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Microbiology

Special Issue on
The Microbiology of NF-κB

Edited by:
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Review Article

NF-κB, Autoimmunity and Mycobacteria

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Submitted: 24 March 2015
Accepted: 13 June 2015
Published: 16 June 2015

Keywords
- NF-κB
- Autoimmunity
- Therapeutics
- Tumor necrosis factor
- Bacillus calmette-guerin

Abstract

Many autoimmune diseases feature functional or genetic defects that can alter NF-kB function. In an animal model of type 1 diabetes and Sjogren's syndrome, a defective proteasome prevents NK-kB-induced gene transcription by precluding cleavage of IκBα from NF-kB in the cytoplasm. Polymorphisms in such NK-kB related genes as SUMO4, NOD2, IKBL, IRF-5, TNFAIP3, TNF, TNFR1, TNFR2, IL-10 and DLG-5 have been associated with autoimmune diseases. Each of these genes has interactions with members of the NF-kB pathway and when defective can disrupt NF-kB function. Treatment of autoimmune diseases can also take advantage of the NF-kB pathway. TNF and the TNF-inducer mycobacterium bacillus calmette-guerin (BCG) selectively destroy autoreactive but not normal T lymphocytes through NF-kB dysregulation. BCG also induces proliferation of immunosuppressive T-regulatory cells by induction of transmembrane TNF, its preferential binding to TNFR2, and transcription of pro-survival genes via the normally functioning NF-kB pathway. Thus, the NF-kB pathway can play a central role in autoimmunity and its treatment.

ABBREVIATIONS

BCG: Bacillus Calmette-Guerin; T Cells: T-Lymphocytes; TNF: Tumor Necrosis Factor; NOD Rat: Non-Obese Diabetic Rat.

INTRODUCTION

This short article reviews the numerous types of genetic and functional defects altering NF-kB activity across autoimmune diseases, ranging from type 1 diabetes to lupus to multiple sclerosis. This article also reviews the benefits of the mycobacterium Bacillus Calmette-Guerin (BCG) in the treatment of autoimmune diseases through two different NF-kB-related mechanisms.

In immune cells, NF-kB's mode of activation varies according to cell type, state of activation, or developmental stage [1,2]. In T-lymphocytes (T cells), which mediate some types of autoimmunity, NF-κB normally is precluded from reaching the nucleus because its subunits are tightly bound to the inhibiting protein IκBα [3]. In response to induction by cytokines such as tumor necrosis factor (TNF) and other signals, IκBα is phosphorylated, ubiquinated, and then degraded by a proteasome. Once liberated from IκBα, NF-κB translocates to the nucleus where it binds to target DNA segments, initiating expression of various genes, including those encoding cytokines (e.g., IL-2, TNF-, and IFN-β), pro-apoptotic genes, or anti-apoptotic

genes [4]. These life and death functions are vital for shaping the T cell repertoire and curtailing T cell proliferation after antigen exposures. More comprehensive reviews of the relationship between T cells, NFkB and autoimmunity are available [5-7].

Type 1 Diabetes

Type 1 diabetes was one of the first autoimmune diseases found to feature dysregulation of NF-kB. Cultured T-cells from an animal model of Type 1 diabetes were found to have reduced or absent expression of the LMP2 catalytic subunit of the proteasome [8]. Without the LMP2 protein, the proteasomes were unable to degrade IκBα from NF-kB, disrupting the signaling pathway. The proteasome defect rendered NOD T-cells vulnerable to Tumor Necrosis Factor (TNF)-induced cell death. T cells do not constitutively express the active form of NF-kB, in contrast to B cells and monocytes [9]. The same deficiency in LMP2 was found in a mouse model of Sjogren's syndrome [10].

A second form of NF-kB dysregulation was found in human type 1 diabetes, owing to a polymorphism in the small ubiquitin-like modifier 4 (SUMO4) genes [11]. In contrast to other SUMO members, SUMO4 expression is restricted to immune cells and pancreatic islets [12]. Multiple research groups confirmed SUMO4 as a Type 1 diabetes susceptibility gene in Asian populations, but some genetic heterogeneity was found in Caucasian populations [12]. More recent meta-analyses have demonstrated an association of SUMO4 M55V polymorphism in both Asian and Caucasian populations [13,14]. SUMO4 interacts with IκBα and inhibits the transcriptional activity of NF-kB. The promoter of SUMO4 has a NF-kB responsive element [12,15]. A polymorphism in SUMO4 has also been reported for Behcet's disease [16].

Multiple Sclerosis

Multiple sclerosis is an autoimmune disease marked by destruction of the myelin sheath surrounding neurons. Studying several genes in the NF-kB cascade with a gene candidate approach, a research team in Germany found overrepresentation of 738C allele in the IKBL gene, a member of the IkB protein family, among patients with a relapsing/remitting course of MS [17]. The allele is an inhibitor of the NF-kB cascade. The researchers excluded an association for the NK-kB1 and NK-kB3 genes. Further, a splice variant of the TNFR1 receptor gene has been found in multiple sclerosis [18]. The investigators found that the altered TNFR1 protein, like TNFR1, is released in abundance into the serum, where it binds to TNF, thus effectively lowering TNF levels.

Table 1: Genes Defects in Autoimmune Disease.

Disease	Gene Defect	Action on NF-kB	References
Type 1 Diabetes	LMP2 (mouse only) SUMO4 TNFA1P3	Prevents activation of NF-kB via proteasomal defect Inhibits NF-kB transcriptional activity Disrupts NF-kB signaling through ubiquitin-editing enzymes	[8,11,12,14,15,22,74]
Sjogren's Syndrome	LMP2 (mouse only) IRF-5	Prevents activation of NF-kB Disrupts NF-kB signaling	[20,75,76]
Multiple Sclerosis	IKBL TNFR1 IRF-5	Inhibitor of NF-kB Disrupts NF-kB signaling Disrupts NF-kB signaling	[17,18,20,77]
Lupus	TNFA1P3 IRF-5 P65-Rel A subunit of NF-kB TNFα TNFR2	Disrupts NF-kB signaling through ubiquitin-editing enzymes Disrupts NF-kB signaling Disrupts NF-kB signaling Disrupts NF-kB signaling Disrupts NF-kB signaling	[22,25-27,78-81]
Crohn's Disease	TNFR2 NOD2 DLG-5 CALCOCO2/NDP52 IRF-5 TNFAIP3	Disrupts NF-kB signaling Decreased ubiquitination of NEMO Disrupts NF-kB signaling through DLG-5's CARD domain Excessive activation of NF-kB through toll-like pathway Disrupts NF-kB signaling Activation of NF-kB- dependent inflammation	[22,33,35,37,82]
Scleroderma	IL-10	Low levels of NF-kB by inhibition of NF-kB activation	[38-40]
Rheumatoid Arthritis	TNFAIP3 TNFR2 (familial rheumatoid arthritis only)	Disrupts NF-kB signaling through ubiquitin-editing enzymes Disrupts NF-kB signaling	[83-86]

IRF5 in Multiple Autoimmune Diseases

Polymorphisms affecting the type 1 interferon system are implicated in lupus, Sjogren's syndrome, multiple sclerosis, Crohn's disease and ulcerative colitis [19]. Attention has been focused on polymorphisms in interferon regulatory factor 5 (IRF-5). IRF-5 relies on four distinct promoters for its four first exons: 1A, 1B, 1C, and 1D. Exons 1A and 1D possess putative NF-kB binding sites [20]. Thus, polymorphisms in IRF-5 potentially disrupt the NF-kB signaling pathway.

TNFAIP3 in Multiple Autoimmune Diseases

Polymorphisms in the tumor necrosis factor α-induced protein 3(TNFAIP3) gene have been uncovered in lupus, rheumatoid arthritis, Crohn's disease, type 1 diabetes, and psoriasis [21,22]. More recently, a polymorphism in TNFAIP3 has been identified in a German case-control cohort [23]. TNFAIP3 is an inhibitor of NF-kB activation [24]. It is a ubiquitin-editing enzyme that exerts a role in multiple steps in the NF-kB signaling pathway, especially through its deubiquitinating and its E3 ubiquitin ligase activities [21].

TNF Defects, Lupus, and other Autoimmune Diseases

In addition to the TNFAIP3 and IRF-5 polymorphisms noted above, lupus features other NF-kB-related defects. Lupus T cells were found to have depressed or undetectable NF-kB binding activity, which was traced to reduced or absent expression of the p65-Rel A subunit of NF-kB [25].Further, lupus susceptibility is associated with a polymorphism in the TNFα gene [26], and a polymorphism in the TNF receptor 2 gene has been implicated in Asian populations with lupus [27]. Polymorphisms in the TNFR2 gene also have been found in some patients with familial rheumatoid arthritis, Crohn's disease, ankylosing spondylitis [28]. TNFR2 is a major activator of the NF-kB pathway through TRAF2 [29].

Crohn's Disease

Three defective genes with NF-kB interactions have been found in Crohn's disease. The first set of variants, in the nucleotide-binding oligomerization domain containing 2 (NOD2) gene, were identified by two independent teams in 2001 [30,31]. Subsequent studies have found an NOD2 gene dosing effect, with one copy of the allele rendering a modest risk of developing Crohn's and two copies being associated with a 20- to 40-fold increase in risk [32]. NOD acts as a general sensor of most, if not all, bacteria. The NOD2 protein consists of two amino-terminal caspase recruitment domains (CARDs) and leucine rich repeat variants. Activation of NOD2 leads to NF-kB-mediated pro-inflammatory gene expression through ubiquitinylation of NEMO, one of the components of the NF-kB signaling complex [33,34]. Another Crohn's susceptibility gene, discs large homolog 5 (DLG-5), also possesses a CARD domain which mobilizes pro-inflammatory NF-kB signaling [35]. Variants in DLG-5 are gender-specific in a meta-analysis of Crohn's patients [36]. Finally, a missense mutation in the autophagy receptor gene CALCOCO2/NDP52 has been identified in Crohn's disease [37]. Functional studies implicate the mutation in excessive activation of NF-kB downstream of toll-like or other receptor pathways [37]. As already noted, polymorphisms in TNFAIP3, IRF-5 and TNFR2 also have been implicated in Crohn's disease.

Scleroderma

Cultured CD8 lymphocytes from scleroderma patients express low levels of NF-kB, and this lowered expression is correlated with increased CD8 apoptosis [38]. The cause of reduced NF-kB expression was thought to be an NF-kB polymorphism, but a more recent study, albeit small, found that an NF-kB promoter polymorphism was not found different between scleroderma cases and controls [39]. However, the same study did find an IL-10 promoter polymorphism associated with scleroderma. IL-10 is known to inhibit NF-kB activation in monocytes [40].

BCG in the Treatment of Autoimmunity

While anti-TNF therapies are widely used in treating some forms of autoimmune disease such as rheumatoid arthritis, they trigger or worsen other forms of autoimmunity in clinical trial testing [41]. This paradox led us to suggest that the opposite therapeutic strategy, the application of TNF, may be beneficial for some forms of autoimmunity, based on its selective destruction of autoreactive but not normal T cells from blood samples of patients with type 1 diabetes, multiple sclerosis, lupus, psoriasis, Crohn's disease, and Grave's disease [8,42]. Autoreactive T cells are vulnerable to TNF-induced apoptosis because of genetic or functional defects in NF-kB that prevent entry of unprocessed NF-kB into the nucleus [41]. Indeed, TNF has been found to prevent onset of lupus, type 1 diabetes, and multiple sclerosis in animal models [41]. The problem with TNF administration to humans is that it carries systemic toxicity largely because the TNFR1 receptor is ubiquitously expressed [43]. Consequently, BCG, a well-known TNF-inducer, has been used as a safer alternative that also selectively triggers death of autoreactive T cells via NF-kB dysregulation [44]. The mycobacterium BCG is a weakened form of the tuberculosis bacterium (*Mycobacterium bovis*) and has been used for nearly 100 years as a highly effective vaccine against tuberculosis and more recently against bladder cancer, with a strong safety record for both indications [45, 46]. Beyond its protection against TB, BCG vaccination is also associated with reduced overall mortality and fewer hospitalizations due to respiratory infection or sepsis [47-49]. The reduction in mortality is associated with vaccination in the neonatal period as opposed to delayed vaccination [50].

BCG administration has been tested as a therapeutic in several autoimmune diseases. The data in spontaneous animal models of autoimmunity has taught us important lessons about how best to use BCG as a therapeutic. In animal models of autoimmunity, the timing of BCG administration in relationship to the disease state is critical. Also similar to the tuberculosis literature, strains of BCG also show differences in efficacy, especially in relation to their ability to induce TNF [51,52]. In animal models, BCG administration reverses full-blown type 1 diabetes [44,53] and advanced Sjogren's syndrome [54] once the disease is clinically expressed. The timing of the vaccine or its surrogate TNF is extremely important. BCG vaccination or TNF administration to diabetes- and Sjogren's-prone NOD mice at birth accelerates autoimmunity, but multi-vaccination of BCG or TNF after disease onset is highly protective [55]. In general the human data mimic

the mouse data. In human clinical trials, BCG has shown promise in treating newly diagnosed multiple sclerosis [56,57] and in treating both new onset and long term type 1 diabetes [58,59], often with multi-dosing showing greatest benefit. Multi-dosing BCG also appears to prevent diabetes onset when three doses are used, but no dose or one dose of BCG shows no benefit [60,61]. Similar to the murine experience, early human trials showed no effect of single BCG vaccinations in new onset Type 1 diabetes especially when BCG strains with less TNF induction were used [62,63]. Also similar to murine findings, epidemiology studies of single BCG administration at birth found no effect [64,65] or increased risk of Type 1 diabetes [66]. Remarkably murine data has matched human data and demonstrated the critical nature of the timing, the dose of BCG and the strain of BCG. Ongoing clinical trials of BCG are aimed at multi-dosing in autoimmunity in such diverse immune diseases as multiple sclerosis, allergy, type 1 diabetes and Sjogren's syndrome.

BCG may be therapeutic for autoimmune diseases by another mechanism involving NF-kB and the induction of T-regulatory (Treg) cells. Tregs are a small subset of CD4 T cells with roles in the prevention of autoimmunity via maintenance of self-tolerance, immune homeostasis, and suppression of cytotoxic T cells [67]. In humans, BCG administration induced proliferation of Tregs when treating type 1 diabetes [59]. The mechanisms by which this occurs are being studied, and appear to occur only during the quiescent phase of BCG infection. During the quiescent phase, BCG-infected macrophages generate transmembrane TNF, which has different activity from soluble TNF [68-70]. Transmembrane TNF is the major ligand for Treg expansion, via its preferential binding to TNFR2 [71]. TNFR2 triggers proliferation of Tregs [72]. Using a TNFR2 agonist, TNFR2 has been found to be the master control switch on Tregs, inducing their homogeneous expansion as opposed to heterogeneous expansion through TNFR1 in adult T cells [73]. In CD4 T cells, the TNFR2 receptor activates the NF-kB pathway through TRAF2/cIAP, triggering transcription of pro-survival genes [28]. Also TNFR2 agonism through either agonistic antibodies or through transmembrane TNF induces IL2R (CD25), TNF, and TRAF2 expression, all components of the TNFR2 signaling pathway for Treg expansion [73].

DISCUSSION AND CONCLUSION

This short review has provided evidence for NF-kB's involvement in autoimmunity and its treatment. It has identified numerous functional and genetic defects that can disrupt the NF-kB pathway in a myriad of autoimmune diseases. It has also provided evidence that the mycobacterium BCG has value in treating autoimmune disease through two different NF-kB mechanisms. One is by selective death of CD8 autoreactive T cells driven in some forms of human and murine autoimmunity through a proteasomal defect that dysregulates NF-kB. The other is by BCG induction of transmembrane TNF, which is the major ligand for Treg cell expansion occurring through preferential binding of transmembrane TNF to TNFR2 and activation of pro-survival genes via the NF-kB pathway. Tregs are major players in the suppression of autoimmunity. Several studies have found BCG as a successful treatment for autoimmunity.

ACKNOWLEDGEMENTS

The authors thank Ms. Lynne Murphy for her secretarial assistance. This work was supported by the Iacocca Foundation.

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Cite this article

Faustman DL, Davis M (2015) NF-κB, Autoimmunity and Mycobacteria. JSM Microbiology 3(1): 1020.