

## Review

# The roles of the classical and alternative nuclear factor- $\kappa$ B pathways: potential implications for autoimmunity and rheumatoid arthritis

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## Abstract

Nuclear factor- $\kappa$ B (NF- $\kappa$ B) is an inducible transcription factor controlled by two principal signaling cascades, each activated by a set of signal ligands: the classical/canonical NF- $\kappa$ B activation pathway and the alternative/noncanonical pathway. The former pathway proceeds via phosphorylation and degradation of inhibitor of NF- $\kappa$ B (I $\kappa$ B) and leads most commonly to activation of the heterodimer RelA/NF- $\kappa$ B1(p50). The latter pathway proceeds via phosphorylation and proteolytic processing of NF- $\kappa$ B2 (p100) and leads to activation, most commonly, of the heterodimer RelB/NF- $\kappa$ B2 (p52). Both pathways play critical roles at multiple levels of the immune system in both health and disease, including the autoimmune inflammatory response. These roles include cell cycle progression, cell survival, adhesion, and inhibition of apoptosis. NF- $\kappa$ B is constitutively activated in many autoimmune diseases, including diabetes type 1, systemic lupus erythematosus, and rheumatoid arthritis (RA). In this review we survey recent developments in the involvement of the classical and alternative pathways of NF- $\kappa$ B activation in autoimmunity, focusing particularly on RA. We discuss the involvement of NF- $\kappa$ B in self-reactive T and B lymphocyte development, survival and proliferation, and the maintenance of chronic inflammation due to cytokines such as tumor necrosis factor- $\alpha$ , IL-1, IL-6, and IL-8. We discuss the roles played by IL-17 and T-helper-17 cells in the inflammatory process; in the activation, maturation, and proliferation of RA fibroblast-like synovial cells; and differentiation and activation of osteoclast bone-resorbing activity. The prospects of therapeutic intervention to block activation of the NF- $\kappa$ B signaling pathways in RA are also discussed.

## Introduction

### Nuclear factor- $\kappa$ B

Detailed reviews of nuclear factor- $\kappa$ B (NF- $\kappa$ B) function and regulation are available in the recent literature [1-5]. Briefly,

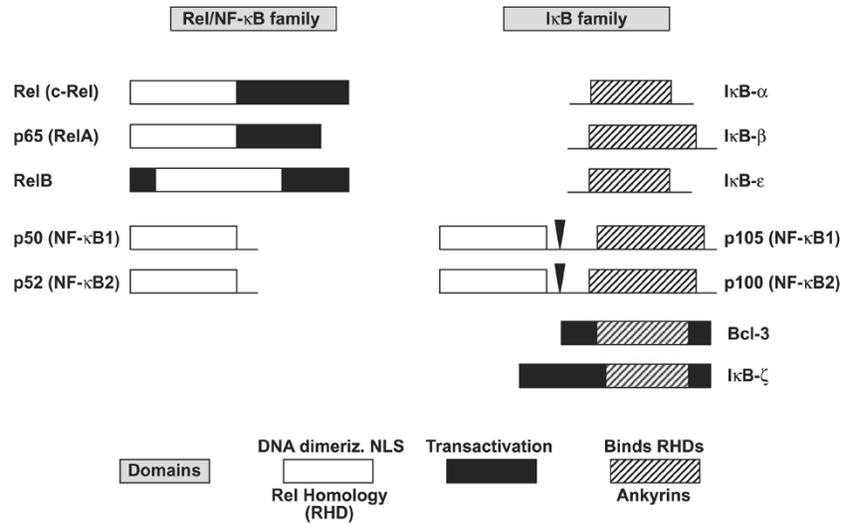
NF- $\kappa$ B is a family of inducible dimeric transcription factors including five members (Figure 1): Rel (c-Rel), RelA (p65), RelB, NF- $\kappa$ B1 (p50/p105) and NF- $\kappa$ B2 (p52/p100). It recognizes a common consensus DNA sequence and regulates a large number of target genes, particularly those involved in the immune system and defense against pathogens, but also genes concerned with inflammation, injury, stress, and the acute phase response. In unstimulated cells, homodimers or heterodimers of NF- $\kappa$ B family members are bound to ankyrin-rich regions of inhibitor of NF- $\kappa$ B (I $\kappa$ B) inhibitory proteins (the closely related I $\kappa$ B $\alpha$ , I $\kappa$ B $\beta$ , and I $\kappa$ B $\epsilon$ ). This binding serves to retain the dimers in the cytoplasm, which are hence unable to initiate transcription of target genes. The NF- $\kappa$ B1/p105 and NF- $\kappa$ B2/p100 precursor proteins, which encode p50 and p52 in their amino-terminal halves, also behave like I $\kappa$ Bs, with ankyrin repeats in their carboxyl-terminal halves being analogous to those of the smaller I $\kappa$ Bs (Figure 1). The I $\kappa$ Bs and NF- $\kappa$ B2/p100 are important targets of inducible regulatory pathways that mobilize active NF- $\kappa$ B to the nucleus [1-6]. These pathways are termed the 'classical' or 'canonical' pathway and the 'alternative' or 'noncanonical' pathway.

### The classical nuclear factor- $\kappa$ B pathway

In the classical or canonical pathway of NF- $\kappa$ B activation, stimulation of a variety of cell membrane receptors (including tumor necrosis factor receptor [TNF]R, IL-1 receptor, Toll-like receptor, T-cell receptor [TCR], and B-cell receptor [BCR]) leads to phosphorylation, ubiquitination, and proteasomal degradation of the I $\kappa$ Bs [1-5] (Figure 2). The phosphorylation occurs at two serines in the amino-terminus of I $\kappa$ B and is

BAFFR = B-cell activating factor receptor; BCR = B-cell receptor; c/EBP = CCAAT/enhancer binding protein; CIA = collagen-induced arthritis; CIKS = connection to I $\kappa$ B kinase and stress-activated protein kinases; DC = dendritic cell; FLS = fibroblast-like synoviocyte; IFN = interferon; I $\kappa$ B = inhibitor of NF- $\kappa$ B; IKK = I $\kappa$ B kinase; IL = interleukin; LT = lymphotoxin; mTEC = medullary thymic epithelial cell; NEMO = NF- $\kappa$ B essential modulator; NF- $\kappa$ B = nuclear factor- $\kappa$ B; NIK = NF- $\kappa$ B-inducing kinase; RAG = recombinase-activating gene; RANK = receptor activator of NF- $\kappa$ B; RANKL = RANK ligand; SEFIR = similar expression to fibroblast growth factor genes and IL-17Rs and TIR; TCR = T-cell receptor; Th = T-helper (cell); TIR = Toll and IL-1R; TLO = tertiary lymphoid organ; TNF = tumor necrosis factor; TNFR = tumor necrosis factor receptor; TRAF = TNFR-associated factor; T<sub>reg</sub> = regulatory T cell; ZAP-70 =  $\zeta$ -associated protein of 70 kDa.

Figure 1



The mammalian families of NF-κB and IκB polypeptides. Conserved domains and their primary functions are indicated. Ankyrins, ankyrin repeat domain (functions by binding and inhibiting RHDs; Bcl-3 and IκBζ are exceptions because they do not function as classical inhibitors of the NF-κB activity); dimeriz., dimerization domain; DNA, DNA binding; NF-κB, nuclear factor-κB; IκB, inhibitor of NF-κB; RHD, Rel homology domain; NLS, nuclear localization sequence; Transactivation, transactivating domain (functions at nuclear target sites).

catalyzed by IκB kinases (IKKs) α and β complexed with the regulatory subunit NEMO (NF-κB essential modulator; IKKγ). Phosphorylation of IκB by the activated IKK complex is predominantly by IKKβ. This triggers lysine 48 (K48)-linked polyubiquitination at adjacent lysine residues initiated by the ubiquitin E3 ligase complex Skp1/Cul1/F-box protein-β-TrCp. This leads to proteolysis of the NF-κB-bound IκB at the 26S proteasome. Free NF-κB dimers (most commonly the p50/p65 heterodimer) then translocate to the nucleus, where they bind NF-κB DNA sites and activate gene transcription.

As will be discussed, the classical pathway is essential at multiple stages of normal development and function of the immune system and, when perturbed, in the initiation and progression of autoimmune pathologies.

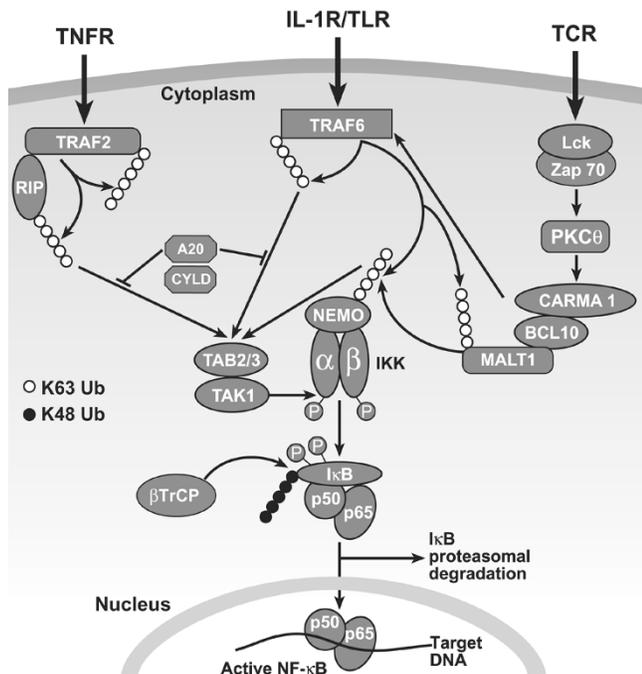
**The alternative nuclear factor-κB pathway**

The more recently described alternative or noncanonical pathway of NF-κB activation depends on IKKα but not IKKβ or NEMO [6-9] (Figure 3). The target for activated IKKα is the inhibitory ankyrin protein NF-κB2/p100 (probably complexed with RelB), which is phosphorylated by IKKα at its carboxyl-terminus and then K48-polyubiquitinated. Proteolysis of the carboxyl-terminal half of p100 follows and p52, containing the Rel homology domain, is released and p52 complexed with RelB is generated. Nuclear translocation of this heterodimer and transcriptional activation of distinct target genes follow [9]. Stimuli that activate the alternative pathway include Lymphotoxin (LT)βR, B-cell activating factor receptor (BAFFR), receptor activator of NF-κB (RANK), and CD40 [4,10,11] (Figure 3).

The alternative pathway is particularly important in the regulation of lymphoid organogenesis, via stromal cells; in the development, selection, and survival of B and T lymphocytes; and in differentiation of antigen-presenting cells such as dendritic cells (DCs) and medullary thymic epithelial cells (mTECs; see below). It thus plays an important role in the regulation of immune central and peripheral tolerance, and hence in autoimmune reactivity of the immune system.

**Autoimmunity**

Autoimmunity is the result of a loss of tolerance (the ability to distinguish 'self' from 'nonself'), in which the body fails to recognize its own cells and tissues as 'self' and mounts an immune response against them [12]. Autoimmune diseases such as diabetes type 1, systemic lupus erythematosus, rheumatoid arthritis (RA), Sjögren's syndrome, Graves' disease, Crohn's disease, celiac disease, and Wegener's granulomatosis result from such immune responses. Provided that they are not too strong, autoimmune responses may be essential for the normal development and function of the immune system and for the development of immunologic tolerance to self-antigens. Furthermore, a state of low autoimmune reactivity may be advantageous, for example in the recognition of cancerous cells and in response to infection [13]. For reasons that are as yet unclear (but possibly because of hormonal effects), autoimmune diseases generally exhibit a gender imbalance, with most occurring more frequently in females than in males [14]. Several mechanisms are responsible for the pathogenesis of autoimmune diseases, but space does not permit a detailed discussion of all of these (see [15-20]). This review focuses on the contributions

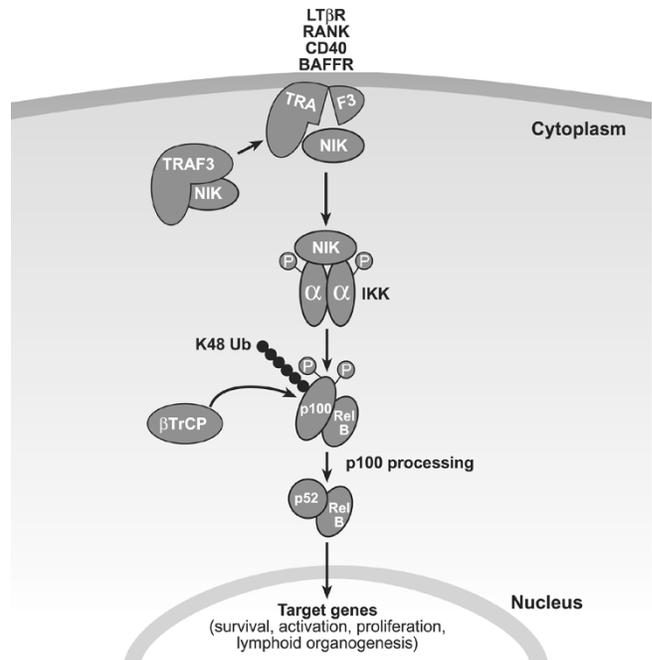
**Figure 2**

Classical pathway of NF-κB activation via IκB degradation. Ligand engagement of specific membrane receptors triggers K63 polyubiquitination of TRAF2, TRAF6, RIP, MALT1, and NEMO. The TAK kinase complex is recruited through association of the polyubiquitin chains with TAB2 and TAB3. Activated TAK1 may phosphorylate and activate IKKβ, which then phosphorylates IκB bound to cytosolic NF-κB, triggering its βTrCP E3 ubiquitin ligase-mediated K48 polyubiquitination and proteasomal degradation. Free NF-κB then translocates to the nucleus and transactivates target genes. CYLD and A20 are deubiquitinating enzymes that may block NF-κB activation by removal of K63 ubiquitinated chains from activated TRAFs, RIP, and NEMO. A20 may also terminate TNF-α induced NF-κB activation by catalyzing the K48 ubiquitination of RIP, leading to its proteasomal degradation. In addition to promoting survival via NF-κB target genes, the TNF receptor (TNFR1) also stimulates competing apoptotic pathways. T cell (and B cell) antigen receptors (TCR and BCR, respectively [not shown]) may in some contexts enhance apoptotic pathways but usually they contribute to survival (see text). IκB, inhibitor of NF-κB; IKK, IκB kinase; MALT, mucosa-associated lymphoid tissue lymphoma translocation gene; NEMO, NF-κB essential modulator; NF-κB, nuclear factor-κB; RIP, receptor interacting protein; TAB, TAK1-binding protein; TAK, transforming growth factor β-activated kinase; TRAF, TNF receptor-associated factor.

of the classical and alternative pathways of NF-κB activation to the onset and maintenance of autoimmune reactivity, and the subsequent inflammation that characterizes autoimmune diseases. Examples will be drawn from several well studied disease models, with particular attention given to RA.

### Nuclear factor-κB in autoimmunity

NF-κB plays a central role in the differentiation, activation, survival, and defense of mammalian cells. It contributes to autoimmune diseases such as RA in multiple ways. First, NF-κB is essential for normal lymphocyte and DC survival, for

**Figure 3**

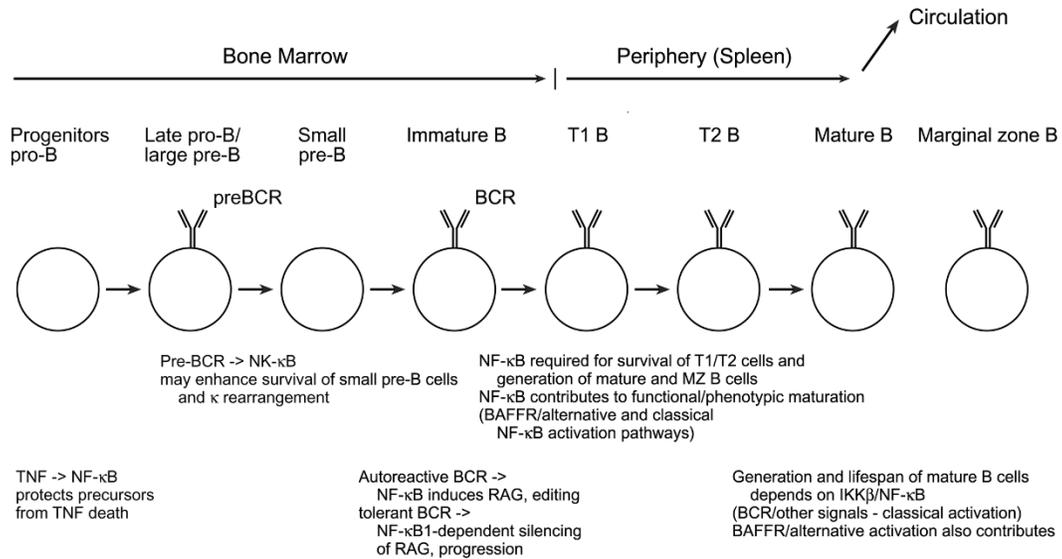
Alternative pathway of NF-κB activation. In unstimulated cells, NIK is destabilized by bound TRAF3. Activation through a subset of receptors of the TNFR superfamily including the BAFFR, CD40, RANK and lymphotoxin-βR leads to the recruitment of TRAF proteins (including TRAF3) to the receptor. TRAF3 is inactivated (possibly by degradation or sequestration) and active NIK is thus released. NIK then phosphorylates and activates IKK; it also recruits NF-κB2/p100 (probably bound to RelB), which is phosphorylated by IKKα. This triggers K48 polyubiquitination of p100 mediated by βTrCP E3 ubiquitin ligase and subsequent proteasomal processing to yield the mature subunit p52. Predominantly RelB/p52 heterodimers are generated, which migrate to the nucleus. The classical pathway is also activated through these receptors with some receptors (BAFFR) activating less strongly than others. Unlike TNFR (Figure 2), BAFFR signaling is associated only with survival functions. BAFFR, B-cell activating factor receptor; IKK, IκB kinase; LT, lymphotoxin; NF-κB, nuclear factor-κB; NIK, NF-κB-inducing kinase; RANK, receptor activator of NF-κB; TNFR, tumor necrosis factor receptor; TRAF, TNF receptor-associated factor.

their activation and development (including negative and positive selection of B and T cells), and for lymphoid organ morphogenesis [21,22]. Defects in NF-κB function or control permit the survival and release into the periphery of autoreactive T cells from the thymus, where subsequent antigenic stimuli may trigger autoimmune disease. Second, numerous investigations into autoimmune disease have provided evidence of NF-κB involvement in the induction of inflammatory cytokines and other mediators of inflammation that drive the pathology.

### Nuclear factor-κB in lymphoid development

Signaling through NF-κB is essential for survival and activation of most if not all mammalian cells, including lymphoid cells of

Figure 4



NF-κB in B-lymphocyte development. A simplified schematic representation of B-lymphocyte development, highlighting some of the contributions of NF-κB at various developmental checkpoints. See text for details. BAFFR, B-cell activating factor receptor; BCR, B-cell receptor; IKK, IκB kinase; NF-κB, nuclear factor-κB; RAG, recombinase-activating gene; T1, transitional 1; T2, transitional 2; TNF, tumor necrosis factor.

the immune system, both in the periphery and in the bone marrow (B cells) and thymus (T cells). In autoimmune diseases such as RA, defects in selection against autoreactive B cells or in thymic selection of T cells may initiate the pathogenic process. It is ultimately in the negative selection of self-reactive B or T cells, in which a somewhat unusual pro-apoptotic activity of NF-κB plays a role (or possibly its other activities; see below), that defects in this activity can initiate RA or other autoimmune disorders. Once B or T cells autoreactive for antigens present at the sites of RA (or reactive to antigens arising from the environment, such as pathogen-derived antigens) are released into the periphery and migrate to those sites, further proinflammatory effects of NF-κB come into play that aggravate and perpetuate the disease.

We recently reviewed the roles played by NF-κB in guiding the survival and differentiation of developing B and T lymphocytes [21,22]. These are summarized in Figures 4 and 5. Brief summaries of positive and negative selection of B and T cells follow.

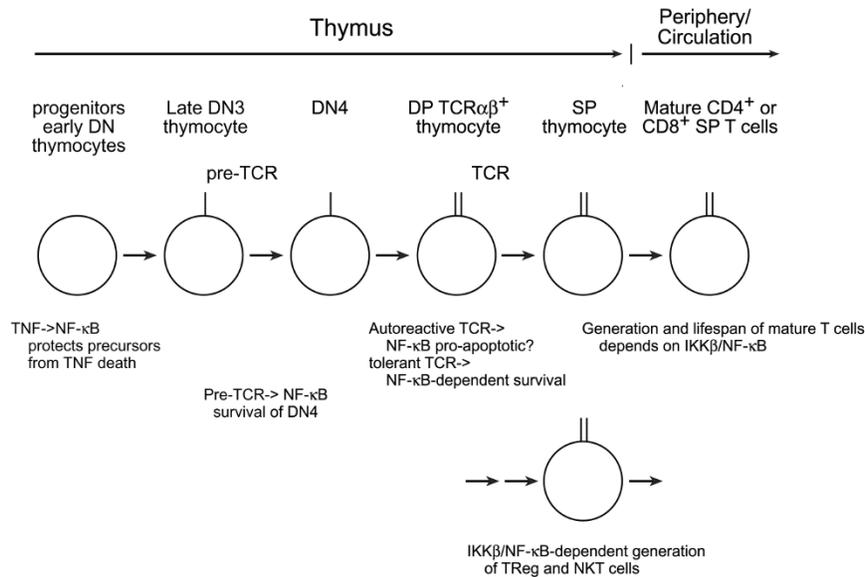
*B-cell development*

During B-cell development, immature B cells in the bone marrow begin to express a BCR. If a given B cell's BCR is autoreactive, then that cell is either eliminated by apoptosis or the BCR is 'edited' by RAG (recombinase-activating gene) recombinase to generate a different BCR. RAG is negatively regulated by NF-κB1 and positively regulated by NF-κB dimers containing RelA and c-Rel [23]. It was suggested that weak tonic signaling of the BCR may provide a positive

selection signal that represses RAG, possibly via NF-κB1/p50 homodimers [24,25], thus blocking BCR editing. A strong autoreactive signal may induce RAG expression (thus facilitating editing) via activation of RelA-containing and c-Rel-containing dimers. Failure to edit would trigger apoptosis and negative selection. Survival of autoreactive cells (for at least some time) may depend on survival factors including BAFF, hemokinin-1, and thymic stromal lymphopoietin [8,26,27]. Defects in NF-κB regulation both in bone marrow and in spleen may allow autoreactive B cells to escape negative selection, either directly via the above process or indirectly because of defects in antigen-presenting cells (DCs) or in bone marrow and splenic microarchitecture and functions including those of stromal cells (see below). B-cell selection can also occur in the periphery, where NF-κB is essential for the maintenance of B-cell homeostasis. If this is impaired, then survival of B cells may be prolonged and autoimmune reactivity result [28] (see below).

*T-cell development*

During T-cell development in the thymus, positive and negative selection occurs at the double-positive stage (Figure 5). Autoreactive thymocytes are eliminated by apoptosis, whereas those that weakly recognize self-antigens are positively selected. The roles played by NF-κB in the process of T-cell selection are complex and not fully elucidated. Apparently contradictory results have been reported. First, negative selection was found to be blocked by inhibition of NF-κB, suggesting that NF-κB promotes apoptosis [29-31] (in contrast to its well known anti-apoptotic activity). However,

**Figure 5**

NF- $\kappa$ B in T lymphocyte development. A simplified schematic representation of T-lymphocyte development, highlighting some of the contributions of NF- $\kappa$ B at various developmental checkpoints. T<sub>Reg</sub> and NKT cells branch off at some point after TCR expression on thymocytes. See text for details. DP, double-positive stage; DN3/DN4, double-negative stages; IKK, I $\kappa$ B kinase; NF- $\kappa$ B, nuclear factor- $\kappa$ B; NKT, natural killer T cell; SP, single-positive stage; TCR, T-cell receptor; T<sub>Reg</sub>, T-regulatory cell.

negative selection was also reported to be due to repression of NF- $\kappa$ B by I $\kappa$ B<sub>NS</sub>, an antigen-induced superrepressor homologue of I $\kappa$ B $\alpha$ , suggesting a positive, anti-apoptotic role for NF- $\kappa$ B in survival [32].

Positive selection of T cells that weakly recognized self-antigens appeared to rely on the conventional anti-apoptotic activity of NF- $\kappa$ B [31]. It is possible that NF- $\kappa$ B activity allows the cell to assess TCR signal strength. Impairment of NF- $\kappa$ B might be sensed by autoreactive cells as a weak TCR signal, resulting in positive selection rather than correct negative selection, thus promoting an autoimmune outcome. Similarly, impairment of NF- $\kappa$ B under positive selection circumstances might be sensed as a null signal, triggering death by neglect [22]. Natural killer T cells and regulatory T cells (T<sub>reg</sub>s) are positively selected by recognition of self-antigens at the double-positive stage [33-36], or they are simply not negatively selected [37] (Figure 5). Both are dependent on NF- $\kappa$ B in their development [22], and the former at least require NF- $\kappa$ B both in a cell-intrinsic role and in thymic stromal cells in the form of RelB [33].

### Nuclear factor- $\kappa$ B and immune tolerance

Both classical and alternative pathways of NF- $\kappa$ B activation are involved in the control of autoimmune reactions exercised by the thymic stroma. mTECs, which provide the thymic microenvironment for developing T lymphocytes and myeloid lineage DCs, play a critical role in preventing autoimmunity in RA through their capacity to present self-antigen to T cells in

the thymus and (for DCs) in the periphery (draining lymph nodes and spleen).

Several authors have shown that NF- $\kappa$ B is required for the development of mTECs and organization of the thymic stroma, and the development and differentiation of DCs [38-43]. Genetic ablation of NF- $\kappa$ B family members in mice and interference with or partial loss of NF- $\kappa$ B activation result in defects in the thymic stromal development, absence of mature mTECs and at least some subclasses of DCs, and defects in the function of DCs. The phenotype of these mice is characterized by severe autoimmunity with autoreactive T cells, multiple organ lymphocytic infiltrates, and - in some cases - early mortality. Both the classical and alternative pathways of NF- $\kappa$ B activation appear to be essential for correct thymic development and regulation of immune self-tolerance. RelB, NF- $\kappa$ B-inducing kinase (NIK), and IKK $\alpha$  are all components of the alternative pathway (leading to NF- $\kappa$ B2 activation and formation of p52/RelB heterodimers; Figure 3), and defects in any one leads to impaired stromal cell functions and autoimmune reactivity [38-42]. Deficiency of NF- $\kappa$ B2 itself leads to a milder phenotype, possibly because of compensation by NF- $\kappa$ B1, which can form heterodimers with RelB (p50/RelB) in the absence of NF- $\kappa$ B2/p100 and thus may be able to functionally replace p52/RelB in the NF- $\kappa$ B2 knockout. Combined deficiency of NF- $\kappa$ B2 and the I $\kappa$ B family member Bcl-3 leads to a full-blown autoimmune phenotype, with complete loss of mTECs and consequent loss of negative selection of autoreactive T cells [43].

Intact upstream activators of the classical and alternative pathways of NF- $\kappa$ B are also essential for normal lymphoid organization and establishment of self-tolerance. TNFR-associated factor (TRAF)6 is an essential component of many signaling paths that activate the classic pathway, and TRAF6 deficiency in mice results in thymic atrophy: a disorganized distribution of medullary epithelial cells, reduced T<sub>reg</sub> production, absence of mature mTECs, and induction of autoimmunity [39,41] (for review [44,45]). TRAF6 activates the classical pathway (and activation of AP1 transcription factors) after stimulation of members of the TNFR superfamily and the Toll-like receptor/IL-1 receptor family (Figure 2). It may indirectly activate the alternative pathway as a consequence of activating the classic pathway [41,44,45]. This is because classically activated NF- $\kappa$ B regulates the transcription of most NF- $\kappa$ B family members, including NF- $\kappa$ B2 and RelB, the principal targets for activation by the alternative pathway [46,47]. TRAF6 deficiency resulted in a lack of RelB expression in mTECs and fetal thymic stroma [41]. It was concluded that reduced T<sub>reg</sub> development and reduced negative selection caused by absence of selecting mTECs were two possible causes of the autoimmunity seen in TRAF6 knockout mice. Others have also shown that TRAF6 and RelB are critical for DC development and maturation, and are essential for proper DC interaction with T cells [38,39].

LT $\beta$  receptors, as well as RANK and CD40 receptors, are expressed on stromal cells and, when stimulated, activate the alternative NF- $\kappa$ B pathway [48-50]. Consistent with a role for LT $\beta$ R-, RANK-, and CD40-mediated activation of the alternative pathway in stromal cells during thymic organogenesis, mutant mouse models deficient in signaling via the LT $\beta$ R, RANK, or CD40 have defects similar to those described above for mice lacking components of the alternative pathway. These include thymic defects and multiple organ lymphocytic infiltrations characteristic of self-autoreactivity [51-54]. However, loss of any one of the receptors and/or their ligands results in relatively mild defects compared with loss of the alternative pathway, most likely because the three receptors are partially redundant.

#### **Autoimmune mouse models associated with defective central or peripheral tolerance**

Several mouse models of autoimmune arthritis and lupus implicate thymic selection defects in the pathogenesis. In the SKG  $\zeta$ -associated protein of 70 kDa (ZAP-70) model, spontaneous mutation in ZAP-70 (a key transduction molecule in T cells that is responsible for transducing signals from the T-cell antigen receptor to the classical pathway of NF- $\kappa$ B activation and to other transcription factors) causes chronic autoimmune arthritis in mice, which develops after encounter with environmental stimuli (in particular, fungal  $\beta$ -glucans and viruses) [55,56]. The disease closely resembles human RA. Thus, although genetic predisposition plays an important role in pathogenesis of this autoimmune disorder, like other

examples of autoimmune disease, exposure to infectious agents also has an important part in the development of this disorder (for review [57]). Altered signal transduction through the mutant ZAP-70 protein changes the sensitivity of developing T cells to both positive and negative selection of thymocytes, thereby leading to the positive selection of otherwise negatively selected self-reactive T cells. These self-reactive T cells apparently overcome the mechanisms of peripheral self-tolerance mediated by T<sub>reg</sub>s. Such potentially arthritogenic T cells might also arise in a subset of humans who go on to develop RA as a result of an SKG-like mutation, driving a selection shift of the T-cell repertoire in the thymus that could lead to the development of RA after exogenous stimulation in the periphery by microbes [55,56].

Sakaguchi and coworkers [55] raised the interesting question of why the general change in the T-cell repertoire in the SKG mice should lead to autoimmune arthritis but not other autoimmune diseases. They suggested that unlike other organ-specific autoimmune diseases, in which self-reactive T cells destroy the target cells (for example, in type 1 diabetes pancreatic  $\beta$  cells are destroyed), in autoimmune arthritis in SKG mice (and in RA in humans) the self-reactive T cells do not destroy synoviocytes but stimulate them to proliferate [55,58-60]. They also secrete proinflammatory cytokines (IL-1, IL-6, and tumor necrosis factor [TNF]- $\alpha$ ) and mediators that destroy the surrounding cartilage and bone.

In the New Zealand Black lupus-prone mouse model a defective NF- $\kappa$ B/RelB pathway leads to disorganization of the thymus and associated thymocyte selection defects [61]. Breakdown of self-tolerance in the periphery (after exit from the bone marrow) during B-cell development and survival has also been reported to lead to autoimmunity. BAFF is a crucial B-lymphocyte survival factor [8,62,63], and one of its receptors - BAFFR - appears to be the only mediator of BAFF-mediated survival signals. BAFFR signals primarily through the alternative NF- $\kappa$ B pathway and interacts directly with TRAF3 (this is essential for its signal transduction). Specific knockout of the gene encoding TRAF3 in mouse B cells led to increased, constitutive activation of NF- $\kappa$ B2, prolonged B-cell survival, and greatly expanded B-cell compartments in secondary lymphoid organs. Splenomegaly, lymphadenopathy, hyperimmunoglobulinemia, and autoimmune reactivity resulted. This implicates TRAF3 and the alternative NF- $\kappa$ B pathway in regulation of B-cell homeostasis and peripheral self-tolerance [28].

#### **Inflammatory effects of nuclear factor- $\kappa$ B in rheumatoid arthritis**

##### **Involvement of the alternative pathway at the site of inflammation**

RA is a chronic inflammatory disease of the joints in which infiltration of immunocompetent cells and the proliferation of synovial fibroblasts of the joint lining leads to formation of a tumor-like tissue called the pannus, which invades and

destroys the joint cartilage and bone [64]. In the inflammatory microenvironment of the synovium, lymphoid neogenesis occurs, generating organized lymphocytic aggregates or tertiary lymphoid organs (TLOs) with B-cell and T-cell areas [65,66]. TLOs are also seen in some other chronic inflammatory diseases and in mouse models of such diseases, including collagen-induced arthritis (CIA) [64]. The identity of stromal cells initiating their development is unknown. The alternative pathway of NF- $\kappa$ B activation may be implicated in TLO generation, because constitutive expression of LT $\beta$  in target tissues has been shown to cause TLO formation [67]. Decoy receptors for LT $\beta$  reduce inflammation in disease models of CIA [68].

A further characteristic of most autoimmune diseases, including RA, is the elevated level in target tissue fluids (in RA, the synovial fluid) of the cytokine BAFF. This correlates with the survival of B lymphocytes, which produce autoantibodies [69]. BAFF is an activator, principally of the alternative NF- $\kappa$ B pathway [8], and is needed for B-cell maturation and for protection of otherwise negatively selected B cells. It is also needed for plasma cell differentiation and survival, and it is these cells that are responsible for antibody production [70]. Antagonists of BAFF, including BAFF antibody (belimumab) and decoy receptors, have been developed and are under examination for targeting B cells in RA and other autoimmune diseases [71,72].

NIK, a key mediator of the alternative pathway (Figure 3), has also been shown in mouse models to be necessary for antigen-mediated induction of the bone erosion caused by inflammation-induced osteoclastogenesis. NIK-deficient mice were largely resistant to RA, exhibiting less periarticular osteoclastogenesis and less bone erosion [73].

#### **Involvement of the classical pathway at sites of inflammation**

The classical pathway of NF- $\kappa$ B is also strongly implicated in the inflammatory stages of RA. Inflammatory cells infiltrate the synovial sublining and produce proinflammatory cytokines, chemokines, and growth factors that stimulate synovial lining hyperplasia. This results in increased numbers and activation of macrophage-like synoviocytes and fibroblast-like synoviocytes. In turn, synoviocytes release additional cytokines, chemokines, and growth factors that help to sustain inflammation and produce enzymes that degrade the organized extracellular matrix, destroying cartilage and bone [74-76]. Ectopic expression of I $\kappa$ B $\alpha$  (a principal inhibitor of classical NF- $\kappa$ B activation; Figure 2) in human macrophages and primary RA synoviocytes inhibited the production of destructive enzymes (matrix metalloproteinases and aggrecanases) and inflammatory cytokines (IL-1 $\beta$ , IL-6, IL-8, and TNF- $\alpha$ ) while sparing anti-inflammatory mediators, indicating that the classical NF- $\kappa$ B pathway is essential for synthesis of matrix-destructive enzymes and inflammatory cytokines [74,75,77,78].

Evidence reviewed by Makarov [79] suggests that NF- $\kappa$ B activation facilitates synovial hyperplasia by promoting proliferation and inhibiting apoptosis of RA fibroblast-like synoviocytes (FLSs). Briefly, NF- $\kappa$ B is a positive regulator of cell growth in FLSs primarily via the induction of c-Myc and cyclin D<sub>1</sub>, proteins required for cell cycle progression, but also via inhibition of the pro-apoptotic effects of c-Myc. Because c-Myc is highly expressed in RA synovium NF- $\kappa$ B may thus contribute to hyperplasia by both inhibiting c-Myc-induced apoptosis and promoting proliferation. NF- $\kappa$ B also delivers an anti-apoptotic signal that counteracts other pro-apoptotic stimuli such as TNF- $\alpha$  (which induces classical NF- $\kappa$ B activation). Activation of NF- $\kappa$ B protected human RA FLSs from the cytotoxic effects of TNF [80], whereas its inhibition in arthritic rat joints by proteasome inhibitors (which blocked I $\kappa$ B degradation) or by genetic introduction of I $\kappa$ B<sub>NS</sub> resulted in increased FLS apoptosis. These results suggest an important role for NF- $\kappa$ B in protecting FLSs against apoptosis in RA synovium, possibly by countering the cytotoxicity of TNF- $\alpha$  and Fas ligand [81]. Because TNF is also a potent mitogen in RA FLSs, NF- $\kappa$ B appears to be critical in determining whether it exerts mitogenic or pro-apoptotic effects.

The foregoing discussion implies that blocking NF- $\kappa$ B activation by either the classical and/or the alternative pathway may be therapeutically beneficial for human RA inflammation. A major consideration, however, is the safety of this approach, given the major roles played by this transcription factor family in a host of essential functions, including immunity and cell development [82,83].

#### **The T-helper-17/IL-17/nuclear factor- $\kappa$ B axis in rheumatoid arthritis**

Continued inflammation and the resulting destruction of bone and cartilage in joints of patients with RA depend on a complex network of cells and cytokines [84]. Cells that are critically involved in RA include synovial fibroblasts, chondrocytes, DCs, macrophages, monocytes, osteoclasts, neutrophils, and B and T cells. T cells may account for up to 40% of the synovial cellular infiltrate [85]. Self-antigen specific T cells play a role in the production of autoantibodies by providing help to B cells, probably both locally and in draining lymph nodes. However, the infiltrating T cells also play a more direct role in RA. A critical T-helper (Th) cell type in RA is the Th17 subset, and these cells produce IL-17, which is emerging as a primary effector of RA pathology [86]. IL-17 induces many chemokines and cytokines, in part by activating NF- $\kappa$ B via the classical pathway; it potently synergizes with TNF- $\alpha$ , which is another cytokine that is critical in RA pathogenesis (see below). Blocking TNF- $\alpha$  signaling with etanercept (a soluble form of the TNFR  $\alpha$ ) has proven to be beneficial to many RA patients [87]. In the following discussion, we first provide some background on the generation of Th17 cells, which are the main producers of IL-17. We then discuss the biologic effects of Th17 and IL-17 in the context of RA, and the direct

and indirect mechanisms by which IL-17 leads to activation of NF- $\kappa$ B.

#### *Th17 cell development*

During the past few years there has been a shift in the paradigm of T-cell help, which was thought to occur exclusively through either Th type 1 (Th1) or type 2 (Th2) cells, but now also includes Th17 cells (for review [88]). Th1 cells are primarily responsible for cell-mediated immunity and Th2 cells for humoral immunity. The exclusive division of T-cell help into these two classes underwent a major correction when an additional helper T-cell type was identified, named Th17 after its signature cytokine IL-17. In mice, Th17 cells require transforming growth factor- $\beta$  and IL-6 for their differentiation from naïve T cells, and their maintenance and expansion is controlled by IL-23, a cytokine that is produced by DCs. Both IFN- $\gamma$  and IL-4 can suppress the differentiation of Th17 cells, and there is some evidence that IL-17 can suppress Th2 responses [89]. Interestingly, transforming growth factor- $\beta$  is not only required for generation of Th17 cells but also for the generation of T<sub>reg</sub>s, at least in the periphery, and so it is the presence or absence of IL-6 that decides between the two T-cell fates. It may be the particularly high levels of IL-6 present in inflamed joints (see below) that shifts the balance from T<sub>reg</sub>s to Th17, thus preventing resolution of the inflammation. The division between Th1 and Th17 cells may not always be absolute, especially at the site of inflammation *in vivo*, because T cells producing IFN- $\gamma$  and IL-17 can coexist, and there is even some evidence that a single T-cell type can coexpress both cytokines, especially in humans [90].

The initial development of Th17 in humans looks to be somewhat different from that in mouse; recent evidence suggests that IL-6 and IL-1 may be the main initiators [91]. Thereafter, IL-23 functions prominently in both human and mice. Interestingly, bacterial peptidoglycan-derived muramyl dipeptide is a particularly potent inducer of IL-23 and IL-1 in DCs, which in turn elicit strong IL-17 responses from the human memory T-cell pool [92]. Muramyl dipeptide signals via the NOD2 adaptor protein to induce transcription of IL-23 (and probably IL-1) via the classical NF- $\kappa$ B pathway and it also activates caspase-1 to process pro-IL-1 $\beta$ .

#### *Th17/IL-17 in autoimmune diseases*

Once the existence of Th17 cells was recognized, it soon became evident that many inflammatory conditions may be partly or largely driven by Th17 and not by Th1, as was erroneously concluded previously [88,93-96]. Th17 and/or IL-17 have been reported to be centrally involved in multiple sclerosis (and its mouse model experimental autoimmune encephalomyelitis) and RA (and its mouse model CIA). In addition, evidence is accumulating for a role of the Th17/IL-17 axis in many other inflammatory conditions and autoimmune diseases, including inflammatory bowel disease, psoriasis, periodontal disease, inflammatory airways diseases, and possibly even systemic lupus erythematosus (see above).

Although there is considerable support for the involvement of Th17/IL-17 in multiple sclerosis and RA (see below), evidence for its roles in the other human diseases is more circumstantial and often rests on the detection of high expression levels of IL-17 at sites of inflammation. Th17 and IL-17 are generally thought to be critical in defense against extracellular bacteria and some fungi, especially at mucosal and epithelial surfaces [88,95,97,98]. IL-17 is particularly potent in inducing chemokines that recruit neutrophils to fight these pathogens. The Th17/IL-17 axis thus represents another instance in which the lines between innate and adaptive immunity become blurred, because the antigen-specific T cells elicit innate responses via IL-17 in this case.

#### *Th17/IL-17 in rheumatoid arthritis*

Regarding RA, multiple lines of investigation support the critical involvement of Th17 and IL-17. For example, synovial fluid from joints of RA patients contains high levels of IL-17, and the T cells present in synovial cultures from RA patients spontaneously secrete IL-17 [96]. Nevertheless, the importance of Th17 cells to the pathogenesis of RA remains to be definitively proven; for example, one publication reports a predominance of Th1 rather than Th17 in RA joints, although it must be kept in mind that the presence of a mixed Th1/Th17 type of helper might have been present (see above) [99,100].

The importance of Th17/IL-17 in mouse RA models, however, has been clearly established. CIA is markedly suppressed in IL-17 deficient mice [101], and treatment of mice with a neutralizing anti-IL-17 antibody in early and later phases of CIA reduces joint inflammation, cartilage destruction, and bone erosion [102]. Furthermore, IL-17 receptor deficient mice are substantially blocked in development of streptococcal cell wall induced arthritis [103]. It is worth noting that IL-17 is produced not only by Th-17 cells, but also by some other cells, including - in particular - oligoclonal  $\gamma/\delta$  T cells; these cells may also contribute to RA/CIA [104]. In the naturally mutated SKG strain of mice discussed above (recessive mutation in ZAP-70), the spontaneously arising self-reactive T cells develop a T-cell mediated autoimmune arthritis, resembling RA [105]. The self-reactive T cells are able to induce expression of IL-6 in antigen-presenting cells, and IL-6 in turn mediates differentiation of self-reactive T cells into arthritogenic Th17 cells. Loss of either IL-6 or IL-17 completely blocks arthritis development in this model. Interestingly, pathologic arthritis does require a trigger, which can be supplied by stimulation of innate immunity or by IFN- $\gamma$  deficiency or any other stimulus that leads to expansion of the Th17 cells [86,106-108]. Toll-like receptors are likely to be involved in pathogen-derived triggers, and a significant part of their intracellular effects is mediated by activation of the classical pathway of NF- $\kappa$ B [109].

Experimentally induced over-expression of IL-17 in naïve mouse joints leads to many of the signs of RA, including

chronic inflammation and bone erosion, and it exacerbates existing pathology in acute arthritis models [109]. Further evidence for a critical role for Th17 cells also comes from investigations into IL-23. Synovial fluid from RA patients contains elevated levels of IL-23 p19 protein, and the degree of elevation was directly correlated with the levels of IL-17, IL-1, and TNF- $\alpha$ ; furthermore, levels were highest in patients with bony erosions [108]. Finally, anti-IL-23 antibodies were reported to attenuate CIA [110].

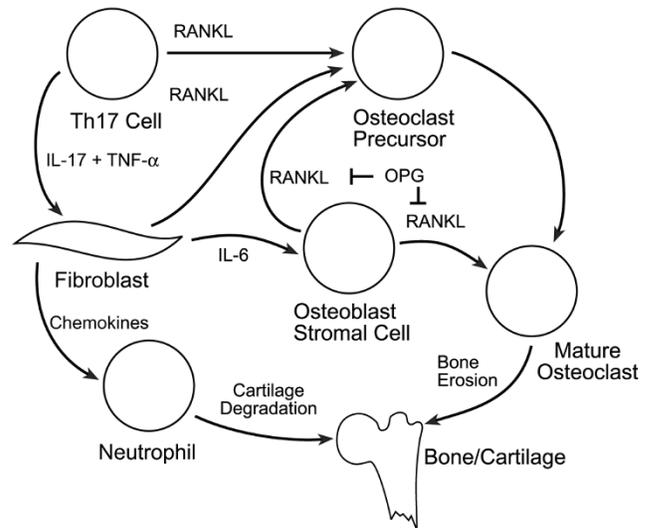
These findings clearly implicate Th17 and IL-17 in the pathogenesis of RA, but why should this be so? IL-17 receptors are fairly ubiquitously expressed, and IL-17 induces many cytokines in various cells, including synovial fibroblasts, such as IL-6, TNF- $\alpha$ , and IL-1, as well as chemokines, especially CXC chemokines that can recruit neutrophils [84,95]. The effect of IL-17 is greatly enhanced by synergy with TNF- $\alpha$ , which is produced by T cells and activated macrophages, among other cells (more details is provided on the synergy between IL-17 and TNF- $\alpha$  below) [94,95]. Activated macrophages also produce IL-6 and IL-1. IL-6 (and by some accounts IL-1, TNF- $\alpha$  and IL-17), in addition to Toll-like receptor-2 and -4 ligands, directly or indirectly lead to expression of RANK ligand (RANKL) on osteoblastic stromal cells and synoviocytes [102,103,107,108,110-113]. RANKL is the primary mediator of osteoclastogenesis and is essential also for the maintenance and function of mature osteoclasts (Figure 6). Th17 cells can directly stimulate this process as well, because only this T-helper class preferentially expresses RANKL [114]. IL-17 in addition leads to downregulation of osteoprotegerin, the natural antagonist of RANKL [111,112]. The increased ratio of RANKL over osteoprotegerin assures generation of osteoclasts from monocyte precursors and continued activation and maintenance of mature osteoclasts; activated osteoclasts erode bone and thus are critically involved in RA pathology (Figure 6). IL-1 and TNF- $\alpha$  also directly contribute to the differentiation of osteoclasts and their activation after maturation [115,116].

IL-17 has additional pathogenic effects in RA. Activated synoviocytes, chondrocytes, and infiltrating mononuclear cells produce a variety of metalloproteases, cathepsin G and elastase, leading to destruction of the extracellular matrix and cartilage, and further bone erosion [113]. IL-17 and IL-6 block matrix synthesis by articular chondrocytes; nitric oxide produced via induction of inducible nitric oxide synthetase in synoviocytes and macrophages leads to further degeneration of chondrocytes; and IL-17-induced cyclo-oxygenase-2 leads to production of prostaglandin E<sub>2</sub> and thus further inflammation, cartilage damage, and bone erosion. Finally, neutrophils recruited via IL-17 induced chemokines further contribute to tissue destruction [86,94,95,103,112,113] (Figure 6).

#### *IL-17 and activation of the classical pathway*

The interdependent network of cytokines in RA involves various positive feedback loops. For example, optimal

**Figure 6**



The immune system regulates bone resorption through enhanced osteoclastogenesis. Cells of the adaptive and innate immune systems contribute to regulation of bone turnover through production of cytokines and direct cell-cell interactions. Proinflammatory cytokines such as IL-6, IL-1 $\beta$ , and TNF- $\alpha$  are secreted by macrophages and fibroblasts secrete IL-6. Th17 lymphocytes produce IL-17, IL-6, and TNF- $\alpha$ . In RA these cytokines drive bone erosion by induction of RANKL expression by osteoblast stromal cells. Th17 lymphocytes also secrete RANKL, which binds to RANK receptor on osteoclast precursors triggering osteoclast maturation and activation, thus enhancing bone loss. Osteoprotegerin (OPG) is a soluble decoy receptor that inhibits RANKL binding to RANK thus limiting bone resorption. IL-17 increases RANKL expression and concomitantly decreases OPG expression in osteoblasts, causing enhanced formation of osteoclasts and bone erosion. Neutrophils also contribute to bone and cartilage degradation by secretion of degradative factors. IL, interleukin; RANK, receptor activator of NF- $\kappa$ B; Th, T-helper; TNF, tumor necrosis factor.

differentiation and expansion of Th17 cells and production of IL-17 requires IL-6, as well as IL-23 and IL-1, but these same cytokines are also induced downstream of IL-17 [112,113,117]. The proinflammatory cytokines discussed here, including TNF- $\alpha$  and IL-1 as well as IL-17, all induce the classical pathway of NF- $\kappa$ B activation (see below), whereas RANKL induces both the classical and the alternative pathway. A number of studies have shown the importance of both pathways in osteoclastogenesis and in subsequent function of matured osteoclasts in response to RANKL stimulation [115,116,118]. Given the central role of cytokines in RA and their interdependence, it may not be too surprising that therapeutic approaches aimed at disrupting this network have shown great promise in patients with RA and in mouse models. Treatments targeting the signaling via IL-6, TNF- $\alpha$ , IL-1, IL-17, and RANKL were all quite effective in attenuating pathogenesis [86,112].

Th17 cells produce IL-17A (also known as IL-17), as well as IL-17F, which thus far appears to have same biologic activity

as IL-17, although it has a weaker affinity for the IL-17 receptor [95]. The receptor may be a heteromeric complex containing the IL-17RA (also known as IL-17R) and RC chains. The ligand family consists of six members (IL-17A-F), whereas the receptor family has five members (IL-17RA-RE) [88,94]. IL-17E (also known as IL-25) and its receptor IL-17RB have been shown to play a role in Th2-type responses [119], whereas relatively little is known about the remaining members of the ligand and receptor families.

IL-17 stimulation induces the recruitment of the adaptor protein CIKS (connection to I $\kappa$ B kinase and stress-activated protein kinases; also known as Act1) to the IL-17R to transduce signals [120,121]. This adaptor has been shown to be essential for the development of experimental autoimmune encephalomyelitis, complementing previous data implicating Th17 and IL-17 in this disease [122]. Both CIKS and the receptor chains contain a so-called SEFIR domain (similar expression to fibroblast growth factor genes and IL-17Rs and Toll and IL-1R), which is distantly related to the Toll and IL-1R (TIR) domain. The recruitment of CIKS to the IL-17R occurs via heterotypic SEFIR domain interactions, similar to the way that Toll-like receptors recruit the adaptor MyD88 via TIR domain interactions. IL-17 activates NF- $\kappa$ B and mitogen-activated protein kinases via CIKS/Act1, although the molecular mechanisms are not well understood at this point [120,121]. CIKS is known to interact with NEMO/IKK $\gamma$ , the regulatory subunit of the IKK complex [123]. CIKS/Act1 can also bind to TRAF3 and may bind to TRAF6 in response to signals; furthermore, activation of NF- $\kappa$ B has been suggested to proceed via TAK1 activation [120-122]. Signaling via the IL-17Rs also activates CCAAT/enhancer binding protein (c/EBP) $\beta$  and c/EBP $\delta$ , which requires not only the SEFIR domain (and CIKS) but also additional receptor domains [124]. Many IL-17 target genes contain both c/EBP and NF- $\kappa$ B binding sites and these appear to function cooperatively on DNA to promote transcription, and IL-17 has been shown to act synergistically with TNF- $\alpha$  in inducing many of its target genes in fibroblasts *in vitro* [94,95].

The synergy between TNF- $\alpha$  and IL-17 may be due in part to the ability of IL-17 to stabilize short-lived mRNAs that are only transiently induced by TNF- $\alpha$  alone [125], although nothing is known about how IL-17 may stabilize such mRNAs. Nevertheless, the synergy is profound because many target genes are affected. Cumulative evidence also suggests that IL-17 can directly and immediately activate a modest level of NF- $\kappa$ B activity, which is probably critical for its functions in the absence of TNF- $\alpha$  or other signals that activate NF- $\kappa$ B. In addition, IL-17, but not TNF- $\alpha$ , induces I $\kappa$ B $\zeta$ , a member of the I $\kappa$ B family that is able to promote NF- $\kappa$ B activity, in contrast to the classic I $\kappa$ Bs, which act as cytoplasmic inhibitors. It has been suggested that I $\kappa$ B $\zeta$  facilitates the synergy between NF- $\kappa$ B and c/EBP transcription factors [126]. This may provide an additional mechanism by which IL-17 synergizes with TNF- $\alpha$ . As discussed above, IL-17 also activates NF- $\kappa$ B

indirectly in other cells through induction of various cytokines, such as RANKL.

## Conclusion

Both classical and alternative pathways of NF- $\kappa$ B activation regulate survival and activation of T and B lymphocytes at their sites of development in thymus, bone marrow and spleen, and in the periphery. In normal conditions of health the immune system balances antigen presentation and pro-inflammatory activity in the periphery in response to pathogens and other environmental challenges to prevent excessive autoreactivity of the T-cell and B-cell complement. Improperly regulated NF- $\kappa$ B function leading to its constitutive activation causes autoimmunity, engendering chronic inflammation, for example in the articular joints in RA. Autoimmune diseases may be initiated by malfunctioning lymphocytes whose apoptotic pathways, normally activated by self-antigens, are blocked by abnormal activation of NF- $\kappa$ B, enabling the survival of self-reactive cells [21,127-130].

The multiple roles of NF- $\kappa$ B in autoimmune diseases make it an important pharmaceutical target. Given its many crucial roles in maintaining health, including roles in acute host defense and lymphocyte development, systemic NF- $\kappa$ B inhibitors are likely to have deleterious side effects, particularly if used for long periods. Such inhibitors, however, might be useful in doses that interfere with disease progression while sparing normal processes. More promising are inhibitors that target a specific subunit of NF- $\kappa$ B or the pathway(s) that leads to its activation in a particular disease. To discover such targets and inhibitors, we need to advance our understanding of the roles of NF- $\kappa$ B and its pathways of activation in healthy and diseased cells. Furthermore, the unwanted effects of blocking NF- $\kappa$ B activity might be reduced by targeting inhibitors to specific tissues or cell types. Genetic delivery of NF- $\kappa$ B inhibitors may be useful in this regard, and local tissue delivery may avoid deleterious side effects of systemic exposure and minimize broader immunosuppression [104]. Recent reviews have outlined the advantages and disadvantages of anti-inflammatory and anti-rheumatic NF- $\kappa$ B inhibitors, and the effects (in animal models of RA and other autoimmune diseases) of genetically inactivated NF- $\kappa$ B subunits and ectopic I $\kappa$ B $\alpha$ . Together, the results support the feasibility of using NF- $\kappa$ B inhibitors in therapeutic strategies for RA and other autoimmune disorders [82,83,131-133].

## Competing interests

The authors declare that they have no competing interests.

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