AOP ID and Title:

SNAPSHOT

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AOP 154: The Adverse Outcome Pathway on binding of FK506-binding protein 12 (FKBP12) by calcineurin inhibitors leading to immunosuppression

Short Title: Immunosuppression

Authors

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Status

Author status	OECD status	OECD project	SAAOP status
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Abstract

FKBP12 is a receptor protein that binds with FK506 (Tacrolimus). FK506 is an immunosuppressant having a macrolide structure, that was first discovered in 1984 as a fermentation product of Streptomyces tsukubaensis. FK506 is similar to cyclosporin A or rapamycin in its inhibition of calcineurin activity, and it is used for its immunosuppressant effects after kidney, liver, and other organ transplants to lower the risk of organ rejection; after bone-marrow transplants to lower the risk of graft-versus-host disease (GVHD); or in the treatment of rheumatoid arthritis. It is also used in ointments for the treatment of atopic dermatitis. This case study describes the effects of FK506 on immune cells as a result of the formation of FKBP12-FK506 complexes. FKBP12 is expressed in T-cells, B-cells, Langerhans cells, and mast cells, and the pathway is complicated. In order to simplify the pathway of FKBP12-FK506, the AOP focus on the pathway through FKBP12 expressing on T cells.

Summary of the AOP

Stressors

Name	Evidence
Tacrolimus	

Molecular Initiating Event

Title	Short name
Formation, Binding of FK506 to FKBP12	Formation, Binding of FK506 to FKBP12

1201: Formation, Binding of FK506 to FKBP12

Short Name: Formation, Binding of FK506 to FKBP12

AOPs Including This Key Event

AOP ID and Name	Event Type
154: The Adverse Outcome Pathway on binding of FK506-binding protein 12 (FKBP12) by calcineurin inhibitors leading to immunosuppression	MolecularInitiatingEvent

Biological Organization

Level of Biological Organization
Molecular

FKBP is found in a wide variety of organisms, from prokaryotes to multicellular organisms (Siekierka et al. 1989a). Multiple subfamilies of FKBP have been reported, with at least eight types having been found in mammals. FKBP12 is reported to be expressed in B-cells, Langerhans cells and mast cells as well as T cells of mammalian species including humans and mice.

How this Key Event Works

FKBP12 is a 12-kDa protein localized in cytoplasm and has been isolated from Jurkat T-cells as a receptor that binds with the calcineurin inhibitor FK506 (Bram et al. 1993). FKBP12 has an FK506-binding domain (FKBD) that comprises 108 amino acids, and it functions as an accessory molecule to classes of intracellular calcium channels, namely IP3 receptors and ryanodine receptors (RyRs) (Schreiber and Crabtree 1992, Cameron et al. 1997). In addition, FKBP12 binds to transforming growth factor-β receptor 1 (TGF-βR1) and acts as a natural ligand to TGF-β.

While FKBP12, FKBP12.6, FKBP13, and FKBP52 are all part of the FK506-binding FKBP family, FKBP12 has a significant involvement in the mechanism of action for FK506-induced immunosuppression (Siekierka et al. 1989a, Kang et al. 2008). FKBP12 demonstrates peptidylprolyl cis-trans isomerase (PPIase) activity as well as the ability to inhibit calcineurin activity when forming a complex with FK506. FKBP12.6 shows similar actions,, however, its influences are weaker than those of FKBP12 and its involvement in immunosuppression is not yet clearly understood. In addition to T-cells, FKBP12 is also expressed in B-cells, Langerhans cells, and mast cells (Siekierka et al. 1990, Panhans-Gross et al. 2001, Hultsch et al. 1991).

How it is Measured or Detected

The binding of FK-506 with FKBP12 can simply be detected by ELISA or competitive ELISA. Siekierka et al. (1989a) conducted that purified FK-506 binding protein coated onto the surface of plate wells and the amount of 3H dihydro FK-506 were incubated. In the competitive ELISA, unlabeled FK506 was used as the competitor.

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Key Events

Title	Short name

Binding, Formation, Binding of calcineurin with FK506-FKBP complexes	Binding, Formation, Binding of calcineurin with FK506-FKBP complexes
Inhibition, Interference of NFAT complex formation at the site of nuclear cytokine promoters	Inhibition, Interference of NFAT complex formation at the site of nuclear cytokine promoter
Suppression, Suppression of cytokine production in the presence of T-cell activation	Suppression, Suppression of cytokine production in the presence of T-cell activation
Activation, Hampered NFAT activation and following nuclear localization	Activation, Hampered NFAT activation and following nuclear localization
Suppression, Suppression of production of cytotoxic T-cells	Suppression, Suppression of production of cytotoxic T-cells
Suppression, Suppression of T-cell dependent antibody production	Suppression, Suppression of T-cell dependent antibody production

980: Binding, Formation, Binding of calcineurin with FK506-FKBP complexes

Short Name: Binding, Formation, Binding of calcineurin with FK506-FKBP complexes

AOPs Including This Key Event

AOP ID and Name	Event Type
154: The Adverse Outcome Pathway on binding of FK506-binding protein 12 (FKBP12) by calcineurin inhibitors leading to immunosuppression	KeyEvent

Biological Organization

Level of Biological Organization
Molecular

Calcineurin is broadly distributed in the body including T and B cells, and the structure of CnA and CnB is highly conserved from yeasts to humans. Also highly conserved are the amino acid sequences of the catalytic and regulatory domains of calcineurin A isoforms from different organisms (Kincaid. 1996).

How this Key Event Works

Calcineurin is a heterodimer that comprises a catalytic subunit (CnA), which handles phosphatase activity as well as calmodulin binding, and a Ca-binding regulatory subunit (CnB), which regulates intracellular calcium as well as CnA (Klee et al. 1988, Zhang et al. 1996). CnA, a 59kDa protein, has a serine-threonine phosphatase domain. A FK506-FKBP complex binds directly to CnA in the cell, causing steric hindrance of substrate binding to calcineurin, which inhibits phosphatase activity of calcineurin (Schreiber and Crabtree 1992, Liu et al. 1993, Bierer et al. 1993, Bram et

al. 1993, Rao et al. 1997, Liu et al. 1991).

How it is Measured or Detected

Phosphatase activity can be measured by phosphatase assay. Calcineurin, calmodulin, FK506, and FKBP are incubated together, and then phosphatase activity is measured at various concentrations of FKBP. Kinetic analysis of FKBP12 concentration-dependent phosphatase activity and calculation of Ki (inhibition of calcineurin by the FKBP12-FK506 complex are conducted. (Bram et al. 1993).

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979: Inhibition, Interference of NFAT complex formation at the site of nuclear cytokine promoters

Short Name: Inhibition, Interference of NFAT complex formation at the site of nuclear cytokine promoter

AOPs Including This Key Event

AOP ID and Name	Event Type

154: The Adverse Outcome Pathway on binding of FK506-binding protein 12 (FKBP12) by calcineurin inhibitors leading to immunosuppression	KeyEvent

Biological Organization

Level of Biological Organization
Molecular

FK506-induced interference with NFAT/AP-1 complex formation at the promoter site of the IL-2 gene might be in common among mammalian T cells including humans and rodents. Synthesis of IL-3, IL-4, IL-5 and GM-CSF by T cells might also be inhibited with FK506 by similar mechanisms as those of IL-2.

How this Key Event Works

Activated NFAT that has localized to the nucleus binds cooperatively at the site of the Interleukin-2 (IL-2) promoter with activator protein AP-1, which is a heterodimer comprising a Fos and a Jun protein (Schreiber and Crabtree 1992, Jain et al. 1992), thereby inducing transcription of IL-2 (Jain et al. 1993). FK506, by interfering with NFAT nuclear localization, hinders the formation of the functional NFAT complexes necessary to binding at the site of IL-2 promoters (Flanagan et al. 1991). NFAT also binds at the site of IL-5 and granulocyte-macrophage colony stimulating factor (GM-CSF) promoters (Foletta et al. 1998). Additionally, NFAT binds cooperatively at the site of IL-2, IL-4, and TNF promoters as well as at the site of IL-3 and IL-4 enhancers with avian musculoaponeurotic fibrosarcoma oncogene homolog (MAF), early growth response 1 (EGR1), early growth response 4 (EGR4), interferon-regulatory factor 4 (IRF4), octamer-binding transcription factor (OCT), and other transcriptional partners to induce transcription of a variety of cytokines (Macian 2005).

How it is Measured or Detected

Inhibition of generation of NFAT/AP-1 complex can be detected by gel shift assay. Jain et al. (1992) conducted that nuclear extracts from unstimulated or stimulated Ar-5 T cells were applied to the gel shift assays with radio-labelled murine NFAT oligonucleotide. Suppression of mRNA levels of cytokines can be measured by RNase protection assay in vitro and ex vivo.

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981: Suppression, Suppression of cytokine production in the presence of T-cell activation

Short Name: Suppression, Suppression of cytokine production in the presence of T-cell activation

AOPs Including This Key Event

AOP ID and Name	Event Type
154: The Adverse Outcome Pathway on binding of FK506-binding protein 12 (FKBP12) by calcineurin inhibitors leading to immunosuppression	KeyEvent

Biological Organization

Level of Biological Organization
Cellular

In human peripheral blood mononuclear cells (PBMC), FK506 suppresses T-cell activation–induced production of IL-1β and TNF-α (Sakuma et al. 2000). It also suppresses production of cytokines such as IL-2, IL-3, IL-4, IL-5, IFN-γ, and GM-CSF, which is induced by CD2/CD3 or CD3/CD26 stimulation, at least as if not more strongly than steroids in human PBMC (Sakuma et al. 2001a). Moreover, it suppresses production of IL-2, IL-3, IL-4, IL-5, IL-6, IL-10, TNF-α, IFN-γ, and GM-CSF, which is induced by CD3/PMA stimulation in human PBMC (Dumont et al. 1998).

How this Key Event Works

Effects on T cell

NFAT/AP-1 complex might bind to the promoter or enhancer regions of the cytokine genes in T cells; therefore, productions of IL-2, IL-3, IL-4, IL-5, GM-CSF and other T-cell-derived cytokines after activation of T cells were reported to be suppressed by FK506 treatment in vitro and in vivo as the result of hindered nuclear translocation of NFAT. FK506 inhibited both IL-2 and IFN-γ mRNA expression in anti-CD3/PMA-activated cells. FK506 had suppressed the expression of IL-4 mRNA in the presence of either anti-CD3or PMA-activated cells after 5h of

culture (Dumont et al. 1998).

Effects on B cell

In B-cells, stimulus passes through the B-cell receptor (BCR), increasing the concentration of calcium in the B-cell, leading to NFAT nuclear localization in the same manner as T-cells (Bhattacharyya et al.2011). Inhibition of calcineurin phosphatase activation by FK506 suppresses induction of TNF-α following anti-Ig or anti-CD40 antibody stimulation (Goldfeld et al. 1992, Goldfeld et al. 1994, Boussiotis et al. 1994).

Effects on dendritic cells

FK506 suppresses expression of IL-2R (CD25) and costimulatory molecules CD80 (B7.1)/CD40 in Langerhans cells.

Effects on natural killer (NK) cells and NKT cells

In human NK cells, FK506 suppresses IL-2 responsive proliferation and cytokine production as well as lowers cytotoxicity directed toward K562 tumor cells (Kim et al. 2010). FK506 suppresses IL-2 production of NKT cell line DN32.D3 induced by stimulus from phorbol 12-myristate 13-acetate (PMA)/calcium-ionophore (van Dieren et al. 2010).

How it is Measured or Detected

Suppression of mRNA levels of cytokines can be measured by RNase protection assay in vitro and ex vivo. Inhibition of IL-2, IL-3, IL-4, IL-5, GM-CSF, IFN-γ, TNF-α production and secretion are measurable by sandwich ELISA.

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1202: Activation, Hampered NFAT activation and following nuclear localization

Short Name: Activation, Hampered NFAT activation and following nuclear localization

AOPs Including This Key Event

AOP ID and Name	Event Type
154: The Adverse Outcome Pathway on binding of FK506-binding protein 12 (FKBP12) by calcineurin inhibitors leading to immunosuppression	KeyEvent

Biological Organization

Level of Biological Organization
Molecular

NFAT expresses in B cells, mast cells, neutrophil granulocytes, dendritic cells, macrophages, and natural killer cells as well as T cells from mammalian species including humans and rodents (Rao et al. 1997).

How this Key Event Works

The nuclear factor of activated T cells (NFAT) is a substrate of calcineurin (Rao et al. 1997). A NFAT has an N-terminal with a plurality of SP motifs rich in serine and proline, which are controlled by means of phosphorylation and dephosphorylation. There is a nuclear localization signal (NLS) held between these SP regions as well as a nuclear export signal (NES) in the N-terminal adjacent to the SP motifs (Beals et al. 1997, Zhu and McKeon 1999, Serfling et al. 2000). SP motifs ordinarily phosphorylate, which covers the NLS and leaves NES exposed, so NFAT localizes in cytoplasm. When calcineurin activates through stimulus from outside the cell, it binds directly to the N-terminal of NFAT in cytoplasm, after which SP motifs dephosphorylate to expose NLS and cover NES, thereby promoting nuclear localization of NFAT (Matsuda and Koyasu 2000, Zhu and McKeon 1999). When T-cell activation takes place, T-cell receptor (TCR)-mediated stimulus increases the intracellular concentration of calcium and activates CnB, which subsequently induces CnA phosphatase activation, leading to dephosphorylation of NFAT followed by nuclear localization. FK506-FKBP complexes inhibit calcineurin phosphatase activation, thereby interfering with NFAT nuclear localization. In B cells, extracellular stimulus passes through the B-cell receptor (BCR) to increase the intracellular concentration of calcium, leading to NFAT nuclear localization in the same manner as T-cells (Bhattacharyya et al.2011).

How it is Measured or Detected

Inhibition of translocation of NFAT to the nucleus is detected by gel mobility shift assay using nuclear extracts and/or cytoplasmic extracts (Flanagan et al. 1991).

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1203: Suppression, Suppression of production of cytotoxic T-cells

Short Name: Suppression, Suppression of production of cytotoxic T-cells

AOPs Including This Key Event

AOP ID and Name	Event Type
154: The Adverse Outcome Pathway on binding of FK506-binding protein 12 (FKBP12) by calcineurin inhibitors leading to immunosuppression	KeyEvent

Biological Organization

Level of Biological Organization
Tissue

FK-506 suppresses production of IL-2, IL-3, and IFN-γ in mouse MLR (Kino et al. 1987b). It also suppresses production of cytotoxic T lymphocytes (CTL) (Kino et al. 1987a).In human MLR, as well, FK-506 has been reported to suppress IL-2 production and expression of IL-2 receptors (Kino et al. 1987a).

How this Key Event Works

FK506-FKBP complex interferes with NFAT nuclear localization to suppress the production of multiple classes of cytokines in T cells including L-2, which develops cytotoxic T cells as well as other actions. The suppressive effect of FK506 on mouse MLR, which has been thought to be the representative of IL-2 dependent T cell growth (Kino et al. 1987b). Main mode of actions for suppression of MLR with FK506 deems to result from the decreased production of cytokines including IL-2

How it is Measured or Detected

Suppression of cytotoxic T lymphocyte (CTL) activity can be measured by 51Cr release CTL assay. Suppression of MLR is also measurable by Incorporation of radioisotope (3H-thymidine).

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1204: Suppression, Suppression of T-cell dependent antibody production

Short Name: Suppression, Suppression of T-cell dependent antibody production

AOPs Including This Key Event

AOP ID and Name	Event Type
154: The Adverse Outcome Pathway on binding of FK506-binding protein 12 (FKBP12) by calcineurin inhibitors leading to immunosuppression	KeyEvent

Biological Organization

Level of Biological Organization
Cellular

In the in vitro experiment using peripheral blood mononuclear cells from blood-bank donors, treatment with FK506 revealed to suppress the production of immunoglobulin (Ig) M and G antibodies specific to T-cell dependent antigens (Heidt et al, 2009), and, in human PBMC cultures, FK506 suppressed the production of IL-6 and IgM antibodies in the presence of T-cell activation (Sakuma et al. 2001b). Oral administration of FK506 to mice for 4 days suppresses the response of plaque forming cells (PFC) using splenocyte after intravenous immunization of sheep erythrocytes (Kino et al. 1987). Oral administration of FK506 to rats over a four-week period reduced production of both anti-KLH-IgG and IgM antibodies after subcutaneous immunization of KLH (Ulrich et al. 2004).

How this Key Event Works

FK506 is known to suppress T-cell dependent antibody response; however, it has not been reported so far to directly affect B-cells on antibody production. FK506 inhibits the production of multiple classes of cytokines by T cells; among them, IL-4 and IL-13 are B-cell stimulating factors to proliferate, stimulate B cells, and to activate and induce class switch. Suppression of such B-cell-related cytokines deems to be the main factor for the suppression of TDAR by FK506.

How it is Measured or Detected

In vitro: T and B cells isolated from human PBMC were co-cultured with FK506 for 9 days in the presence of polyclonal T cell stimulation, after which supernatants were tested for immunoglobulin IgM and IgG levels by sandwich ELISA (Heidt et al, 2009). Human PBMC were stimulated with anti-CD3/CD28 for 24 h in the presence of FK506. IL-6 produced in the culture supernatants was measured using ELISA (Sakuma et al. 2001b). SKW6.4 cells

were cultured with anti-CD3/CD28 stimulated PBMC culture supernatant. After 4 days culture, IgM produced in the culture supernatants was measured by ELISA (Sakuma et al. 2001b). In vivo: Rats are repeated-administered FK506 orally and immunized by KLH, and its serum is examined for T cell-dependent antigen-specific IgM and IgG levels by sandwich ELISA. Mice are repeated-administered FK506 orally and immunized by SRBC, and its spleen cells are examined by plaque forming cell assay (Heidt et al, 2009, Kino et al. 1987, Ulrich et al. 2004). Class switch: T cells derived from human PBMCs were cultured with FK506, and cytokine mRNA levels of B cell stimulatory cytokines such as IFN-gamma, IL-2, IL-4, IL-5, IL-10, and IL-13 produced by T cells are measured by quantitative PCR (Ulrich et al. 2004).

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Adverse Outcomes

Title	Short name
Suppression, Suppression of transplant rejection	Suppression, Suppression of transplant rejection
Relief, Relief of atopic dermatitis	Relief, Relief of atopic dermatitis
Increase, Increased susceptibility to infection	Increase, Increased susceptibility to infection

984: Suppression, Suppression of transplant rejection

Short Name: Suppression, Suppression of transplant rejection

AOPs Including This Key Event

AOP ID and Name	Event Type
154: The Adverse Outcome Pathway on binding of FK506-binding protein 12 (FKBP12) by calcineurin inhibitors leading to immunosuppression	AdverseOutcome

Biological Organization

Level of Biological Organization
Individual

How this Key Event Works

In kidney transplant recipients, the administration of FK506 suppresses acute rejection and maintains favorable conditions for graft survival and function (Pirsch et al. 1997, Sonoda et al. 2003, Ekberg et al. 2007, Ekberg et al. 2009). Also, in recipients of liver, kidney, heart, pancreas, and small-intestine transplants, acute rejection was suppressed (Astellas Pharma Inc. 2014).

985: Relief, Relief of atopic dermatitis

Short Name: Relief, Relief of atopic dermatitis

AOPs Including This Key Event

AOP ID and Name	Event Type
154: The Adverse Outcome Pathway on binding of FK506-binding protein 12 (FKBP12) by calcineurin inhibitors leading to immunosuppression	AdverseOutcome

Biological Organization

Level of Biological Organization
Individual

How this Key Event Works

Patients with atopic dermatitis who were treated with FK506 ointment for a period of one year enjoyed relief from skin damage (FK506 Ointment Study Group. 1998). Generally, the skin of patients with atopic dermatitis has a higher expression of TLR-1 and a lower expression of TLR-2 than that of healthy subjects, but application of FK506 ointment suppressed expression of TLR-1 and increased expression of TLR-2 (Antiga et al. 2011).

986: Increase, Increased susceptibility to infection

Short Name: Increase, Increased susceptibility to infection

AOPs Including This Key Event

AOP ID and Name	Event Type
154: The Adverse Outcome Pathway on binding of FK506-binding protein 12 (FKBP12) by calcineurin inhibitors leading to immunosuppression	AdverseOutcome

Biological Organization

Level of Biological Organization
Individual

How this Key Event Works

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

Scientific evidence supporting the linkages in the AOP

Upstream Event	Relationship Type	Downstream Event	Evidence	Quantitative Understanding
Formation, Binding of FK506 to FKBP12	directly leads to	Binding, Formation, Binding of calcineurin with FK506-FKBP complexes	Strong	
Binding, Formation, Binding of calcineurin with FK506-FKBP complexes	directly leads to	Activation, Hampered NFAT activation and following nuclear localization	Strong	
Activation, Hampered NFAT activation and following nuclear localization	directly leads to	Inhibition, Interference of NFAT complex formation at the site of nuclear cytokine promoters	Strong	
Inhibition, Interference of NFAT complex formation at the site of nuclear cytokine promoters	directly leads to	Suppression, Suppression of cytokine production in the presence of T-cell activation	Strong	
Suppression, Suppression of cytokine production in the presence of T-cell activation	directly leads to	Suppression, Suppression of production of cytotoxic T-cells	Strong	
Suppression, Suppression of cytokine production in the presence of T-cell activation	indirectly leads to	Suppression, Suppression of T-cell dependent antibody production	Moderate	
Suppression, Suppression of cytokine production in the presence of T-cell activation	indirectly leads to	Relief, Relief of atopic dermatitis	Moderate	
Suppression, Suppression of	directly leads	Suppression, Suppression of	Strong	

production of cytotoxic T-cells	to	transplant rejection		
Suppression, Suppression of T-cell dependent antibody production	indirectly leads to	Increase, Increased susceptibility to infection	Moderate	
Suppression, Suppression of cytokine production in the presence of T-cell activation	indirectly leads to	Increase, Increased susceptibility to infection	Moderate	
Suppression, Suppression of production of cytotoxic T-cells	indirectly leads to	Increase, Increased susceptibility to infection	Moderate	

Formation, Binding of FK506 to FKBP12 leads to Binding, Formation, Binding of calcineurin with FK506-FKBP complexes

Binding, Formation, Binding of calcineurin with FK506-FKBP complexes leads to Activation, Hampered NFAT activation and following nuclear localization

Activation, Hampered NFAT activation and following nuclear localization leads to Inhibition, Interference of NFAT complex formation at the site of nuclear cytokine promoter

Inhibition, Interference of NFAT complex formation at the site of nuclear cytokine promoter leads to Suppression, Suppression of cytokine production in the presence of T-cell activation

Suppression, Suppression of cytokine production in the presence of T-cell activation leads to Suppression, Suppression of production of cytotoxic T-cells

Suppression, Suppression of cytokine production in the presence of T-cell activation leads to Suppression, Suppression of T-cell dependent antibody production

Suppression, Suppression of cytokine production in the presence of T-cell activation leads to Relief, Relief of atopic dermatitis

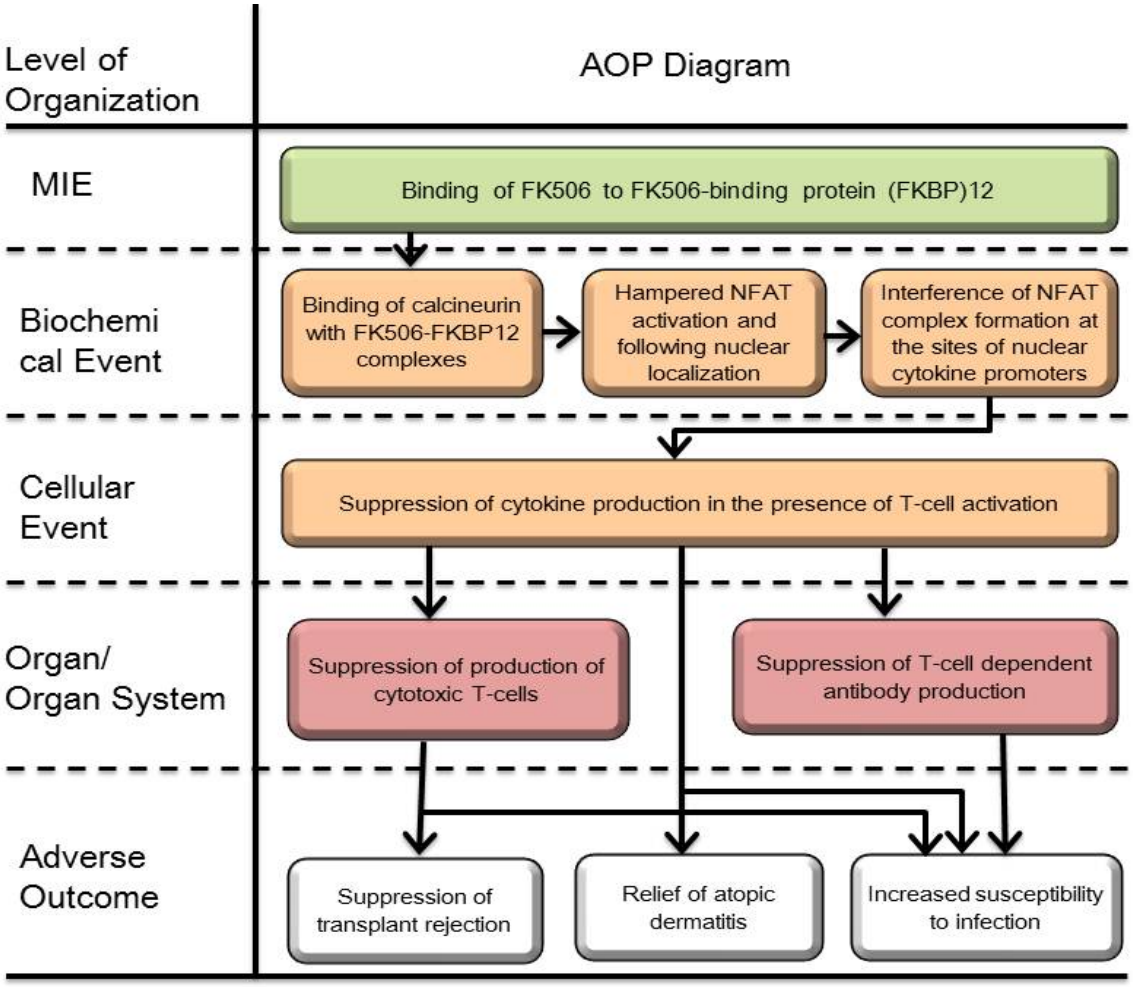
Suppression, Suppression of production of cytotoxic T-cells leads to Suppression, Suppression of transplant rejection

Suppression, Suppression of T-cell dependent antibody production leads to Increase, Increased susceptibility to infection

Suppression, Suppression of cytokine production in the presence of T-cell activation leads to Increase, Increased susceptibility to infection

Suppression, Suppression of production of cytotoxic T-cells leads to Increase, Increased susceptibility to infection

Graphical Representation



Overall Assessment of the AOP

Domain of Applicability

Life Stage Applicability

Life Stage	Evidence
all life stages	Moderate

Taxonomic Applicability

Term	Scientific Term	Evidence	Links
Since FK506-induced outcomes in humans are mimicked by similar responses in a variety of animal models, immunosuppression induced by FK506-FKPBP12 complexes are considered to be preserved across a variety of mammalian species.	Since FK506-induced outcomes in humans are mimicked by similar responses in a variety of animal models, immunosuppression induced by FK506-FKPBP12 complexes are considered to be preserved across a variety of mammalian species.		NCBI

Sex Applicability

Sex	Evidence
Mixed	Strong

The proposed AOP of FKBP12-FK506 complex-induced immunosuppression is not associated with life stage-, sex- or age-dependency. The relevant life stages for the AOP are through child to adult, since the ointment (Protopic) is approved for the pediatric atopic dermatitis; the MOA for immunosuppression deems to be applicable to all of the life stages. Since FK506-induced outcomes in humans are mimicked by similar responses in a variety of animal models, immunosuppression induced by FK506-FKPBP12 complexes are considered to be preserved across a variety of mammalian species.

Weight of Evidence Summary

Immunosuppression induced by FK506-FKBP12 complexes in T-cells is a known pharmacological effect of this drug, which has been well characterized and reported on extensively in related literature. The MIE of the immunosuppressive effects of FK506 have been clearly characterized as the formation of FKBP12-FK506 complexes. FK506-FKBP12 complex–induced immunosuppression is a known pharmacological effect of this drug; the outcomes of the immunosuppression are well known to lower tumor immunity and to increase susceptibility to infection are clear outcomes. FKBP12 is expressed in a plurality of immune cells; among them, involvement of T cells in the FK506-induced multiple immunosuppressive events deems to be clear and the MOA is explainable with clear relationships between each of the key events. FKBP12 and its downstream factors of calcineurin and NFAT are also expressed in B cells, dendritic cells and other immune cells as well as T cells; however, their involvement in the FK506-related immunosuppressive outcomes is unclear at present. FK506 was reported to increase the incidences of lymphoma or UV-induced skin tumors in the mouse carcinogenicity studies. FK506-induced immunosuppressive status might be related to the increased susceptibility to tumorigenesis; however, the precise MOA of the tumorigenesis remains unclear.

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