## Editorial

## NF- $\kappa$ B in life/death decisions: an introduction

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NF- $\kappa$ B plays a key role in the regulation of the immune, inflammatory and stress responses. Most importantly for the ultimate fate of the individual cell, however, NF- $\kappa$ B arbitrates between death and life, with dramatic implications for normal homeostasis and major human diseases. This is the topic of the current Special Issue of *Cell Death and Differentiation*.

NF- $\kappa$ B is composed of homo- or heterodimers of five proteins belonging to the Rel family of transcription factors. In the vast majority of cell types, NF- $\kappa$ B is kept inactive in the cytoplasm through association with inhibitory proteins of the I $\kappa$ B family. This family includes I $\kappa$ B $\alpha$ , I $\kappa$ B $\beta$  and I $\kappa$ B $\varepsilon$ , as well as p105 and p100, the cytoplasmic precursors of the p50 and p52 NF-kB subunits. In response to multiple stimuli, such as cytokines, various stress signals, viral and bacterial infections, IkB molecules become phosphorylated on specific residues. This modification allows their recognition by an ubiquitination complex, and, following polyubiquitination, they are degraded by the proteasome machinery (entirely for  $I\kappa B\alpha$ ,  $I\kappa B\beta$  and  $I\kappa B\varepsilon$ , partially for p105 and p100). As a consequence, free, unrestrained NF-kB enters the nucleus and activates transcription of its target genes. The kinase responsible for phosphorylation of the inhibitors has been identified only recently. This kinase, IKK, is a high molecular weight complex that contains two related catalytic subunits, IKK $\alpha$  and IKK $\beta$ , as well as a structural and regulatory subunit, NEMO/IKKy.

One of the quintessential conundra in the field is the question how do so many apparently unrelated NF- $\kappa$ B-activating stimuli lead to activation of the IKK complex. It came as a surprise that a critical element of this activation process is a nondegradative polyubiquitination program, which targets some of the components of the tumor necrosis factor, interleukin-1, lipopolysaccharide or T-cell receptor-elicited pathways (and possibly other pathways) and probably allows specific protein–protein interactions to take place, leading to kinase activation.<sup>1</sup> Another enigma relates to the specificity of induction of certain genes by certain stimuli, and the specific function exerted by each of the five members of the Rel family. This question has only recently begun to be addressed in a systematic fashion.<sup>2</sup> Part of the specificity of

the NF- $\kappa$ B activation cascades lies in the crosstalk that exists between the NF- $\kappa$ B cascade and other signaling pathways. One example of such a crosstalk is given by an atypical member of the protein kinase C family, PKC $\zeta$ , which seems to function both upstream and downstream of the IKK complex, and mediates a crosstalk between the NF- $\kappa$ B and Jak/STAT pathway.<sup>3</sup> Another crosstalk concerns NF- $\kappa$ B and JNK. Thus, it has been established that NF- $\kappa$ B exerts its antiapoptotic role in part by negatively regulating the JNK cascade, through suppression of the accumulation of reactive oxygen radicals.<sup>4,5</sup>

The cell death-suppressive function of NF- $\kappa$ B plays a critical role in oncogenesis and cancer progression. Numerous reports have shown that various types of tumor cells become resistant to proapoptotic drugs through constitutive activation of NF- $\kappa$ B.<sup>6</sup> In addition, NF- $\kappa$ B may participate in the control of proliferation, angiogenesis and metastasis. In the case of hematologic malignancies, inhibitors of IKK and of the proteasome are beginning to be tested in clinical trials, with encouraging preliminary results.<sup>7,8</sup> However, the NF- $\kappa$ B response is highly complex, critically depending on the signal, its duration and intensity, as well as on the cell type, and in certain cases NF- $\kappa$ B may even behave like a tumor suppressor.<sup>9</sup>

One of the major oncogenic stressors is DNA-damage, and the molecular mechanisms by which DNA damage leads to NF- $\kappa$ B activation have only recently been identified. Most DNA-damage signals relay to NF- $\kappa$ B activation via an active IKK complex, although they use an entirely specific upstream pathway. In contrast, NF- $\kappa$ B activation by UV does not require IKK. In addition, some of these signals seem to turn relA/p65 from a transcriptional activator to a repressor.<sup>10</sup>

Among the multiple roles played by NF- $\kappa$ B, the most studied one is probably its function in the regulation of distinct steps of hematopoiesis, and its pathological derangements.<sup>11</sup> The critical role played by NF- $\kappa$ B in the innate immune response against bacterial and viral pathogens relies largely on its role in TLR signaling. In addition, it involves signals elicited by the family of intracellular microbial sensors that include the NODlike receptors and the newly discovered RIG-I and Mda-5 proteins.<sup>12,13</sup> Beyond its role in the innate response, NF- $\kappa$ B also plays a role in controlling the generation and activity of T and B cells.<sup>14</sup> In particular, activation of T cells through stimulation of the antigen receptor (TCR) and its costimulatory molecules relies in part on NF- $\kappa$ B activation.<sup>15,16</sup>

Human genetic diseases caused by partial or complete inactivation of the NF- $\kappa$ B cascade have only recently been discovered<sup>17</sup> and the mutations that have been identified thus far target NEMO,  $I\kappa$ B $\alpha$  and a novel deubiquitinase. It can be anticipated that the extensive phenotypic characterization of these mutants will further our understanding of the subtleties of the NF- $\kappa$ B signaling pathway in the human system.

The function of NF- $\kappa$ B in neurons has for long remained a matter of debate, because NF- $\kappa$ B may behave as an

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antiapoptotic and as a proapoptotic factor, in a contextdependent fashion. Brand new data obtained by transgenic approaches have shed some light on NF- $\kappa$ B's role in the central nervous system, demonstrating its impact on transcription-dependent changes in the structure and function of neuronal circuits.<sup>18</sup>

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Deciphering the role played by NF- $\kappa$ B in the brain is just another example of the power of modern mouse genetics. Knocking out the individual members of the NF- $\kappa$ B and I $\kappa$ B families furnished important informations regarding their function, although prenatal or perinatal lethality was often a limiting factor for the in-depth exploration of the system. The more recent use of tissue-specific or inducible knockout or knock-in techniques has made a major contribution to our current understanding of the physiological functions of the NF- $\kappa$ B/I $\kappa$ B proteins and the multiple positive and negative regulators of this pathway.<sup>19</sup>

Thus, progress in the NF- $\kappa$ B field is continuous and inexorable. NF- $\kappa$ B definitively is a central player – or how System Biologist' would say – a 'hub' in the intricate signal transduction pathways that shape our intellect, protect the organism from damage including infectious agents, and keep our cells alive, yet normally prevent their oncogenic transformation.

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