AOP ID and Title:

SNAPSHOT

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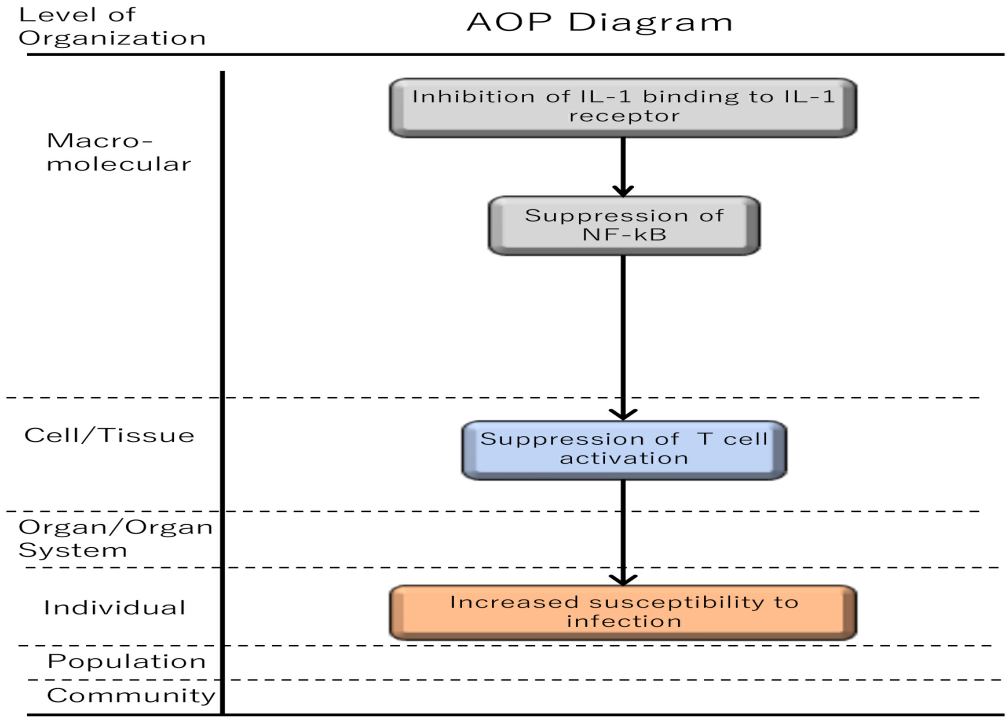
AOP 277: Inhibition of IL-1 binding to IL-1 receptor leading to increased susceptibility to infection

Short Title: IL-1 inhibition

Graphical Representation



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Status

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Open for citation & comment			

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
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).

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

Table summarize the empirical support obtained from the experiment using several inhibitor or gene targeting mice.

Quantitative understanding

MG132

Wang et al. 2011

Nishioka et al. 2008

Quantitative Consideration

So far, we could not find appropriate reports that speak the quantitative aspects of three KERs.

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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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

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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

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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.

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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.

Weih, F., Carrasco, D., Durham, S.K., et al., 1995. Multiorgan inflammation and hematopoietic abnormalities in mice with a targeted disruption of RelB, a member of the NF-kappa B/Rel family. Cell 80, 331-340.

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)

Term	Scientific Term	Evidence	Links
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).

References

Alessiani, M., Kusne, S., Martin, M., et al., 1991. Infections in adult liver transplant patients under FK 506 immunosuppression. Transplant Proc 23, 1501-1503.

Ekberg, H., Grinyo, J., Nashan, B., et al., 2007. Cyclosporine sparing with mycophenolate mofetil, daclizumab and corticosteroids in renal allograft recipients: the CAESAR Study. Am J Transplant 7, 560-570

Fung, J.J., Todo, S., Tzakis, A., et al., 1991. Current status of FK 506 in liver transplantation. Transplant Proc 23, 1902-1905.

Soares, M.P., Teixeira, L., Moita, L.F., 2017. Disease tolerance and immunity in host protection against infection. Nat Rev Immunol 17, 83-96.