BIOCHEMICAL PHARMACOLOGY 72 (2006) 1069–1080

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Deregulated NF-κB activity in haematological malignancies

Aurore Keutgens [1], *Isabelle Robert* [1], *Patrick Viatour* [2], *Alain Chariot* [*]

Laboratory of Medical Chemistry, Center for Cellular and Molecular Therapy, Center for Biomedical Integrative Genoproteomics, University of Liege, Tour de Pathologie, +3 B23, CHU Sart-Tilman, 4000 Liège, Belgium

ARTICLE INFO

Article history:
Received 10 May 2006
Accepted 9 June 2006

Keywords:
NF-κB
IκB
IKK
p100
BCL-3
Lymphoma
Leukemia
Hodgkin disease

Abbreviations:
ABC, activated B-cell-like
ALCL, anaplastic large cell lymphoma
ALL, acute lymphoblastic leukaemia
AML, acute myeloid leukaemia
BAFF, B cell-activating factor
BCL-2, B-cell lymphoma 2
B-CLL, B-cell chronic lymphocytic leukemia
BCR, B-cell receptor
Blk, B-lymphoid kinase
Btk, Bruton's tyrosine kinase
CARD11, caspase recruitment domain-containing protein 11
c-IAP2, cellular inhibitor of apoptosis 2

ABSTRACT

The NF-κB family of transcription factors plays key roles in the control of cell proliferation and apoptosis. Constitutive NF-κB activation is a common feature for most haematological malignancies and is therefore believed to be a crucial event for enhanced proliferation and survival of these malignant cells. In this review, we will describe the molecular mechanisms underlying NF-κB deregulation in haematological malignancies and will highlight what is still unclear in this field, 20 years after the discovery of this transcription factor.

* *Corresponding author*. Tel.: +32 4 366 2486; fax: +32 4 366 4534.
E-mail address: Alain.chariot@ulg.ac.be (A. Chariot).

[1] These authors equally contributed to this paper and are listed by alphabetical order.

[2] Present address: Departments of Pediatrics and Genetics, Stanford University School of Medicine, Stanford, CA, USA.

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doi:10.1016/j.bcp.2006.06.011

CLL, chronic lymphocytic leukaemia
CML, chronic myeloid leukaemia
CTCL, cutaneous T-cell lymphoma cell line
DLBCL, diffuse large B-cell lymphoma
EBV, Epstein-Barr virus
FL, follicular lymphoma
GCB, germinal center-B-like
HD, Hodgkin's disease
HSC, hematopoetic stem cell
HTLV-1, human T-cell leukaemia virus type 1
IκB, IkappaB
IKK, IκB kinase
IL-1, interleukine 1
LMP-1, EBV-encoded protein latent membrane protein 1
LSC, leukemic stem cell
LT-βR, lymphotoxin-β receptor
MALT, mucosal-associated lymphoid tissue
MDS, myelodysplastic syndrome
MLBCL, mediastinal large B-cell lymphoma
NEMO, NF-κB essential modulator
NF-κB, nuclear factor-kappa B
NHL, non-Hodgkin's lymphoma
NIK, NF-κB-activating kinase
PCD, programmed cell death
PKC, protein kinase C
RANK, receptor activator of nuclear factor-kappaB
Rev-T, reticuloendotheliosis virus strain T
RHD, rel homology domain
RIP, receptor interacting protein
RS, Reed–Sternberg
SLPI, secretory leukocyte protease inhibitor
SODD, silencer of death domain
STAT5, signal transducers and activators of transcription
Syk, spleen tyrosine kinase
TAK, TGFβ-activated protein kinase
TCR, T-cell receptor
TNF, tumour necrosis factor
TNF-R, TNF-receptor
TRADD, TNF-receptor-associated death domain protein
TRAF, TNF receptor-associated factor
Ub, Ubiquitination
ZAP70, ζchain-associated protein kinase of 70 kDa

1. Introduction

Nuclear factor (NF)-κB/Rel is a structurally and evolutionary conserved family of transcription factors sharing a 300 amino acid domain named the Rel homology domain (RHD) which is required for DNA-binding, dimerization, nuclear translocation and binding to the so called inhibitory IκB proteins [1]. The NF-κB proteins include five members, namely RelA (p65), RelB and c-Rel synthesized as mature products and harbouring a C-terminal transactivating domain and also p50 and p52 which are generated through a C-terminal proteolytic processing of longer precursors, NF-κB1 (p105) and NF-κB2 (p100), respectively (Fig. 1). Of interest, whereas both p50 and p52 harbour the RHD domain, they lack any transactivating region, which

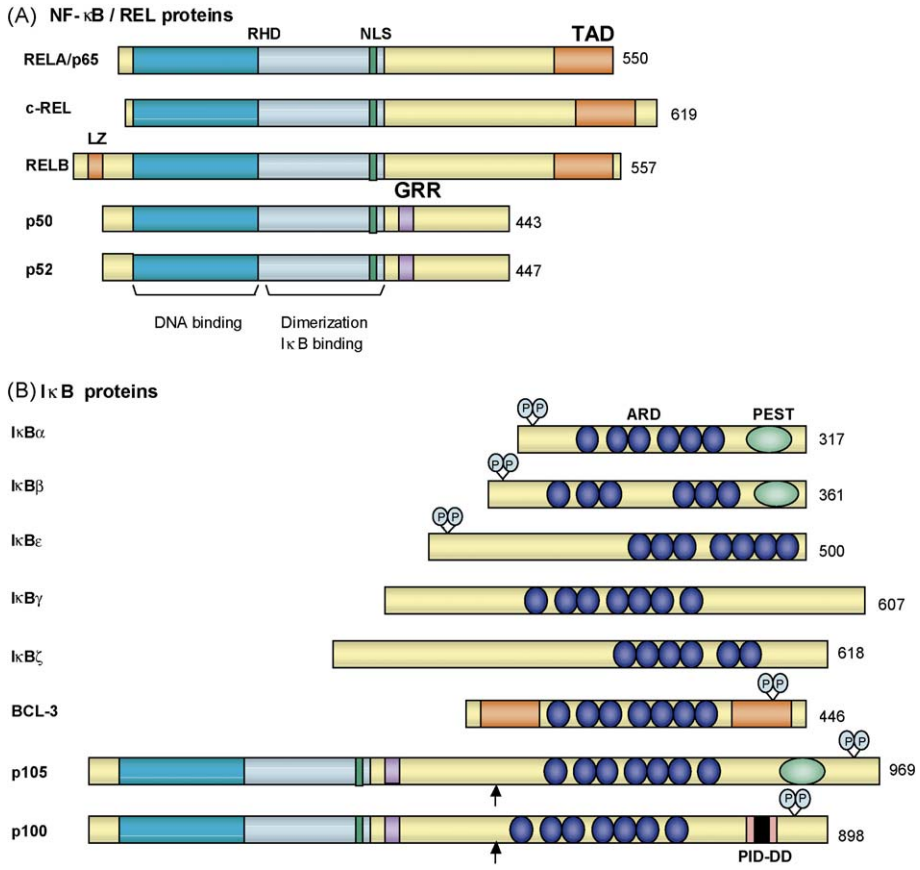

Fig. 1 – Schematic representation of NF-κB/Rel and IκB proteins. (A) NF-κB/Rel proteins: the five mammalian NF-κB/Rel proteins (RelA/p65, c-Rel, RelB, p50 and p52) are characterized by the presence of a well-conserved N-terminal ~300 amino acids Rel homology domain (RHD), which is responsible for binding to DNA, dimerization and interaction with IκBs. The RHD also contains at its C-terminus, a nuclear localization signal (NLS) which allows the protein to translocate to the nucleus in response to cell stimulation. RelA, c-Rel and RelB are synthesized as mature proteins and share a carboxy-terminal transactivation domain (TAD) that allows them to function as transcriptional activators. The Leucine zipper (LZ) of RelB is required for transactivation abilities. p50 and p52, which are first synthesized as large precursors (p105 and p100), lack such transactivation domain and therefore have no transcription activity. (B) IκB proteins (inhibitors of NF-κB): these proteins are related to each other by the presence of six to seven ankyrin repeats. This Ankyrin Repeats Domain (ARD) mediates binding to the Rel Homology Domain of the NF-κB/Rel factors, which masks their NLS and sequesters them into the cytoplasm. Upon stimulation, the IκB proteins become phosphorylated on two serine residues which leads to their polyubiquitination and proteosomal degradation. As a result, NF-κB/Rel proteins are free and translocate to the nucleus where they can regulate target gene expression. In contrast to the other IκB proteins, BCL-3 is predominantly localized in the nucleus and can activate gene transcription when bound to homodimers p50 or p52, due to its two transactivation domains. The C-terminal regions of the precursors p100 and p105, which contain 7 ankyrin repeats, function as auto-inhibitory IκB-like domains and retain p52 or p50 and their partners in the cytoplasm. While the processing of p105 is mostly constitutive, the p100 processing is tightly regulated due to the presence at its C-terminal extremity of a processing inhibitory domain (PID). Both processings are dependent on glycine-rich sequences (GRR). RHD: Rel homolgy domain, NLS: nuclear localization signal, TAD: transactivation domain, LZ: leucine zipper, GRR: glycine-rich region, ARD: ankyrin repeats domain, PEST: polypeptide sequence enriched in proline, PID: processing inhibitory domain, DD: death domain, P: phosphorylation site. The number of amino acids of each protein is indicated on the right. The arrows indicate the presumed sites of cleavage for p100 and p105.

therefore means that they have to form hetero-complexes with other members of this family to transactivate defined target genes.

NF-κB is the prototype for latent cytoplasmic transcription factor whose activation is regulated largely via control of nuclear translocation [1,2]. Indeed, NF-κB is sequestered in the cytoplasm in most untransformed and unstimulated cells, with the notable exception of B lymphocytes, through binding to the inhibitory proteins whose prototype is IκBα (Fig. 1). Entry of so called "activated NF-κB" into nuclei is the final step of signalling cascades initiated by numerous stimuli such as pro-inflammatory cytokines, bacterial and viral components and

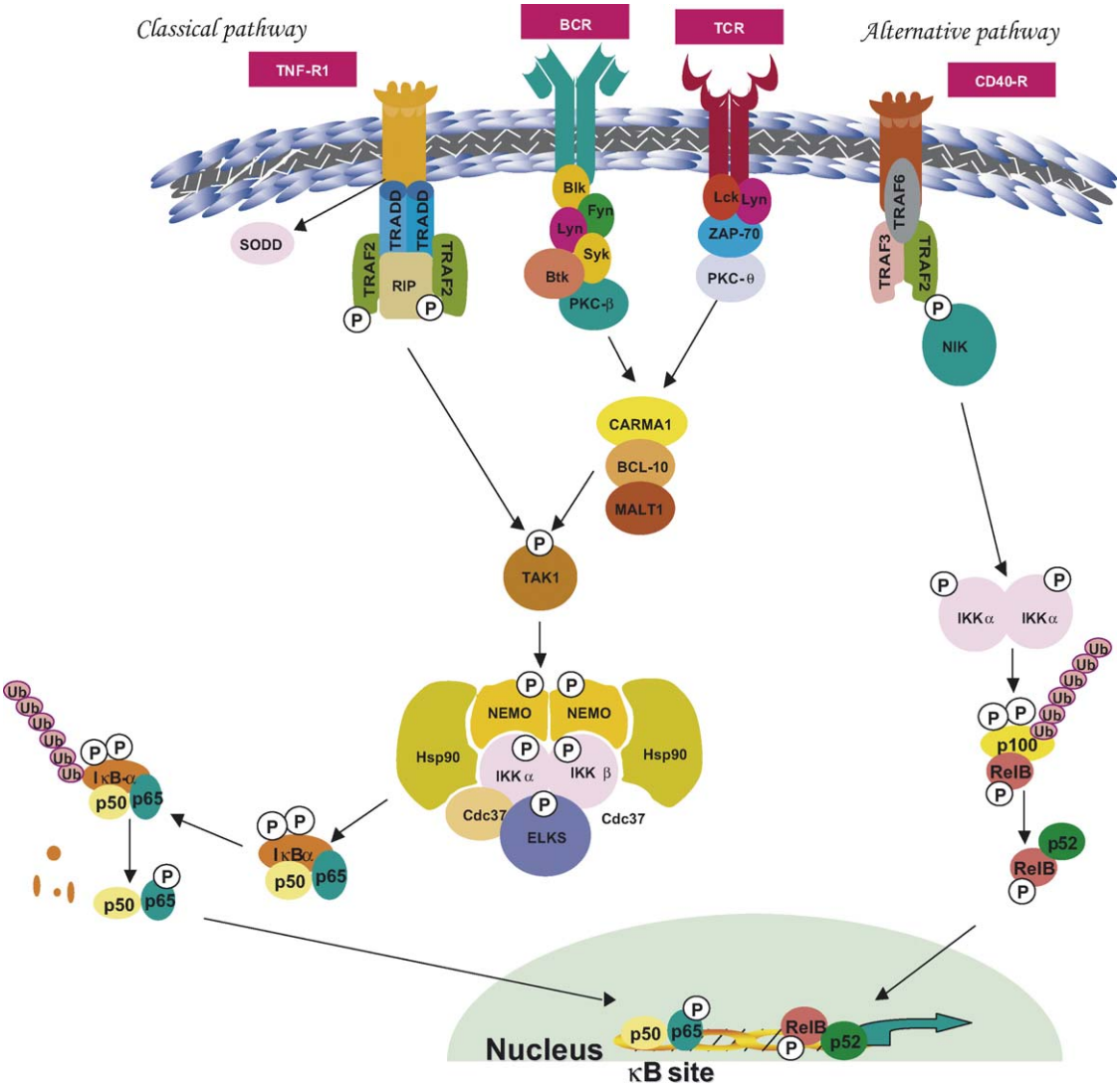

Fig. 2 – The IKK-dependent NF-κB-activating signalling pathways. NF-κB is activated through two main signalling cascades, namely the classical and the alternative pathways. Both pathways rely on the IKK-mediated IκBα or p100 phosphorylation, subsequent ubiquitination (Ub) and degradation through the proteasome pathway, respectively. Receptors such as the TNFα-receptor (TNFR), the B-cell receptor (BCR) or the T-cell receptor (TCR) exclusively signal through the classical pathway and therefore trigger IκBα phosphorylation via an IKKα/β and NEMO-dependent pathway whereas receptors such as CD40, BAFFR, LT-βR or RANK signal through both the classical but also through the alternative pathway via an IKKα and NIK-dependent but NEMO-independent pathway. Upon binding of TNFα to the TNFR1, SODD is released from the receptor and triggers the sequential recruitment of TRADD, RIP, TRAF2 and the IKK complex to the membrane which is activated through a TAK1-dependent pathway. Stimulation of B-cells through the BCR triggers a sequential activation of multiple kinases that include Blk, Fyn, Lyn, Syk and Btk and subsequently PKC-β whereas TCR-mediated NF-κB activation relies on the kinases Lck and Lyn and subsequently on PKC-θ activation. Both pathways converge to a signalling complex that includes CARMA1, BCL-10 and MALT1 which subsequently activates TAK1 and the IKK complex through ubiquitination of NEMO/IKKγ [9,88]. The alternative pathway triggered by binding of CD154 to the CD40R causes NIK activation through a TRAF2-dependent pathway and ultimately leads to IKKα-mediated p100 phosphorylation and processing into p52. Once the IKK complex is activated through the classical or alternative pathway, p50/p65 or p52/RelB hetero-dimers are released following IκBα or p100 degradation, respectively, and move into the nucleus where they bind to specific κB sites and activate a variety of NF-κB target genes.

oxidative stress for example [1,2]. These stimuli trigger signalling cascades involving sequential phosphorylation of critical proteins which ultimately culminate in the activation of the IKK complex, at least in most cases. IKKs in turn phosphorylate inhibitory proteins, such as IκBα, on specific residues to bring about the rapid proteolytic degradation of the inhibitors in an ubiquitin- and proteasome-dependent manner [2]. NF-κB is thus released and free to migrate into the nucleus to regulate the expression of multiple target genes. Two main NF-κB activating signalling cascades have been identified and referred to as the ''classical'' or ''canonical'' pathway and the ''alternative'' or ''non-classical'' pathway (Fig. 2) [3]. Although they share many common features such as the proteasome-mediated processing of an inhibitory molecule, they differ by the nature of the stimuli, the upstream activated kinases, the composition of the IKK complex itself and the identity of the regulated target genes (Fig. 2). Indeed, the classical pathway, which is triggered by pro-inflammatory cytokines such as TNFα, IL-1β, or the ligand for the T-cell or the B-cell receptor leads to IκBα degradation through an IKKβ and NEMO/IKKγ-dependent pathway and is mainly involved in the innate immunity [3–5]. On the other hand, the alternative pathway, which is triggered by some members of the TNF cytokine family such as lymphotoxin-β, BAFF and CD40, relies on the IKKα-mediated p100 phosphorylation through a NIK-dependent and NEMO/IKKγ-independent pathway and is mainly involved in adaptive immunity [3,6–8]. The numerous NF-κB-activating signals explain why the NF-κB family of transcription factor plays such key roles in regulating immune, inflammatory responses, cell proliferation and survival in many cell types.

NF-κB is critical for the development of T and B lymphocytes and how NF-κB is activated in these cells is highly dependent on their developmental stage and the initiating signal [9]. Mice deficient for NF-κB, IκB proteins or NF-κB activating-kinases have been generated and their phenotypical analyses undoubtedly proved the critical role of NF-κB as a survival factor from early lymphopoiesis [10] to latter stages of development and maturation of B and T cells [9,11–14]. Because NF-κB activation counteracts death threat in developing lymphocytes and in mature B and T cells, it is not surprising to observe that deregulated, constitutive NF-κB activity seen in many haematological malignancies causes enhanced expression of cell cycle regulatory and anti-apoptotic proteins and largely contributes to abnormal proliferation and survival of malignant cells [15–17].

In this review, we will describe the main types of haematological disorders and explain through which molecular mechanisms NF-κB is deregulated in these diseases. Finally, we will highlight the still unclear issues in this field of research and will conclude on the latest advances currently used to address them.

1.1. Molecular alterations underlying haematological malignancies

Malignant haematological diseases occur because mutated somatic cells expand, invade, subvert and erode normal tissues because they express oncogenic proteins that disrupt the equilibrium between cell proliferation and cell death [17,18]. Molecular alterations underlying the development of malignant diseases typically involve disruption of tumour suppressors genes (point mutations, chromosomal deletions) and also chromosomal translocations that ultimately activate a proto-oncogene or create an oncogenic fusion protein. Activation of a proto-oncogene typically involves its translocation in the vicinity of the immunoglobulin loci or the TCR (depending whether this is a B- or T cell lymphoid tumour, respectively), which drives inappropriate expression of this proto-oncogene whose coding sequence remains however unaltered. On the other hand, creation of a fusion and oncogenic protein is due to a breakpoint occurring within the coding sequences of the rearranged genes. Both types of chromosomal translocations have been described for *IκB* genes in malignant disorders.

Disruption of tumour suppressor genes by chromosomal deletion of one allele and mutational loss of function of the other allele frequently occurs in solid tumours and has also been described in aggressive lymphomas. It is believed that progression from low to high-grade tumours is associated with inactivation of the tumour suppressor pathways, as evidenced by combinatorial p53 and p27/p16 (two cyclin-dependent kinase inhibitors) mutations [19]. It is therefore important to keep this fact in mind when integrating the consequences of deregulated NF-κB activities on the progression of malignant haematological disorders.

1.2. NF-κB activity in lymphomas

The molecular alterations summarized here can apply for any malignant disease and therefore to lymphomas. According to the WHO classification, lymphoid malignancies can be divided into three main categories, namely the B-cell neoplasms, the T and NK-cell neoplasms (also both referred as to the non-Hodgkin's lymphoma (NHL)) and the Hodgkin lymphomas (Table 1) [20,21]. Further classifications can be established based on additional parameters such as the developmental stage of the cell that initiated the disease, the morphologic, immunophenotypic, molecular and cytogenetic features of the cells as well as the prognostic of the neoplasm [22].

1.2.1. NF-κB in B-cell malignancies

B-cell differentiation involves rearrangement of the immunoglobulin genes of the B-cell precursors in the bone marrow to generate the B-cell receptor. This process, referred as to the V(D)J recombination, is tightly regulated but mistakes such as chromosomal translocations occur and can ultimately lead to B-cell neoplasms. B-cell malignancies include the precursor and the mature neoplasms, the latter representing 90% of all B-cell lymphomas.

The most common types of B-cell malignancies are the follicular lymphoma (FL) and the diffuse large B-cell lymphoma (DLBCL). Most FL are characterized by BCL-2 overexpression owing to t(14,18) chromosomal translocation. *c-Rel* gene amplifications and rearrangements have been reported in some follicular lymphomas [23] and NF-κB contributes to enhanced BCL-2 expression in this disease [24,25]. *c-Rel* gene amplification is however not specific to FL but can also be found in DLBCL [26] and it is still unclear exactly how c-Rel, as a transactivating protein, is required for lymphomagenesis.

Table 1 – WHO classification of lymphoid neoplasms

1. B-cell neoplasms
   - Precursor B-cell neoplasm
   - Mature (peripheral) B-cell neoplasm
     - B-cell chronic lymphocytic leukemia
     - Extranodal marginal zone B-cell lymphoma of MALT type
     - Follicular lymphoma
     - Mantle cell lymphoma
     - Diffuse large B-cell lymphoma
       - Activated B-cell-like DLBCL
       - Germinal center-B-like DLBCL
       - Primary mediastinal B-cell lymphoma
   - Burkitt' s lymphoma
   - Plasma cell myeloma
2. T- and NK-cell neoplasms
   - Precursor T-cell neoplasm
   - Mature (peripheral) T-cell neoplasms
     - T-cell prolymphocytic leukemia
     - Aggressive NK-cell leukemia
     - Adult T-cell lymphoma/leukemia (HTLV+)
     - Extranodal NK/T-cell lymphoma
     - Anaplastic large cell lymphoma
3. Hodgkin's lymphoma
   - Nodular lymphocyte predominance Hodgkin's lymphoma
   - Classical Hodgkin's lymphoma

Only major diseases in which NF-κB activity was extensively studied are listed.

DLBCL, the most common type of NHL, are clinically, morphologically and molecularly heterogeneous [18]. They can be further divided into three diseases, namely activated B-cell-like (ABC) DLBCL, germinal center-B-like (GCB) DLBCL and type III also referred as to primary mediastinal B-cell lymphoma (MLBCL). Importantly, ABC DLBCLs have an inferior prognosis and typically over-express NF-κB target genes such as interferon regulatory factor 4 and cyclin D2 because of constitutive IKK activity whereas GCB DLBCLs harbours a distinct gene expression profile where many NF-κB target genes are not deregulated [27]. Enhanced IKK activation in ABC DLBCL is required for survival effects and for cell cycle progression but the upstream signalling pathways activating the IKKs remain undefined. In any case, constitutive NF-κB activity play a major role in ABC DLBCL and can be therefore seen as a very promising molecular target for drug development. This conclusion was further experimentally supported by a recent study whose goal was to define therapeutic targets using a loss-of function screen for genes required for proliferation and survival of cancer cells. This screen performed with ABC DLBCL cells uncovered key candidates such as CARD11 and others which were all previously described as regulators of the NF-κB signalling pathways [28]. MLBCLs are also characterized by constitutive NF-κB activity as evidenced by prominent c-REL nuclear staining that was however not due to *c-Rel* gene amplification in most cases [29]. Therefore and although both ABC DLBCLs and MLBCLs harbour a typical NF-κB target genes signature, the identity of these up-regulated genes is different. Indeed, whereas MLBCLs over-express a variety of NF-κB target genes including modulators of TNFα-induced cell survival such as TRAF1, BCL-2-related protein A1, BCLxL, A20 and ABIN2, as well as inflammatory cytokines and adhesion molecules, ABC DLBCLs harbour a much more restricted signature [29].

The extranodal marginal zone B-cell lymphomas of mucosal-associated lymphoid tissue (MALT) type is the most common extranodal NHL and is derived from a background of chronic inflammation and auto-immune disease, the best example being the gastric MALT lymphoma which arises after *Helicobacter Pylori* chronic infection [30]. A couple of chromosomal translocations have been described in these diseases and have in common their ability to ultimately cause enhanced NF-κB activity. A first type of translocation causes activation of *BCL-10*, a proto-oncogene whose inappropriate expression leads to abnormal cell proliferation/survival and malignant transformation through an antigen-independent mechanism [31,32]. BCL-10, which is required for NF-κB activation in response to antigen receptor signalling in B and T cells [33], can activate this transcription factor when over-expressed and this pathway involves NEMO/IKKγ K63-mediated polyubiquitination through a MALT1/paracaspase-dependent pathway [34]. A second and more frequent translocation identified in MALT lymphoma generates a chimeric transcript and subsequently creates a NF-κB-activating oncogenic fusion protein, namely c-IAP2/MALT1, which harbours deregulated ubiquitin ligase activity. Here again, the target of the oncogenic c-IAP2/MALT1 ubiquitin ligase is NEMO/IKKγ which indeed shows enhanced polyubiquitination in the MALT lymphoma samples [35]. Therefore, both translocations found in MALT lymphomas cause antigen-independent NF-κB activation through a common NEMO polyubiquitination-dependent mechanism.

The other mature B-cell malignancies include mantle-cell lymphoma and multiple myeloma, both of which also harbouring constitutive NF-κB activation [36,37]. How NF-κB is deregulated in these diseases is currently unknown. The underlying mechanism may, at least partially, rely on high casein kinase 2 (CK2) activity seen in malignant plasma cells as the use of CK2 inhibitors resulted in decreased NF-κB-dependent transcription in these cells [38]. Of note, chromosomal translocations involving the *NF-κB2* gene (see here after) have also been described in some cases of multiple myeloma.

1.2.2. *NF-κB in T-cell malignancies*

T cell lymphomas are neoplasms derived from T-lineage precursors where clonal rearrangements of the TCR gene is a very common event [17]. These diseases include cutaneous T cell lymphomas and peripheral T cell lymphomas as well as less frequent neoplasms. Here again, constitutive NF-κB activity and consequently enhanced expression of NF-κB target genes has been reported in many but not all cases of T-cell lymphomas [39]. Although initially identified in a rare case of B-cell lymphoma, rearrangement of the NF-κB2 locus is frequent in cutaneous T cell lymphomas and results in the synthesis of truncated nuclear and oncogenic p100 proteins harbouring transactivation abilities (Fig. 3) [40,41]. The oncogenic properties of these truncated p100 proteins may be due to enhanced p52 production but the target genes specifically induced by these oncogenic proteins are currently unknown. Anaplastic large cell lymphoma (ALCL) is another example of T-cell malignant disease where deregulated NF-κB activation has been described. Interestingly, although p50 expression was increased in the nucleus of ALCL cells, IKK activation remained unaltered [42]. Rather, enhanced expression of BCL-3, a

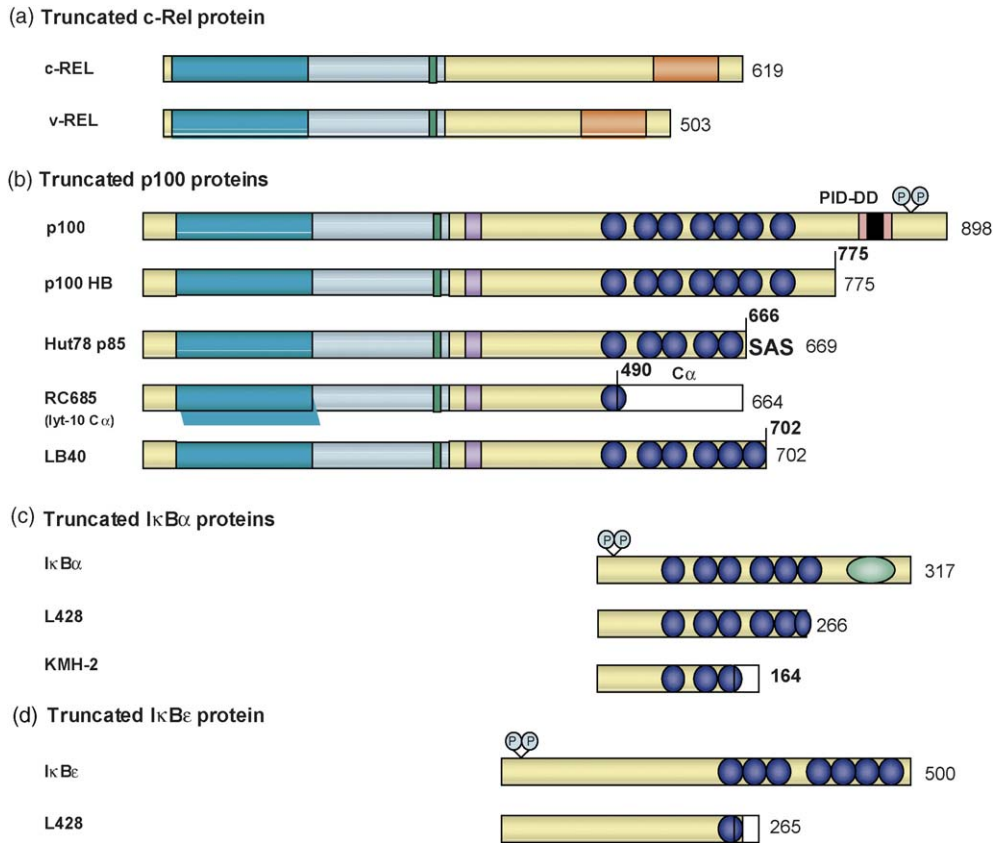

Fig. 3 – Schematic representation of truncated NF-κB and IκB proteins found in hematological disorders. (a) Truncated c-REL protein: v-REL, a derivative of c-REL, is a viral oncoprotein and causes aggressive and fatal leukemia/lymphomas in chickens and transgenic mice. Mutations within the transactivating domain of v-Rel have also been reported but are not illustrated here. (b) Truncated p100 proteins: rearrangements in the 3′ coding region of the *NF-κB2/p100* gene have been found in various types of lymphoid neoplasm. They all lead to the production of C-terminal truncated proteins which lack variable portions of the ankyrin domain. The variant p100HB is a 775 amino acids protein observed in some human tumor cell lines and results from a mutation generating a premature stop codon at position 2576 of the p100 sequence [89]. The Hut78p85 mutant was identified in a cutaneous T-cell lymphoma (CTCL) cell line and is composed of the first 666 amino acids of p100 fused to three extra amino acids (serine-alanine-serine) [90,91]. Lyt10-Cα (RC685) was cloned from a case of B-cell non Hodgkin's lymphoma and is a fusion protein in which the first ankyrin repeat of p100 is linked to a 174 amino acids alternative reading frame derived from the immunoglobulin Cα gene [40]. The LB40 protein is derived from a B-cell chronic lymphocytic leukemia (B-CLL) and presents a stop codon within the sixth ankyrin repeat [92]. (c) Truncated IκBα proteins: these proteins lacking the COOH-terminus domain are found in two Hodgkin's disease cell lines, L428 and KMH-2. In L428, a point mutation in the sixth ankyrin domain results in a truncated, stable protein which is unable to associate with NF-κB heterodimers. In KMH-2, two deletions in the third and fourth ankyrin domains result in a frame shift followed by a premature stop codon. The truncated protein is unstable. (d) Truncated IκBε protein: in one Hodgkin's disease cell line, L428, a deletion of four bases in exon 1 generates a frame shift followed by a premature stop codon and results in a severely truncated protein. The number of amino acids of each protein is indicated on the right.

member of the IκB family originally identified through molecular cloning of the breakpoint of a chromosomal translocation from a rare human B-cell chronic lymphocytic leukaemia [43,44] was found in ALCL cells [42,45]. How over-expressed BCL-3 contribute to ALCL but also to peripheral T-cell lymphomas remains unclear even if it is known that this oncogenic protein is part of p50 and p52-containing transcriptional complexes and transforms cells in a phospho-dependent manner [46,47]. Moreover, BCL-3 protects B and T lymphocytes from apoptotic cell death [48,49], through suppression of p53 activation [50] and upregulates expression of target genes such as *SerpinB1* and *SLPI* [42,47]. It is also worth mentioning that whereas BCL-3 over-expression is due to chromosomal translocation of the corresponding gene in the rare B-cell CLL harbouring the t(14,19) translocation, the exact mechanisms underlying BCL-3 enhanced expression in ALCL and in peripheral T-cell lymphomas remain unclear.

1.2.3. *NF-κB in Hodgkin's lymphoma*

This type of lymphoma accounts for 10% of all lymphoid malignancies. It is worth mentioning that some authors classify the Hodgkin lymphomas as mature B-cell malignancies because 98% of the Reed–Sternberg cells (see here after)

are of B lineage, still this disease is not considered sensu stricto as B-cell lymphoma, based on the WHO classification [20]. Hodgkin's disease (HD) was first described by Thomas Hodgkin more than a century ago and can be classified in two main categories, namely classic Hodgkin's lymphoma and nodular lymphocyte-predominant Hodgkin's [20]. Despite an early classification as a distinct clinical entity, the molecular mechanisms underlying this disease remained elusive for a very long time because of the less than 1% of clonal and malignant mononucleated Hodgkin (H) and multinucleated Reed–Sternberg (RS) cells surrounded by reactive cells, namely T cells, histocytes, eosinophils and plasma cells found in infiltrated lymph nodes [51,52]. These H/RS cells derive from clonally expanded germinal center B-cells which escaped from FAS-mediated apoptosis, a critical event in negative selection of B-cells [52]. Because cultured and primary H/RS cells harbours heterogeneous phenotypes as they express T cell, B-cell and myeloid markers [51], the search for a common molecular feature for these cells remained challenging for a while. However, because H/RS cells derive from germinal center B-cells, which harbour constitutive NF-κB activity, and because NF-κB plays a critical role in the expression of a variety of pro-inflammatory cytokines, which are strongly produced by H/RS cells, deregulated activation of this transcription factor was postulated to contribute to HD and a constitutive NF-κB activity was indeed experimentally demonstrated in all tested H/RS cells [53]. Moreover, this constitutive NF-κB activity turned out to be required for proliferation and also survival of H/RS cells under stress conditions through enhanced expression of anti-apoptotic genes such as *Bfl-1/A1*, *cIAP2*, *TRAF1* and *Bcl-x*$_L$ [54,55]. Other NF-κB-dependent genes were upregulated as well and included receptors such as CD40 and CD86 and transcription factors such as STAT5a [56].

Several mechanisms account for this enhanced NF-κB activity in H/RS cells. First, mutations of the *IκBα* gene which cause the expression of either an unstable or a truncated protein unable to bind NF-κB was reported in a subset of HD (Fig. 3) [57–59]. Cases of mutations of the *IκBε* was reported as well [60]. Still, the fact that most H/RS cells express a wild type IκBα protein implies that other mechanisms underlying the constitutive NF-κB activation seen in H/RS cells are involved. Among them, Notch1, which belongs to a family of transmembrane receptors, is highly expressed in HD and activated Notch1 signalling may induce NF-κB activity [61]. Another mechanism involves a constitutive IKK activity [62] and the underlying mechanism may, at least in part, relies on cytokines such as TNFα secreted by the H/RS cells which triggers IKK activation in an autocrine fashion. This latter mechanism demonstrates how critical the ligand-TNF family receptors interaction is for H/RS survival [63] even if ligand-independent signalling due to overexpressed CD30 for example can also cause NF-κB activation in H/RS cells [64]. Also and importantly, Epstein-Barr Virus (EBV) infection has been suggested to be an environmental factor contributing to HD and a significant percentage of HD cases are indeed EBV positive [65]. The EBV-encoded protein latent membrane protein 1 (LMP-1) activates NF-κB through both the classical and the alternative IKK-dependent pathways [66,67] and can therefore protect H/RS cells from cell death through upregulation of anti-apoptotic genes, even in cells that do not harbour IκBα mutations. Therefore, while it is clear that other actors beside NF-κB are crucial for the transformation process underlying HD (for example deregulated c-Jun and JunB which cooperate with NF-κB for the expression of genes involved in cell proliferation [68]), this latter transcription factor plays a central role in this malignant disease, even if such critical role is not specific to HD.

1.3. *NF-kappa B in acute and chronic leukaemias*

Acute leukaemias are characterized by invasion of the bone marrow by leukemic and proliferative blasts arrested at various maturation steps. A constitutive NF-κB activity due to enhanced IKK activation has been reported in acute lymphoblastic leukaemia (ALL) and myeloid leukaemia (AML) [69–72]. In both cases and although the underlying mechanism remains unclear, this deregulated NF-κB activity is reflected by nuclear localization of p50/p65 complexes which plays a critical role for leukaemia cell survival. Interestingly, this constitutive NF-κB activity is a hallmark of the leukemic stem cell (LSC) but not the hematopoetic stem cells (HSC) population found in patients with AML [70]. Because LSCs are responsible for disease relapse, these cells are promising targets for future therapies which include IKK inhibitors [73].

Chronic lymphocytic leukaemia (CLL) is a clinically heterogeneous disease originating from B lymphocytes that accumulate because of survival signals delivered to leukemic cells through a variety of receptors including the BCR and CD40 [74]. Therefore and although a higher level of proliferation than initially thought has been observed in CLL cells, it remains true that this disease is caused by a defect in the induction of apoptosis or ''programmed cell death'' (PCD). Consistent with the pro-survival properties of NF-κB proteins, an enhanced NF-κB activity was indeed detected in CLL cells when compared to non-malignant B-cells and this activity was further enhanced through CD40 ligation by the physiological ligand CD154, a critical pathway for CLL cell survival [75,76]. As expected, the anti-apoptotic proteins TRAF1 and TRAF2 were upregulated in CLL cells but it is still unclear whether this really occurs through a NF-κB-dependent mechanism [77].

Chronic myeloid leukaemia (CML) is characterized by the expansion of cells harbouring the Philadelphia (Ph[1]) chromosome, which is the result of a reciprocal translocation between the *bcr* gene and the *abl* gene. This chromosomal rearrangement creates a chimeric protein known as Bcr-Abl whose oncogenic potential is due to deregulated tyrosine kinase activity. Bcr-Abl constitutively turns on a variety of signalling pathways including the ones leading to NF-κB activation [78]. Interestingly, IKK activation is not enhanced in primary CML cells but increased NF-κB activity is rather due to enhanced p65 transactivation potential [78,79].

1.4. *NF-κB in myelodysplastic syndrome*

Myelodysplastic syndrome (MDS) are defined as haematological disorders characterized by bone marrow failure and a risk (from low to intermediate and high) progression to acute myeloid leukaemia. Although the molecular mechanisms

underlying MDS and its stage progression remain poorly defined, enhanced NF-κB activity has also been observed in bone marrow cells from MDS patients [80]. Interestingly, p65 nuclear staining has been proposed as a surrogate marker for disease progression as the degree of NF-κB activation, which is restricted to cells that carry MDS-associated cytogenetic aberrations, correlates with high-risk MDS [80]. Still, how NF-κB is deregulated in MDS blasts remains unknown.

1.5. *NF-κB/Rel proteins and virally-induced haematological malignancies*

The first experimental evidence linking NF-κB/Rel proteins with cancer came from the tumors induced in birds and transgenic animal models by the highly oncogenic *v-rel* gene carried by the avian reticuloendotheliosis virus strain T (Rev-T) [81]. An oncogenic potential of human c-Rel, was subsequently supported by the following experimental evidences. First, c-Rel transforms primary chicken lymphoid cells [82] and second, the *c-rel* gene amplifications and rearrangements were seen in 20% of NHL [81] and in some follicular lymphomas, respectively.

Other oncogenic viruses are known to induce haematological malignancies by activating NF-κB. Among them is the human T-cell leukaemia virus type 1 (HTLV-1) which exerts its biological effects through expression of the transcriptional activator Tax. This latter oncogenic protein constitutively activates the IKK complex through binding with NEMO/IKKγ in the cytoplasm [83,84] and also induces specific cellular NF-κB-target gene expression when co-localized in the nuclear bodies with p65 and IKKγ [85]. Moreover, Tax also induces the NF-κB-activating alternative pathway [86], similarly to what has been described with the Epstein-Barr virus (EBV), another NF-κB-activating virus, as explained here above.

2. Conclusions and perspectives

Most malignant haematological disorders harbour constitutive NF-κB activation and although the underlying mechanisms are distinct (gene amplifications, chromosomal translocations causing proto-oncogene activation or creating a chimeric oncogenic protein, or point mutations), they ultimately alter the balance between cell proliferation and apoptosis. So what can we learn from the data accumulated so far on the deregulated NF-κB activities seen in these disease 20 years after the initial identification of this transcription factor? First, mutations of the genes coding for NF-κB proteins have not been identified so far. Indeed, with the notable exception of c-Rel whose gene is amplified and rearranged in some lymphomas, no similar findings were made for p65 (RelA) nor RelB. On the other hand, several chromosomal translocations (*BCL-3*, *p100*) or point mutations (IκBα, IκBε) were identified for the IκB family members in a variety of T and B-cell lymphomas and all have identical consequences, namely the inability of the resulting proteins to act as NF-κB inhibitors. Second, constitutive NF-κB activity is reflected by nuclear localization of p50 and p65 due in enhanced IKK-mediated IκBα degradation in many cases, but it is still unclear to which extent the alternative pathway, which does not rely of IκBα degradation, contribute to cell survival in haematological disorders, especially in cases where no translocation of the *NF-κB2/p100* gene have been identified. Even in cases where the *NF-κB2/p100* gene is rearranged, which presumably alter the NF-κB-activating alternative pathway, how do the truncated and nuclear p100 proteins modulate gene transcription and what is the identity of their target genes? This issue remains unclear today. Third, enhanced expression of an IκB family member such as BCL-3 has been detected in T-cell lymphomas but also in CLL and in HD, yet the causes for this deregulated expression are different. Indeed, whereas a chromosomal translocation and sometimes gene amplifications of the *BCL-3* locus are involved, still unclear mechanisms are responsible of this deregulation in other cases. To which extent post-translational modifications such as phosphorylation of BCL-3 has anything to do with this remains unclear. Another still unclear issue is the fact that NF-κB actually promotes apoptosis in some circumstances and may in fact act as a tumor-suppressor at early stages of cancer [87]. To which extent this finding can be relevant in haematological cancers also remains unclear.

Most laboratories can now have access to powerful experimental approaches such as micro-array, FACS analyses and loss-of function screen for genes required for cell proliferation and survival [28]. Moreover, in vivo models for any type of haematological diseases are getting better year after year. It is therefore likely that the following years will bring substantial new findings in this field of research.

In conclusion, the last 20 years brought tremendous new information on the knowledge of the haematological disorders at the molecular level and unquestionably demonstrated the central role played by NF-κB in these diseases. Still, many issues remain unclear and deserve further investigations to more precisely know when and how this transcription factor should be targeted for therapeutic purposes.

Acknowledgements

The authors thanks all the members of the laboratory for helpful discussions as well as Drs. M.P. Merville, V. Bours and J.P. Chapelle for their support. A.K. and I.R. are Research Assistant and A.C. Research Associate at the Belgian National Funds for Research (''F.N.R.S.''). P.V. is supported by post-doctoral grants from EMBO and HFSP. This work was supported by grants from the Concerted Research Action Program (University of Liege), the F.N.R.S., TELEVIE, the Belgian Federation against Cancer, the ''Centre Anti-Cancéreux'' and the ''Leon Fredericq'' Fundation (University of Liege).

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