB is a double-edged sword. Indeed, while this transcription factor is essential for a proper immune response to a variety of environmental stress conditions, enhanced NF-κB activity causes chronic inflammation and cancer. Moreover, diseases as diverse as acute and chronic neurodegenerative disorders (reviewed by S. Mémet in this issue), atherosclerosis, among many others are also characterized by deregulated NF-κB activation. NF-κB is thus seen as a promising target for therapy in inflammatory diseases and cancer (as reviewed by S. Olivier and colleagues in this issue). Equally importantly, impaired NF-κB activation has also been linked to several human diseases, such as incontinenta pigmenti for example, as reviewed by G. Courtois in this issue. Therefore, NF-κB activation has to be tightly regulated, as evidenced by the 20 years of research dedicated to this transcription factor.

1. An historical perspective

The story began in 1986 with the identification of NF-κB as a transcription factor binding the enhancer of the immunoglobulin κ light-chain in activated B cells [1,2]. Subsequent studies demonstrated that NF-κB, rather than a B-cell specific protein, is actually a pleiotropic factor and the prototype of a latent cytoplasmic transcription factor whose activation is largely regulated via control of its nuclear translocation [3,4]. Indeed, NF-κB is sequestered in the cytoplasm in most unstimulated cells through binding to inhibitory proteins, collectively referred to as IκBs [5,6]. Upon stimulation by a variety of signals, IκBs, the prototype of which is IκBα, are phosphorylated and subsequently degraded through the proteasome pathway, and the activated, ''free'' NF-κB moves into the nucleus to regulate gene transcription. NF-κB proteins include several members (p50, p52, p65, RelB and cRel) and their cDNAs were cloned in 1989 and the following years [7–12].

Definitive evidence for NF-κB acting as a key player in the immune response came from the analysis of mice deficient for each NF-κB proteins and whose phenotypes were recently summarized [2]. Interestingly and because p65 deficiency causes embryonic lethality due to massive apoptosis of the fetal liver [13], a pro-survival role of NF-κB was subsequently reported [14–16]. It became clear indeed that NF-κB activation induces cell survival in lymphocytes and many other cell types through transcriptional induction of specific anti-apoptotic genes. This finding was of great importance, as chromosomal translocations targeting genes coding for inhibitory IκB proteins were identified in some haematological malignancies [17,18]. Such translocations cause constitutive NF-κB activity and it is still believed today that these molecular alterations are the causal event for enhanced proliferative and survival abilities of the mutated cells as reviewed by A. Keutgens and colleagues in this issue. What is true for haematological disorders turned out to be also true for solid tumors, as reviewed by F. Pacifico and A. Leonardi in this issue. The pro-survival role of NF-κB also implies a TNFα-mediated attenuation of JNK activation through multiple mechanisms [19], as reviewed by A. Wullaert and colleagues in this issue.

The early demonstration that NF-κB activation does not require protein synthesis but rather relies on the signal-induced phosphorylation of the IκBs on specific residues [20,21] initiated an intense research activity dedicated to the

characterization of the signalling pathways ultimately causing phosphorylation and subsequent degradation of these inhibitory molecules. A first breakthrough came with the identification of the IKK complex that includes the catalytic subunits IKKα and IKKβ as well as the regulatory subunit, NEMO/IKKγ [22–26]. This pathway referred to as the ''canonical'' pathway is triggered by pro-inflammatory cytokines and is mainly involved in innate immunity. Among these stimuli are the TLR ligands, as reviewed by Sarah Doyle and Luke O'Neill in this special issue. The next breakthrough occurred with the identification of the ''alternative'' or ''non-canonical'' pathway. This latter pathway is triggered by other stimuli (lymphotoxin β, ...), does not involve NEMO/IKKγ and ultimately regulates a distinct subset of target genes, namely genes involved in secondary lymphoid organ development and in adaptive immunity [27–30], as reviewed by E. Dejardin in this issue. Both pathways rely on sequentially activated kinases, which ultimately target an IκB protein for phosphorylation. Importantly, these pathways do not exclusively involve protein phosphorylation but also non-degradative polyubiquitination of numerous scaffold proteins [31–33].

NF-κB proteins themselves are also targeted by a variety of kinases and this mechanism is required for optimal gene activation [34,35]. Other modifications such as acetylation [36] have been described too and it is now well established that the so-called epigenetic settings and the chromatin structure are both critical for the regulation of NF-κB-mediated gene transcription as reviewed by W. Vanden Berghe and colleagues in this special issue. More recently, a nuclear role for IKKα was reported [37,38], as reviewed by G. Gloire and colleagues in this issue and this finding reflects the ability of the IKK complex to phosphorylate multiple substrates, besides IκBα in the cytoplasm and also in the nucleus. Very recent reports actually demonstrated that the IKK complex harbours NF-κB-independent functions by targeting newly discovered substrates [39] and it is likely that the next months will bring substantial amount of data illustrating this fact.

The critical role played by a family of proteins is often exemplified by the diseases caused by their deregulation. This statement is certainly true for NF-κB and for the multiple molecules involved in the NF-κB-activating signalling pathways. In this context, the report demonstrating that incontinenta pigmenti (IP), a human genetic disease, is caused by inherited mutations of the NEMO-encoding gene [40] was the first demonstration that impaired NF-κB signalling is also severely detrimental. Moreover, the fact that NF-κB is the molecular link between chronic inflammation and cancer [41,42] actually demonstrates that NF-κB can be linked to human diseases even in the absence of acquired mutations of the NF-κB/IκB-encoding genes.

In conclusion, and despite the feeling sometimes shared by the ''NF-κB scientists'' that ''we are almost reaching the end of the story'', the still increasing scientific literature dedicated to this transcription factor actually proves that this is not the case. Let's ask for 20 more years then...

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Alain Chariot*
Laboratory of Medical Chemistry,
Center for Cellular and Molecular Therapy,
Center for Biomedical Integrative Genoproteomics,
University of Liege,
Liege, Belgium

*Tel.: +32 4 366 2486; fax: +32 4 366 4534
E-mail address: alain.chariot@ulg.ac.be
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