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SNAPSHOT

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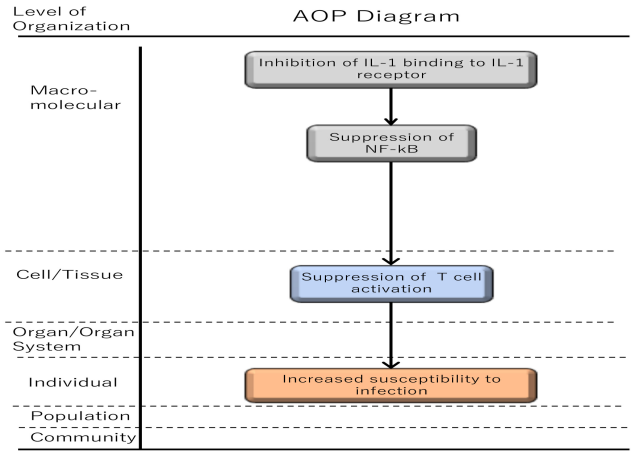
AOP 277: Inhibition of IL-1 binding to IL-1 receptor leading to increased susceptibility to infection

Short Title: IL-1 inhibition

Graphical Representation



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Abstract

The pleiotropic cytokine IL-1 mediates its biological functions via association with the signaling receptor IL-1R1. These may include initiation of innate immunity as well as acquired immunity, which are essential for assistance of host defense against infection. The trimeric complex consists of IL-1, IL-1R1 and IL-1R3 (a coreceptor, formerly IL-1R accessory protein) allows for the approximation of the Toll-IL-1-Receptor (TIR) domains of each receptor chain. MyD88 then binds to the TIR domains. The binding of MyD88 triggers a cascade of kinases that produce a strong pro-inflammatory signal leading to activation of NF-κB. The activation of NF-κB plays a principle role in the immunological function of IL-1. Namely, it stimulates innate immunity such as activation of dendritic cells and macrophages. It also stimulates T cells via activated dendritic function or directly. The activation of T cells is crucial for B cell proliferation and their antibody production. The cooperation by T cells and B cells constitutes a main part of host defense against infection.

In this AOP, we considered the inhibition of IL-1 binding to IL-1 receptor as a MIE. The biological plausibility of the signaling cascade from IL-1 receptor activation to the activation of NF-kB is already confirmed. In addition, the biological plausibility that suppressed NF-kB activation leads to impaired T cell activation, resulting in impaired antibody production and increased susceptibility to infection is supported by quite a few published works.

IL-1 also mediates several autoinflammatory syndromes. Therefore, several inhibitors against IL-1R stimulation such as IL-1Ra (generic anakinra), canakinumab (anti-IL-1β antibody) and rilonacept (soluble IL-1R) have been developed. Indeed, after these inhibitors became available to treat these disorders, it became clear that these inhibitors increased the frequency of serious bacterial infection. Taken together, developing the AOP for "inhibition of IL-1 binding to IL-1 receptor leading to increased susceptibility to infection" is mandatory.

Background

The pleiotropic cytokine IL-1 mediates its biological functions via association with the signaling receptor IL-1R1. These may include initiation of innate immunity and assistance of host defense against infection, and sometimes, mediation of autoinflammatory, such as cryopyrin-associated periodic syndrome, neonatal-onset multisystem inflammatory disease and familial Mediterranean fever. The trimeric complex consists of IL-1, IL-1R1 and IL-1R3 (a coreceptor, formerly IL-1R accessory protein) allows for the approximation of the Toll-IL-1-Receptor (TIR) domains of each receptor chain. MyD88 then binds to the TIR domains. The binding of MyD88 triggers a cascade of kinases that produce a strong pro-inflammatory signal leading to activation of NF-κB and fundamental inflammatory responses such as the induction of cyclooxygenase type 2, production of multiple cytokines and chemokines, increased expression of adhesion molecules, or synthesis of nitric oxide. (Dinarello, 2018) (Weber et al., 2010a, b).

IL-1 also mediates autoinflammatory, such as cryopyrin-associated periodic syndrome, neonatal-onset multisystem inflammatory disease and familial Mediterranean fever. Therefore, several inhibitors against IL-1 signaling have been developed. Recombinant IL-1Ra (generic anakinra) is fully active in blocking the IL-1R1, and therefore, the activities of IL-1α and IL-1β. (Dripps et al., 1991) Anakinra was approved for the treatment of rheumatoid arthritis and cryopyrin-associated periodic syndrome (CAPS). Although anakinra is a safe drug in general, several papers reported that anakinra increased susceptibility to bacterial and tuberculosis infection (Genovese et al., 2004; Kullenberg et al., 2016; Lequerre et al., 2008; Migkos et al., 2015). Similarly, other IL-1 signaling antagonists, canakinumab (anti-IL-1β antibody) and rilonacept (soluble IL-1R) have been reported increase susceptibility to infection. (De Benedetti et al., 2018; Imagawa et al., 2013; Lachmann et al., 2009; Schlesinger et al., 2012; Yokota et al., 2017). In addition to these human data, the experiments using knockout mice revealed that the lack of IL-1 signaling led to bacterial, tuberculosis or viral infection. (Guler et al., 2011; Horino et al., 2009; Juffermans et al., 2000; Tian et al., 2017; Yamada et al., 2000).

In this AOP, we considered inhibition of IL-1R activation, as a MIE. The biological plausibility of the signaling cascade from the activation of IL-1R to the activation of NF-kB is already accepted. In addition, the biological plausibility that suppressed NF-kB activation leads to impaired T cell activation, resulting in impaired antibody production and impaired T cell and antibody production lead to increased susceptibility to infection is confirmed.

Summary of the AOP

Events

Molecular Initiating Events (MIE), Key Events (KE), Adverse Outcomes (AO)

Sequence	Type	Event ID	Title	Short name
1	MIE	1700	Inhibition of IL-1 binding to IL-1 receptor (https://aopwiki.org/events/1700)	Inhibition of IL-1 binding to IL-1 receptor
2	KE	202	Inhibition, Nuclear factor kappa B (NF-kB) (https://aopwiki.org/events/202)	Inhibition, Nuclear factor kappa B (NF-kB)
3	KE	1702	Suppression of T cell activation (https://aopwiki.org/events/1702)	Suppression of T cell activation

Sequence	Type	Event ID	Title	Short name
4	AO	986	Increase, Increased susceptibility to infection (https://aopwiki.org/events/986)	Increase, Increased susceptibility to infection

Key Event Relationships

Upstream Event	Relationship Type	Downstream Event	Evidence	Quantitative Understanding
Inhibition of IL-1 binding to IL-1 receptor (https://aopwiki.org/relationships/2002)	adjacent	Inhibition, Nuclear factor kappa B (NF-kB)	High	Not Specified
Inhibition, Nuclear factor kappa B (NF-kB) (https://aopwiki.org/relationships/2003)	adjacent	Suppression of T cell activation	High	Not Specified
Suppression of T cell activation (https://aopwiki.org/relationships/2004)	adjacent	Increase, Increased susceptibility to infection	High	Not Specified

Stressors

Name	Evidence
IL-1 receptor antagonist IL-1Ra (Anakinra)	High
anti-IL-1b antibody (Canakinumab)	High
soluble IL-1R (Rilonacept)	High
anti-IL-1b antibody (Gevokizumab)	High

Overall Assessment of the AOP

Domain of Applicability

Life Stage Applicability

Life Stage	Evidence
Not Otherwise Specified	High

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
Homo sapiens	Homo sapiens	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=9606)
Mus musculus	Mus musculus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10090)
Rattus norvegicus	Rattus norvegicus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10116)

Sex Applicability

Sex	Evidence
Mixed	High

Although sex differences in immune responses are well known (Klein and Flanagan, 2016), there is no reports regarding the sex difference in IL-1 production, IL-1 function or susceptibility to infection as adverse effect of IL-1 blocking agent. Again, age-dependent difference in IL-1 signaling is not known.

The IL1B gene is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, and frog (https://www.ncbi.nlm.nih.gov/homologene/481 (https://www.ncbi.nlm.nih.gov/homologene/481)), and the Myd88 gene is conserved in human, chimpanzee, Rhesus monkey, dog, cow, rat, chicken, zebrafish, mosquito, and frog (https://www.ncbi.nlm.nih.gov/homologene?Db=homologene&Cmd=Retrieve&list_uids=1849 (https://www.ncbi.nlm.nih.gov/homologene?Db=homologene&Cmd=Retrieve&list_uids=1849)).

The NFKB1 gene is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, chicken, and frog.

275 organisms have orthologs with human gene NFKB1.

(https://www.ncbi.nlm.nih.gov/gene/4790 (https://www.ncbi.nlm.nih.gov/gene/4790))

The RELB gene is conserved in chimpanzee, Rhesus monkey, dog, cow, mouse, rat, and frog.

216 organisms have orthologs with human gene RELB.

(https://www.ncbi.nlm.nih.gov/gene/5971 (https://www.ncbi.nlm.nih.gov/gene/5971))

These data suggest that the proposed AOP regarding inhibition of IL-1 signaling is not dependent on life stage, sex, age or species.

Essentiality of the Key Events

The experiments using knockout mice revealed that the deficiency of IL-1 signaling led to bacterial, tuberculosis or viral infection (Guler et al., 2011; Horino et al., 2009; Juffermans et al., 2000; Tian et al., 2017; Yamada et al., 2000).

IL-1 receptor antagonist IL-1Ra (generic anakinra) is fully active in blocking the IL-1R1, and therefore, the activities of IL-1α and IL-1β. Anakinra is approved for the treatment of rheumatoid arthritis and cryopyrin-associated periodic syndrome (CAPS). Since its introduction in 2002 for the treatment of rheumatoid arthritis, anakinra has had a remarkable record of safety. However, there are several reports indicating that serious infectious episodes were observed more frequently in the anakinra group (Fleischmann et al., 2003)(Genovese et al., 2004; Kullenberg et al., 2016; Lequerre et al., 2008; Migkos et al., 2015). Two IL-1 signaling antagonists, canakinumab (anti-IL-1b antibody) and rilonacept (soluble IL-1R) had been reported to increase susceptibility to infection (De Benedetti et al., 2018; Imagawa et al., 2013; Lachmann et al., 2009; Schlesinger et al., 2012, Hoffman et al. 2008).

Weight of Evidence Summary

The recent review of IL-1 pathway by Weber et al. has clearly described the intracellular signaling event from the binding of IL-1a or IL-1b to IL-1R to the activation of NF-kB through the assemble of MyD88. The sequentiality and essentiality of each signaling molecule have been demonstrated by mice lacking relevant molecules (Weber et al., 2010a, b).

Biological plausibility

Inhibition of IL-1 binding to IL-1 receptor leads to Inhibition, Nuclear factor kappa B (NF-kB)

IL-1α and IL-1β independently bind the type I IL-1 receptor (IL-1R1), which is ubiquitously expressed. The IL-1R3 (formerly IL-1R accessory protein (IL-1RAcP)) serves as a co-receptor that is required for signal transduction of IL-1/IL-1RI complexes.

The initial step in IL-1 signal transduction is a ligand-induced conformational change in the first extracellular domain of the IL-1RI that facilitates recruitment of IL-1R3. the trimeric complex rapidly assembles two intracellular signaling proteins, myeloid differentiation primary response gene 88 (MYD88) and interleukin-1 receptor–activated protein kinase (IRAK) 4. This is paralleled by the (auto)phosphorylation of IRAK4, which subsequently phosphorylates IRAK1 and IRAK2, and then this is followed by the recruitment and oligomerization of tumor necrosis factor–associated factor (TRAF) 6. Activation of NF-κB by IL-1 requires the activation of inhibitor of nuclear factor B (IκB) kinase 2 (IKK2). Activated IKK phosphorylates IκBα, which promotes its K48-linked polyubiquitination and subsequent degradation by the proteasome. IκB destruction allows the release of p50 and p65 NF-κB subunits and their nuclear translocation, which is the central step in activation of NF-κB. Both NF-κBs bind to a conserved DNA motif that is found in numerous IL-1–responsive genes. (Weber et al. 2010)

Inhibition, Nuclear factor kappa B (NF-kB) leads to Suppression of T cell activation

In T lineage cells, the temporal regulation of NF-kb controls the stepwise differentiation and antigen-dependent selection of conventional and specialized subsets of T cells in response to T cell receptor and costimulatory, cytokines and growth factor signals. Cytokines include cytokines produced from macrophage or monocyte such as IL-1b. (Gerondakis et al. 2014)

Suppression of T cell activation leads to Increase, Increased susceptibility to infection

First type immunity drives resistance to viruses and intracellular bacteria, such as Listeria monocytogenes, Salmonella spp. and Mycobacteria spp., as well as to intracellular protozoan parasites such as Leishmania spp. The T helper 1 signature cytokine interferon-γ has a central role in triggering cytotoxic mechanisms including macrophage polarization towards an antimicrobial response associated with the production of high levels of reactive oxygen species and reactive nitrogen species, activation of CD8 cytotoxic T lymphocytes and natural killer cells to kill infected cells via the perforin and/or granzyme B-dependent lytic pathway or via the ligation of surface death receptors; and B cell activation towards the production of cytolytic antibodies that target infected cells for complement and Fc receptor-mediated cellular cytotoxicity.

Resistance to extracellular metazoan parasites and other large parasites is mediated and/or involves second type immunity. Pathogen neutralization is achieved via different mechanisms controlled by T 2 signature cytokines, including interleukin-4, IL-5 and IL-13, and by additional type 2 cytokines such as thymic stromal lymphopoietin, IL-25 or IL-33, secreted by damaged cell. T 2 signature cytokines drive B cell activation towards the production of high-affinity pathogen-specific IgG1 and IgE antibodies that function via Fc-dependent mechanisms to trigger the activation of eosinophils, mast cells and basophils, expelling pathogens across epithelia.

T17 immunity confers resistance to extracellular bacteria such as Klebsiella pneumoniae, Escherichia coli, Citrobacter rodentium, Bordetella pertussis, Porphyromonas gingivalis and Streptococcus pneumoniae, and also to fungi such as Candida albicans, Coccidioides posadasii, Histoplasma capsulatum and Blastomyces dermatitidis. Activation of T 17 cells by cognate T cell receptor (TCR–MHC class II interactions and activation of group 3 innate lymphoid cells (ILC3s) via engagement of IL-1 receptor (IL-1R) by IL-1β secreted from damaged cells lead to the recruitment and activation of neutrophils. T 17 immunopathology is driven to a large extent by products of neutrophil activation, such as ROS and elastase (reviewed by Soares et al. (Soares et al., 2017)).

Based on these evidences, the insufficient T cell or B cell function causes impaired resistance to infection.

Empirical support

This table summarizes the empirical support obtained from the experiment using several inhibitor or gene targeting mice.

concordance table empirical data

Reference	Chmical Initiator or deleted gene	dose	Species	MIE Inhibition of IL-1 binding to IL-1 receptor	KE1 Inhibition, Nuclear factor kappa B (NF-kB)	KE2 Suppression of T cell activation
Dripps et al. 1991	IL-1Ra (anakinra)			Equilibrium binding and kinetic experiments show that IL-1ra binds to the 80-kDa IL-1 receptor on the murine thymomcae II line EL4 with an affinity (K_D = 150 pM) approximately equal to that of IL-la and IL-1b for this receptor		
Sigma-Aldrich Specification Sheet	IL-1Ra (anakinra)			Determined by its ability to inhibit the IL-1alpha stimulation of murine D10S cell. The expected ED50 is 20-40 ng/ml in the presence of 50 pg/ml of IL-1alpha.		
Fleischmann et al. 2003	IL-1Ra (anakinra)	100 mg of anakinra or placebo, administered daily by subcutaneous injection	human			
Genovese et al. 2004	IL-1Ra (anakinra)	treated with subcutaneous etanercept only (25 mg twice weekly), full-dosage etanercept (25 mg twice weekly) plus anakinra (100 mg/day), or half-dosage etanercept (25 mg once weekly) plus anakinra (100 mg/day) for 6 months	human			
Kullenberg et al. 2016	IL-1Ra (anakinra)	administered as daily s.c. injections	human			
Lequerre et al. 2008	IL-1Ra (anakinra)	treated with anakinra (1–2 mg/kg/day in children, 100 mg/day in adults)	human			
Migkos et al. 2015	IL-1Ra (anakinra)		human			
Settas et al. 2007	IL-1Ra (anakinra)		human			
Lee et al. 2004	IL-1Ra (anakinra)		intrathecal administration of IL-1ra (6 mg)		intrathecal pretreatment with IL-1ra (6 mg) or YVAD (0.5 mg) significantly inhibited NF-kB DNA-binding activity upregulation bilaterally (Fig. 3C). The intrathecal administration of IL-1ra or YVAD into non-inflamed animals produced no significant change in the DNA-binding activity of NF-kB p65.	
Vallejo et al. 2014	IL-1Ra (anakinra)	In diabetic rats treated with anakinra (100 or 160 mg/Kg/day for 3 or 7 days before sacrifice)	rat		In diabetic rats treated with anakinra (100 or 160 mg/Kg/day for 3 or 7 days before sacrifice) a partial improvement of diabetic endothelial dysfunction occurred, together with a reduction of vascular NADPH oxidase and NF-κB activation.	
Dhimolea et al. 2010	canakinumab			Canakinumab binds to human IL-1β with high affinity; the antibody-antigen dissociation equilibrium constant is approximately 35–40 pM. Cmax was 1.2, 1.2 and 1.5 pM for 1, 3 and 10 mg/kg antibody respectively, at days 42–56 after the first infusion.		
De Benedetti et al. 2018	canakinumab	150 mg subcutaneously every 4 weeks	human			
Imagawa et al. 2013	canakinumab	either 150 mg s.c. or 2 mg/kg for patients with a body weight ≤ 40 kg every 8 weeks for 24 weeks received	human			
Lachmann et al. 2009	canakinumab	150 mg of canakinumab subcutaneously every 8 weeks for up to 24 weeks	human			
Schlesinger et al. 2012	canakinumab	one dose of canakinumab 150 mg	human			
Textbook of Pediatric Rheumatology (Sixth Edition), 2011	rilonacept		human	Rilonacept has a very high binding affinity for IL-1 (dissociation constant ~1 pM), and it is specific for IL-1β and IL-1α.		
Hoffman et al. 2008	rilonacept	weekly subcutaneous injections (160 mg)	human			
Roell et al. 2010	gevokizumab (XOMA 052)		human		XOMA 052 neutralizes IL-1b stimulation of NFkB activation in HeLa cells stably expressing an NFkB-luciferase reporter construct with an IC_{50} of ~1 pM at the EC_{50} for this assay (25 pg/ml IL-1b).	
Mansouri et al. 2015	gevokizumab (XOMA 052)	receive gevokizumab 60 mg subcutaneously every 4 weeks for a total of three injections (12 weeks) with a 4-week follow-up period	human			

Issafras et al. 2014	gevokizumab (XOMA 052)		human (HeLa cells stably transfected with a nuclear factor-kB (NF-kB) luciferase reporter plasmid)	an average K_B value (mean±S.D., n=3) of 4.8±4.4 pM	
Palombella et al. 1994	MG-132		human (in vitro)	Both MG115 and MG132 (at 20-40 mM) markedly inhibited the formation of p50 in HeLa S100 extracts (Figure 4A, lanes 8-13).	
Hellerbrand et al. 1998	MG-132		rat (in vitro)	ALLN (Fig. 3A) and MG132 (Fig. 3B) (10 mg/mL = 21mM) reduced the cytokine-mediated NFkB activation.	
Arlt et al. 2001	MG-132		human (in vitro)	In all cell lines, gliotoxin, MG132 (10 mM) or sulfasalazine strongly reduced VP16-induced NF-kB-driven luciferase expression.	
Ortiz-Lazareno et al. 2008	MG-132		human (in vitro)	The increase in NF-kB activation induced by LPS+PMA diminished significantly from 3.27-fold to 0.94-fold in the group treated with MG132(10 mM) and later stimulated with LPS+PMA ($P < 0.002$). The activation of NF-kB induced by LPS+PMA was blocked by MG132.	
Yu and Malek 2001	MG-132		mice (in vitro)		MG132 (50mM) stabilized IL-2- phosphorylated STAT5, which after 2 h in culture (Fig. 5A, lan
Wang et al. 2011	MG-132		human (in vitro)		CMV-specific cytotoxicity of CD decreased in the presence of M
Ohkusu-Tsukada et al. 2018	MG-132	repeatedly i.p. injected 200 nmol of MG132 on days 0, 3, 5, 7, 9, 11, 13, 15, 17, and 19.	mice (in vivo)		In vivo MG132 administration t DNFB-induced dermatitis reduc maintained the level of Th1 cel alleviation of dermatitis lesions serum IgE hyperproduction and
Satou et al. 2004	bortezomib		human (in vitro, in vivo)		potently inhibits the growth of a cells both in vivo and in vitro
Orciuolo et al. 2007	bortezomib	0.1 mM, 1 mM, 10 mM	human (in vitro)		the percentage of CD69/TNFa with the increment of bortezom
Matsumoto et al. 2005	dehydroxymethylepoxyquinomicin (DHMEQ)		human	The addition of DHMEQ (10 mg/mL) completely inhibited the activated NF-KB for at least 8 hours.	
Nishioka et al. 2008	dehydroxymethylepoxyquinomicin (DHMEQ)		human (in vitro)	DHMEQ (1mg/mL) blocked PHA-induced nuclear translocation of NF-kB in Jurkat cells via inhibition of degradation of IkBa.	Exposure of PBMC to PHA grea expression of IFN-g, IL-2 and TNF-a (Fig. these cells with DHMEQ (1 mg/ reduced PHA-stimulated expression of t (Fig. 3a). Similarly, PHA increa and IFN-c in Jurkat cells and pr cells with DHMEQ (1 mg/ml) de by approximately half (Fig. 3b).
Alessiani et al. 1991	FK 506		human		Five of eight deaths were due t Overall, 50% of patients develo 38% suffered severe ones.
Fung et al. 1991	FK 506		human		The incidence of serious infecti of FK 506, has not appeared to incidence of serious infections seen in a historical group of pa is that the incidence of cytomeg not appear to be increased wh patients on CyA.
Ekberg et al. 2007	cyclosporine		human		The most commonly reported s were cytomegalovirus (CMV) v infection and lymphocele (Tabl patients with opportunistic infec serious) was also similar amon cytomegalovirus infection was f opportunistic infection (Table 3
Guler et al. 2011	i) IL-1RI$^{-/-}$ ii) Autologous Qb virus-like particle-based vaccines against IL-1a and IL-1b	ii) immunized s.c. three times before (at week: –5, –3 and –1) and once at week 10 post-infection	mice		
Parnet et al. 2003	IL-1RI$^{-/-}$			Activation of NFkB in response to IL-1b was no longer apparent in IL-1RI knockout mice, confirming that this receptor is essential for the transduction of IL-1 signal in the pituitary,	
Yamada et al. 2001	NF-kB p50$^{-/-}$	knockout mice	mice		
Weih et al. 1995	RelB$^{-/-}$	knockout mice	mice		RelB-deficient animals also hac immunity, as observed in conta experiments.
Lin et al. 2015	Secreted IL-1α expression		mice		Both the percent and number c CD8+ T cells, and CD69+ CD4- the expression of secreted IL-1
Nambu et al. 2006	IL-1a$^{-/-}$, IL-1b$^{-/-}$, IL-1a/b$^{-/-}$	knockout mice	mice		IL-1b, but not IL-1a, is required T cell activation and the inducti inflammation in the delayed-typ responses

Quantitative Consideration

So far, we could find only a few appropriate reports that speak the quantitative aspects of three KERs.

Inhibition, Nuclear factor kappa B (NF-kB) leads to Suppression of T cell activation

MG132 suppresses NF-kB activity at 10-40 mM. MG132 also suppresses IL-2-induced activation of phosphorylated STAT5, (CMV-specific cytotoxicity of CD8(+) T cells), at 50 mM or . (Yu and Malek 2001, (Wang et al. 2011))

DHMEQ (1microg/mL) blocked PHA-induced nuclear translocation of NF-kB in Jurkat cells via inhibition of degradation of IkBa. In the same report, exposure of PBMC to PHA greatly stimulated expression of IFN-g, IL-2 and TNF-a. Preincubation of these cells with DHMEQ (1 microg/ml, 3 hr) greatly reduced PHA-stimulated expression of these cytokine genes. Similarly, PHA increased expression of IL-2 and IFN-g in Jurkat cells and pre-incubation of these cells with DHMEQ (1 microg/ml) decreased these levels by approximately half.(Nishioka et al. 2008)

Considerations for Potential Applications of the AOP (optional)

The impaired IL-1 signaling can lead to decreased host resistance to various infections. Therefore, the test guideline to detect chemicals that decrease IL-1 signaling is required to support regulatory decision-making. This AOP can promote the understanding of the usefulness of the test guideline.

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Weber, A., Wasiliew, P., Kracht, M., 2010b. Interleukin-1beta (IL-1beta) processing pathway. Sci Signal 3, cm2.

Yamada, H., Mizumo, S., Horai, R., Iwakura, Y., Sugawara, I., 2000. Protective role of interleukin-1 in mycobacterial infection in IL-1 alpha/beta double-knockout mice. Lab Invest 80, 759-767.

Yokota, S., Imagawa, T., Nishikomori, R., Takada, H., Abrams, K., Lheritier, K., Heike, T., Hara, T., 2017. Long-term safety and efficacy of canakinumab in cryopyrin-associated periodic syndrome: results from an open-label, phase III pivotal study in Japanese patients. Clin Exp Rheumatol 35 Suppl 108, 19-26.

Appendix 1

List of MIEs in this AOP

Event: 1700: Inhibition of IL-1 binding to IL-1 receptor (https://aopwiki.org/events/1700)

Short Name: Inhibition of IL-1 binding to IL-1 receptor

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:277 - Inhibition of IL-1 binding to IL-1 receptor leading to increased susceptibility to infection (https://aopwiki.org/aops/277)	MolecularInitiatingEvent

Stressors

Name
IL-1 receptor antagonist IL-1Ra (Anakinra)
anti-IL-1b antibody (Canakinumab)
soluble IL-1R (Rilonacept)

Biological Context

Level of Biological Organization
Molecular

Cell term

Cell term
macrophage

Organ term

Organ term
immune system

Evidence for Perturbation by Stressor

Overview for Molecular Initiating Event

IL-1 is known to mediates autoinflammatory syndrome, such as cryopyrin-associated periodic syndrome, neonatal-onset multisystem inflammatory disease and familial Mediterranean fever. The stressors of this MIE, such as anakinra, canakinumab, and rilonacept have been already used to treat these autoinflammatory syndrome associated with overactivation of IL-1 signaling (Quartier, 2011).

Domain of Applicability

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
Homo sapiens	Homo sapiens	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=9606)
Mus musculus	Mus musculus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10090)
Rattus norvegicus	Rattus norvegicus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10116)

Life Stage Applicability

Life Stage	Evidence
All life stages	High

Sex Applicability

Sex	Evidence
Unspecific	High

Although sex differences in immune responses are well known (Klein and Flanagan, 2016), there is no reports regarding the sex difference in IL-1 production, IL-1 function or susceptibility to infection as adverse effect of IL-1 blocking agent. Again, age-dependent difference in IL-1 signaling is not known.

The IL1B gene is conserved in chimpanzee, rhesus monkey, dog, cow, mouse, rat, and frog (https://www.ncbi.nlm.nih.gov/homologene/481 (https://www.ncbi.nlm.nih.gov/homologene/481)), and the Myd88 gene is conserved in human, chimpanzee, rhesus monkey, dog, cow, rat, chicken, zebrafish, mosquito, and frog (https://www.ncbi.nlm.nih.gov/homologene?Db=homologene&Cmd=Retrieve&list_uids=1849 (https://www.ncbi.nlm.nih.gov/homologene?Db=homologene&Cmd=Retrieve&list_uids=1849)).

These data suggest that the proposed AOP regarding inhibition of IL-1 signaling is not dependent on life stage, sex, age or species.

Key Event Description

IL-1α and IL-1β independently bind the type I IL-1 receptor (IL-1R1), which is ubiquitously expressed. IL-1Ra binds IL-1R but does not initiate IL-1 signal transduction (Dripps et al., 1991). Recombinant IL-1Ra (anakinra) is fully active in blocking the IL-1R1, and therefore, the biological activities of IL-1α and IL-1β. The binding of IL-1α and IL-1β to IL-1R1 can be suppressed by soluble IL-1R like rilonacept (Kapur and Bonk, 2009). The binding of IL-1β to IL-1R1 can be inhibited by anti-IL-1β antibody (anti-IL-1β antibody) (Church and McDermott, 2009).

How it is Measured or Detected

1. Competitive inhibition binding experiments using ^{125}I-IL-1a to type I IL-1R present on EL4 thymoma cells, 3T3 fibroblasts, hepatocytes, and Chinese hamster ovary cells expressing recombinant mouse type I IL-1R (McIntyre et al., 1991; Shuck et al., 1991).
2. Measure the ability of the reagent to neutralize the bioactivity of human IL-1β on primary human fibroblasts in vitro(Alten et al., 2008)

References

Alten, R., Gram, H., Joosten, L.A., et al., 2008. The human anti-IL-1 beta monoclonal antibody ACZ885 is effective in joint inflammation models in mice and in a proof-of-concept study in patients with rheumatoid arthritis. Arthritis Res Ther 10, R67.

Church, L.D., McDermott, M.F., 2009. Canakinumab, a fully-human mAb against IL-1beta for the potential treatment of inflammatory disorders. Curr Opin Mol Ther 11, 81-89.

Dripps, D.J., Brandhuber, B.J., Thompson, R.C., et al., 1991. Interleukin-1 (IL-1) receptor antagonist binds to the 80-kDa IL-1 receptor but does not initiate IL-1 signal transduction. J Biol Chem 266, 10331-10336.

Kapur, S., Bonk, M.E., 2009. Rilonacept (arcalyst), an interleukin-1 trap for the treatment of cryopyrin-associated periodic syndromes. P t 34, 138-141.

Klein, S.L., Flanagan, K.L., 2016. Sex differences in immune responses. Nat Rev Immunol 16, 626-638.

McIntyre, K.W., Stepan, G.J., Kolinsky, K.D., et al., 1991. Inhibition of interleukin 1 (IL-1) binding and bioactivity in vitro and modulation of acute inflammation in vivo by IL-1 receptor antagonist and anti-IL-1 receptor monoclonal antibody. J Exp Med 173, 931-939.

Quartier, P., 2011. Interleukin-1 antagonists in the treatment of autoinflammatory syndromes, including cryopyrin-associated periodic syndrome. Open Access Rheumatol 3, 9-18.

List of Key Events in the AOP

Event: 202: Inhibition, Nuclear factor kappa B (NF-kB) (https://aopwiki.org/events/202)

Short Name: Inhibition, Nuclear factor kappa B (NF-kB)

Key Event Component

Process	Object	Action
I-kappaB kinase/NF-kappaB signaling	transcription factor NF-kappa-B subunit	decreased

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:14 - Glucocorticoid Receptor Activation Leading to Increased Disease Susceptibility (https://aopwiki.org/aops/14)	KeyEvent
Aop:278 - IKK complex inhibition leading to liver injury (https://aopwiki.org/aops/278)	KeyEvent
Aop:277 - Inhibition of IL-1 binding to IL-1 receptor leading to increased susceptibility to infection (https://aopwiki.org/aops/277)	KeyEvent

Stressors

Name
IL-1 receptor antagonist IL-1Ra (Anakinra)
anti-IL-1b antibody (Canakinumab)
soluble IL-1R (Rilonacept)

Biological Context

Level of Biological Organization
Molecular

Cell term

Cell term
macrophage

Organ term

Organ term
immune system

Domain of Applicability

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
Homo sapiens	Homo sapiens	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=9606)
Mus musculus	Mus musculus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10090)
Rattus norvegicus	Rattus norvegicus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10116)

Life Stage Applicability

Life Stage	Evidence
All life stages	High

Sex Applicability

Sex	Evidence
Unspecific	High

The binding of sex steroids to their respective steroid receptors directly influences NF-κB signaling, resulting in differential production of cytokines and chemokines (McKay and Cidlowski, 1999; Pernis, 2007). 17b-estradiol regulates pro-inflammatory responses that are transcriptionally mediated by NF-κB through a negative feedback and/or transrepressive interaction with NF-κB (Straub, 2007). Progesterone suppresses innate immune responses and NF-κB signal transduction reviewed by Klein et al. (Klein and Flanagan, 2016). Androgen-receptor signaling antagonises transcriptional factors NF-κB(McKay and Cidlowski, 1999).

Key Event Description

The NF-kB pathway consists of a series of events where the transcription factors of the NF-kB family play the key role. The NF-kB pathway can be activated by a range of stimuli, including TNF receptor activation by TNF-a, or IL-1R1 activation by IL-1a or b. Upon pathway activation, the IKK complex will be phosphorylated, which in turn phosphorylates IkBa. This NF-kB inhibitor will be K48-linked ubiquitinated and degradated, allowing NF-kB to translocate to the nucleus. There, this transcription factor can express pro-inflammatory and anti-apoptotic genes. (Frederiksson 2012). (Gupta et al. 2010).(Huppelschoten 2017).(Liu et al. 2017). Therefore, inhibition of IL-1R1 activation suppresses activation of NF-κB.

How it is Measured or Detected

NF-kB transcriptional activity: Beta lactamase reporter gene assay (Miller et al. 2010). NF-kB transcription: Lentiviral NF-kB GFP reporter with flow cytometry (Moujalled et al. 2012)

NF-κB translocation: RelA-GFP reporter assay (Frederiksson 2012) (Huppelschoten 2017)

IκB phosphorylation: Western blotting (Miller et al. 2010)

NF-κB p65 (Total/Phospho) ELISA

ELISA for IL-6, IL-8, and Cox

References

Frederiksson, L., 2012. *TNFalpha-signaling in drug induced liver injury*. University of Leiden.

Gupta, S.C. et al., 2010. Inhibiting NF-??B activation by small molecules as a therapeutic strategy. *Biochimica et Biophysica Acta - Gene Regulatory Mechanisms*, 1799(10–12), pp.775–787. Available at: http://dx.doi.org/10.1016/j.bbagrm.2010.05.004.

Huppelschoten, S., 2017. *Dynamics of TNFalpha signaling and drug-related liver toxicity*. Leiden University.

Klein, S.L., Flanagan, K.L., 2016. Sex differences in immune responses. Nat Rev Immunol 16, 626-638.

Liu, T. et al., 2017. NF-κB signaling in inflammation. *Signal Transduction and Targeted Therapy*, 2(March), p.17023. Available at: http://www.nature.com/articles/sigtrans201723.

McKay, L.I., Cidlowski, J.A., 1999. Molecular control of immune/inflammatory responses: interactions between nuclear factor-kappa B and steroid receptor-signaling pathways. Endocr Rev 20, 435-459.

Miller, S.C. et al., 2010. Identification of known drugs that act as inhibitors of NF-κB signaling and their mechanism of action. *Biochemical Pharmacology*, 79(9), pp.1272–1280. Available at: http://dx.doi.org/10.1016/j.bcp.2009.12.021.

Moujalled, D.M. et al., 2012. In mouse embryonic fibroblasts, neither caspase-8 nor cellular FLICE-inhibitory protein (FLIP) is necessary for TNF to activate NF-?B, but caspase-8 is required for TNF to cause cell death, and induction of FLIP by NF-?B is required to prevent it. *Cell Death and Differentiation*, 19(5), pp.808–815. Available at: http://dx.doi.org/10.1038/cdd.2011.151.

Pernis, A.B., 2007. Estrogen and CD4+ T cells. Curr Opin Rheumatol 19, 414-420.

Straub, R.H., 2007. The complex role of estrogens in inflammation. Endocr Rev 28, 521-574.

Event: 1702: Suppression of T cell activation (https://aopwiki.org/events/1702)

Short Name: Suppression of T cell activation

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:277 - Inhibition of IL-1 binding to IL-1 receptor leading to increased susceptibility to infection (https://aopwiki.org/aops/277)	KeyEvent

Biological Context

Level of Biological Organization
Cellular

Cell term

Cell term
T cell

Organ term

Organ term
immune system

Domain of Applicability

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
Homo sapiens	Homo sapiens	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=9606)
Mus musculus	Mus musculus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10090)
Rattus norvegicus	Rattus norvegicus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10116)

Life Stage Applicability

Life Stage	Evidence
All life stages	High

Sex Applicability

Sex	Evidence
Unspecific	High

Key Event Description

T cells are key orchestrators of the response against pathogens and are also fundamental in maintaining self-tolerance. A number of clinically important conditions have been described in which T-cell functions are altered, as in AIDS or upon immunosuppression after application of various immunosuppressive drugs to treat autoimmune disorders or allogeneic graft rejection. T-cell progenitors differentiate in the thymus into immature T cells that acquire the expression of the T-cell receptor (TCR), which recognizes antigen peptides from pathogens presented along with major histocompatibility complex (MHC). In addition to the TCR, T cells are characterized by expression of the co-receptor molecules CD4 and CD8 on their cell surface. CD4+ T cells, also called T helper (Th) cells, recognize antigen/MHC-II complexes on antigen presenting cells (APCs) and coordinate the activation of other immune cells including B cells, macrophages, etc.

Therefore, CD4+ T cells are crucial for coordination of the immune response and for the elimination of invading pathogens. On the other hand, CD8+ T cells, referred to as T cytotoxic cells, recognize antigen/MHC-I complexes and are responsible for the killing of pathogen-infected cells.

T-cell activation and differentiation depends on antigen presenting cells (APCs) such as dendritic cells (DCs), macrophages and B cells. depending on the insult affecting a given tissue. Different subsets of DCs can be generated that in turn are able to coordinate the differentiation of a particular Th subset. To date, the following Th subsets have been described: Th1, Th2, Th9, Th17, Th22, Tfh (follicular helper T cells), Tr1 (type 1regulatory T cells) and Treg (regulatory T cells), each possessing a specific function in the elimination of pathogens. (reviewed by Simeoni et al. (Simeoni et al., 2016))

Although CD4 T cells are able to commit to Th1, Th2 and Th17 lineages in the absence of IL-1R signaling at steady state, these committed CD4 T cells are unable to effectively secrete their cytokines upon TCR ligation. Namely, IL-1 is indispensable for CD4 T cell effector function. (Lin et al, 2015)

Moreover, since full activation of B cells and antibody production and class switch depends on T cell help. The impaired activation of T cells leads to impaired B cell activation and antibody production (reviewed by Mok (Mok, 2010)).

How it is Measured or Detected

T cell activation can be evaluated by measuring IL-2 production by ELISA or T cell proliferation by incorporation of the analysis of CFSE labeled T cells or [^{3}H]thymidine incorporation.

References

Lin, D., Lei, L., Zhang, Y., et al., 2015. Secreted IL-1alpha promotes T-cell activation and expansion of CD11b(+) Gr1(+) cells in carbon tetrachloride-induced liver injury in mice. Eur J Immunol 45, 2084-2098.

Mok, M.Y., 2010. The immunological basis of B-cell therapy in systemic lupus erythematosus. Int J Rheum Dis 13, 3-11.

Simeoni, L., Thurm, C., Kritikos, A., et al., 2016. Redox homeostasis, T cells and kidney diseases: three faces in the dark. Clin Kidney J 9, 1-10.

List of Adverse Outcomes in this AOP

Event: 986: Increase, Increased susceptibility to infection (https://aopwiki.org/events/986)

Short Name: Increase, Increased susceptibility to infection

AOPs Including This Key Event

AOP ID and Name	Event Type
Aop:277 - Inhibition of IL-1 binding to IL-1 receptor leading to increased susceptibility to infection (https://aopwiki.org/aops/277)	AdverseOutcome

Stressors

Name
IL-1 receptor antagonist IL-1Ra (Anakinra)
anti-IL-1b antibody (Canakinumab)
soluble IL-1R (Rilonacept)

Biological Context

Level of Biological Organization
Individual

Domain of Applicability

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
Homo sapiens	Homo sapiens	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=9606)
Mus musculus	Mus musculus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10090)
Rattus norvegicus	Rattus norvegicus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10116)

Life Stage Applicability

Life Stage	Evidence
All life stages	High

Sex Applicability

Sex	Evidence
Unspecific	High

The increased susceptibility to infection caused by IL-1RA or anti-IL-1 antibody has been reported in both humans and mice. (Fleischmann et al., 2003; De Benedetti et al., 2018; Hirsch et al., 1996)

Key Event Description

The protection of host against microbial infection depends on both innate and acquired immunity. In particular, both T cell and antibody production by B cells play a principal role.

How it is Measured or Detected

By comparison of the incidence of infection between individuals exposed to stressors and non-exposed individuals.

Regulatory Significance of the AO

It is crucial to notice chemicals that potentially induce immunosuppression leading to increased susceptibility to infection in public health.

References

De Benedetti, F., Gattorno, M., Anton, J., et al., 2018. Canakinumab for the Treatment of Autoinflammatory Recurrent Fever Syndromes. N Engl J Med 378, 1908-1919.

Fleischmann, R.M., Schechtman, J., Bennett, R., et al., 2003. Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1ra), in patients with rheumatoid arthritis: A large, international, multicenter, placebo-controlled trial. Arthritis Rheum 48, 927-934.

Hirsch, E., Irikura, V.M., Paul, S.M., et al., 1996. Functions of interleukin 1 receptor antagonist in gene knockout and overproducing mice. Proc Natl Acad Sci U S A 93, 11008-11013.

Appendix 2

List of Key Event Relationships in the AOP

List of Adjacent Key Event Relationships

Relationship: 2002: Inhibition of IL-1 binding to IL-1 receptor leads to Inhibition, Nuclear factor kappa B (NF-kB) (https://aopwiki.org/relationships/2002)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
Inhibition of IL-1 binding to IL-1 receptor leading to increased susceptibility to infection (https://aopwiki.org/aops/277)	**adjacent**	**High**	**Not Specified**

Evidence Supporting Applicability of this Relationship

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
Homo sapiens	Homo sapiens	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=9606)
Mus musculus	Mus musculus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10090)
Rattus norvegicus	Rattus norvegicus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10116)

Life Stage Applicability

Life Stage	Evidence
All life stages	High

Sex Applicability

Sex	Evidence
Unspecific	High

Key Event Relationship Description

The signaling cascade after IL-1R activation leads to NF-kB activation via the interaction with various signaling molecules.

Evidence Supporting this KER

Biological Plausibility

The initial step in IL-1 signal transduction is a ligand-induced conformational change in the first extracellular domain of the IL-1RI that facilitates recruitment of IL-1RacP (Cavalli et al., 2015). Through conserved cytosolic regions called Toll- and IL-1R–like (TIR) domains (Radons et al., 2003), the trimeric complex rapidly assembles two intracellular signaling proteins, myeloid differentiation primary response gene 88 (MyD88) and interleukin-1 receptor–activated protein kinase (IRAK) 4 (Brikos et al., 2007; Li et al., 2002). IL-1, IL-1RI, IL-RAcP, MyD88, and IRAK4 form a stable IL-1–induced first signaling module. The binding of MyD88 triggers a cascade of kinases that produce a strong pro-inflammatory signal leading to activation of NF-κB. (Brikos et al., 2007)(Weber et al., 2010)

Empirical Evidence

Mice lacking MyD88 or IRAK4 show severe defects in IL-1 signaling (Adachi et al., 1998; Medzhitov et al., 1998; Suzuki et al., 2002). Similarly, humans with mutations in the IRAK4 gene have defects in IL-1RI and Toll-like receptor (TLR) signaling (Picard et al., 2003).

References

Adachi, O., Kawai, T., Takeda, K., et al., 1998. Targeted disruption of the MyD88 gene results in loss of IL-1- and IL-18-mediated function. Immunity 9, 143-150.

Brikos, C., Wait, R., Begum, S., et al., 2007. Mass spectrometric analysis of the endogenous type I interleukin-1 (IL-1) receptor signaling complex formed after IL-1 binding identifies IL-1RAcP, MyD88, and IRAK-4 as the stable components. Mol Cell Proteomics 6, 1551-1559.

Cavalli, G., Franchini, S., Aiello, P., et al., 2015. Efficacy and safety of biological agents in adult-onset Still's disease. Scand J Rheumatol 44, 309-314.

Li, W.D., Ran, G.X., Teng, H.L., et al., 2002. Dynamic effects of leflunomide on IL-1, IL-6, and TNF-alpha activity produced from peritoneal macrophages in adjuvant arthritis rats. Acta Pharmacol Sin 23, 752-756.

Medzhitov, R., Preston-Hurlburt, P., Kopp, E., et al., 1998. MyD88 is an adaptor protein in the hToll/IL-1 receptor family signaling pathways. Mol Cell 2, 253-258.

Picard, C., Puel, A., Bonnet, M., et al., 2003. Pyogenic bacterial infections in humans with IRAK-4 deficiency. Science 299, 2076-2079.

Radons, J., Dove, S., Neumann, D., et al., 2003. The interleukin 1 (IL-1) receptor accessory protein Toll/IL-1 receptor domain: analysis of putative interaction sites in vitro mutagenesis and molecular modeling. J Biol Chem 278, 49145-49153.

Suzuki, N., Suzuki, S., Duncan, G.S., et al., 2002. Severe impairment of interleukin-1 and Toll-like receptor signalling in mice lacking IRAK-4. Nature 416, 750-756.

Weber, A., Wasiliew, P., Kracht, M., 2010. Interleukin-1 (IL-1) pathway. Sci Signal 3, cm1.

Relationship: 2003: Inhibition, Nuclear factor kappa B (NF-kB) leads to Suppression of T cell activation (https://aopwiki.org/relationships/2003)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
Inhibition of IL-1 binding to IL-1 receptor leading to increased susceptibility to infection (https://aopwiki.org/aops/277)	**adjacent**	**High**	**Not Specified**

Evidence Supporting Applicability of this Relationship

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
Homo sapiens	Homo sapiens	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=9606)
Mus musculus	Mus musculus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10090)
Rattus norvegicus	Rattus norvegicus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10116)

Life Stage Applicability

Life Stage	Evidence
All life stages	High

Sex Applicability

Sex	Evidence
Unspecific	High

Key Event Relationship Description

In T cells, NF-kB can be activated by several pathways of signal transduction. The engagement of the TCR by major histocompatibility complex (MHC) plus antigen initiates downstream CD3 immunotyrosine activation motif (ITAM) phosphorylation by the Src family kinases, FYN and leukocyte C-terminal src kinase (LCK). Phosphorylated CD3 activates the T cell specific tyrosine kinase, zeta-chain associated protein kinase (ZAP-70), which ultimately trigger calcium release and protein kinase (PK)C activation, respectively. Activation of a specific PKC isoform, PKC*u*, connects the above described TCR proximal signaling events to distal events that ultimately lead to NF-*k*B activation. Importantly, PKC*u* activation is also driven by engagement of the T cell co-stimulatory receptor CD28 by B7 ligands on antigen presenting cells (APCs). In addition, the stimulation of T cells by IL-1 activates NF-*k*B as already described before. Once in the nucleus, NF-*k*B governs the transcription of numerous genes involved in T cell survival, proliferation, and effector functions (Paul and Schaefer, 2013).

Evidence Supporting this KER

Biological Plausibility

Although CD4 T cells are able to commit to Th1, Th2 and Th17 lineages in the absence of IL-1R signaling at steady state, these committed CD4 T cells are unable to effectively secrete their cytokines upon TCR ligation. Namely, IL-1 is indispensable for CD4 T cell effector function. (Lin et al, 2015)

Empirical Evidence

Indeed, RelB deficient mice had an impaired cellular immunity, as observed in contact sensitivity reaction (Weih et al., 1995).

Quite a few NF-kB inhibitors have been reported. MG132, bortezomib, curcumin, DHMEQ(Dehydroxymethylepoxyquinomicin), naringin, sorafenib, genistein and parthenolide are some of representatives (Pordanjani and Hosseinimehr, 2016).

Interferon-γ (IFN-γ) production in response to CMV-infected fibroblasts was reduced under the influence of MG132 in a dose-dependent manner. A marked reduction was observed at 0.5 µM. Likewise, CMV-specific cytotoxicity of CD8(+) T cells was decreased in the presence of MG132 (Wang et al., 2011).

In vivo MG132 administration to NC/Nga mice with DNFB-induced dermatitis reduced Th17 cells but maintained the level of Th1 cells, resulting in the alleviation of dermatitis lesions by decreasing both serum IgE hyperproduction and mast cell migration (Ohkusu-Tsukada et al., 2018).

Proteasome inhibitor, bortezomib, potently inhibits the growth of adult T-cell leukemia cells both in vivo and in vitro (Satou et al., 2004). Bortezomib inhibits T-cell function versus infective antigenic stimuli in a dose-dependent manner in vitro (Orciuolo et al., 2007).

DHMEQ, a novel nuclear factor-kappaB inhibitor, induces selective depletion of alloreactive or phytohaemagglutinin-stimulated peripheral blood mononuclear cells, decreases production of T helper type 1 cytokines, and blocks maturation of dendritic cells (Nishioka et al., 2008).

Regarding the suppression of NF-kB by impaired IL-1 signaling, it was reported that delayed-type hypersensitivity (DTH) responses were significantly suppressed in IL-1b-deficient and IL-1a/b-deficient mice. Lymph node cells derived from antigen-sensitized IL-1b-deficient and IL-1a/b-deficient mice and IL-1R type I-deficient mice, exhibited reduced proliferative responses against antigen. These data suggest that IL-1b is necessary for the efficient priming of T cells. In addition, CD4+ T cell-derived IL-1 plays an important role in the activation of DCs during the elicitation phase, resulting in the production of TNF, that activate allergen-specific T cells (Nambu et al., 2006).

References

Lin, D., Lei, L., Zhang, Y., et al., 2015. Secreted IL-1alpha promotes T-cell activation and expansion of CD11b(+) Gr1(+) cells in carbon tetrachloride-induced liver injury in mice. Eur J Immunol 45, 2084-2098.

Nambu, A., Nakae, S., Iwakura, Y., 2006. IL-1beta, but not IL-1alpha, is required for antigen-specific T cell activation and the induction of local inflammation in the delayed-type hypersensitivity responses. Int Immunol 18, 701-712.

Nishioka, C., Ikezoe, T., Jing, Y., et al., 2008. DHMEQ, a novel nuclear factor-kappaB inhibitor, induces selective depletion of alloreactive or phytohaemagglutinin-stimulated peripheral blood mononuclear cells, decreases production of T helper type 1 cytokines, and blocks maturation of dendritic cells. Immunology 124, 198-205.

Ohkusu-Tsukada, K., Ito, D., Takahashi, K., 2018. The Role of Proteasome Inhibitor MG132 in 2,4-Dinitrofluorobenzene-Induced Atopic Dermatitis in NC/Nga Mice. Int Arch Allergy Immunol 176, 91-100.

Orciuolo, E., Galimberti, S., Petrini, M., 2007. Bortezomib inhibits T-cell function versus infective antigenic stimuli in a dose-dependent manner in vitro. Leuk Res 31, 1026-1027.

Paul, S., Schaefer, B.C., 2013. A new look at T cell receptor signaling to nuclear factor-kappaB. Trends Immunol 34, 269-281.

Pordanjani, S.M., Hosseinimehr, S.J., 2016. The Role of NF-kB Inhibitors in Cell Response to Radiation. Curr Med Chem 23, 3951-3963.

Satou, Y., Nosaka, K., Koya, Y., et al., 2004. Proteasome inhibitor, bortezomib, potently inhibits the growth of adult T-cell leukemia cells both in vivo and in vitro. Leukemia 18, 1357-1363.

Wang, Y., Sun, B., Volk, H.D., et al., 2011. Comparative study of the influence of proteasome inhibitor MG132 and ganciclovir on the cytomegalovirus-specific CD8(+) T-cell immune response. Viral Immunol 24, 455-461.

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Relationship: 2004: Suppression of T cell activation leads to Increase, Increased susceptibility to infection (https://aopwiki.org/relationships/2004)

AOPs Referencing Relationship

AOP Name	Adjacency	Weight of Evidence	Quantitative Understanding
Inhibition of IL-1 binding to IL-1 receptor leading to increased susceptibility to infection (https://aopwiki.org/aops/277)	**adjacent**	**High**	**Not Specified**

Evidence Supporting Applicability of this Relationship

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
Homo sapiens	Homo sapiens	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=9606)
Mus musculus	Mus musculus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10090)
Rattus norvegicus	Rattus norvegicus	High	NCBI (http://www.ncbi.nlm.nih.gov/Taxonomy/Browser/wwwtax.cgi?mode=Info&id=10116)

Life Stage Applicability

Life Stage	Evidence
All life stages	High

Sex Applicability

Sex	Evidence
Unspecific	High

Key Event Relationship Description

Normal T cell and B cell function is indispensable for host defense mechanism.

Evidence Supporting this KER

Biological Plausibility

To protect the infection from different pathogens, different types of immune response depending on the pathogens are required.

1). Type 1 immunity drives resistance to viruses and intracellular bacteria, such as *Listeria monocytogenes*, *Salmonella* spp. and *Mycobacteria* spp., as well as to intracellular protozoan parasites such as *Leishmania* spp. The T helper 1 (T_H1) signature cytokine interferon-γ (IFNγ) has a central role in triggering cytotoxic mechanisms including macrophage polarization towards an antimicrobial response associated with the production of high levels of reactive oxygen species (ROS) and reactive nitrogen species (RNS), activation of $CD8^+$ cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells to kill infected cells via the perforin and/or granzyme B-dependent lytic pathway or via the ligation of surface death receptors; and B cell activation towards the production of cytolytic antibodies that target infected cells for complement and Fc receptor-mediated cellular cytotoxicity.

2) Resistance to extracellular metazoan parasites and other large parasites is mediated and/or involves type 2 immunit. Pathogen neutralization is achieved via different mechanisms controlled by T_H2 signature cytokines, including interleukin-4 (IL-4), IL-5 and IL-13, and by additional type 2 cytokines such as thymic stromal lymphopoietin (TSLP), IL-25 or IL-33, secreted by damaged cell. T_H2 signature cytokines drive B cell activation towards the production of high-affinity pathogen-specific IgG1 and IgE antibodies that function via Fc-dependent mechanisms to trigger the activation of eosinophils, mast cells and basophils, expelling pathogens across epithelia.

3) T_H17 immunity confers resistance to extracellular bacteria such as *Klebsiella pneumoniae, Escherichia coli, Citrobacter rodentium, Bordetella pertussis, Porphyromonas gingivalis* and *Streptococcus pneumoniae,* and also to fungi such as *Candida albicans, Coccidioides posadasii, Histoplasma capsulatum* and *Blastomyces dermatitidis*. Activation of T_H17 cells by cognate T cell receptor (TCR–MHC class II interactions and activation of group 3 innate lymphoid cells (ILC3s) via engagement of IL-1 receptor (IL-1R) by IL-1β secreted from damaged cells lead to the recruitment and activation of neutrophils. T_H17 immunopathology is driven to a large extent by products of neutrophil activation, such as ROS and elastase (reviewed by Soares et al. (Soares et al., 2017)).

Based on these evidences, the insufficient T cell or B cell function causes impaired resistance to infection.

Empirical Evidence
Recipients of liver transplants treated with FK506 that strongly suppress T cell function were found to have suffered from bacterial, viral, and fungal infections (Alessiani et al. 1991, Fung et al. 1991). Complications from infection as a side-effect of administering FK506 was found to be similar to that of cyclosporin A (Ekberg et al. 2007).

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