Cytokine Signaling in Immune System

Abdul-Sater, AA., Garapati, P V., Goffin, V., Herington, AC., Joshi, S., Jupe, S., Pinteaux, E., Rajput, A., Ray, KP., Schindler, C., Traer, E., Virgen-Slane, R., Ware, CF., Waters, MJ.

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30/03/2020
**Introduction**

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.

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**Literature references**


Reactome database release: 72

This document contains 7 pathways (see Table of Contents)

https://reactome.org
Cytokine Signaling in Immune System

Stable identifier: R-HSA-1280215

Cytokines are small proteins that regulate and mediate immunity, inflammation, and hematopoiesis. They are secreted in response to immune stimuli, and usually act briefly, locally, at very low concentrations. Cytokines bind to specific membrane receptors, which then signal the cell via second messengers, to regulate cellular activity.

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Interferons (IFNs) are cytokines that play a central role in initiating immune responses, especially antiviral and antitumor effects. There are three types of IFNs: Type I (IFN-alpha, -beta and others, such as omega, epsilon, and kappa), Type II (IFN-gamma) and Type III (IFN-lambda). In this module we are mainly focusing on type I IFNs alpha and beta and type II IFN-gamma. Both type I and type II IFNs exert their actions through cognate receptor complexes, IFNAR and IFNGR respectively, present on cell surface membranes. Type I IFNs are broadly expressed heterodimeric receptors composed of the IFNAR1 and IFNAR2 subunits, while the type II IFN receptor consists of IFNGR1 and IFNGR2. Type III interferon lambda has three members: lambda1 (IL-29), lambda2 (IL-28A), and lambda3 (IL-28B) respectively. IFN-lambda signaling is initiated through unique heterodimeric receptor composed of IFN-LR1/IF-28Ralpha and IL10R2 chains.

Type I IFNs typically recruit JAK1 and TYK2 proteins to transduce their signals to STAT1 and 2; in combination with IRF9 (IFN-regulatory factor 9), these proteins form the heterotrimeric complex ISGF3. In nucleus ISGF3 binds to IFN-stimulated response elements (ISRE) to promote gene induction.

Type II IFNs in turn rely upon the activation of JAKs 1 and 2 and STAT1. Once activated, STAT1 dimerizes to form the transcriptional regulator GAF (IFNG activated factor) and this binds to the IFNG activated sequence (GAS) elements and initiate the transcription of IFNG-responsive genes.

Like type I IFNs, IFN-lambda recruits TYK2 and JAK1 kinases and then promote the phosphorylation of STAT1/2, and induce the ISRE3 complex formation.
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Signaling by Interleukins

Location: Cytokine Signaling in Immune system

Stable identifier: R-HSA-449147

Compartments: plasma membrane

Interleukins are low molecular weight proteins that bind to cell surface receptors and act in an autocrine and/or paracrine fashion. They were first identified as factors produced by leukocytes but are now known to be produced by many other cells throughout the body. They have pleiotropic effects on cells which bind them, impacting processes such as tissue growth and repair, hematopoietic homeostasis, and multiple levels of the host defense against pathogens where they are an essential part of the immune system.

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Growth hormone receptor signaling

Location: Cytokine Signaling in Immune system

Stable identifier: R-HSA-982772

Compartments: extracellular region, plasma membrane, cytosol

Growth hormone (Somatotropin or GH) is a key factor in determining lean body mass, stimulating the growth and metabolism of muscle, bone and cartilage cells, while reducing body fat. It has many other roles; it acts to regulate cell growth, differentiation, apoptosis, and reorganisation of the cytoskeleton, affecting diverse processes such as cardiac function, immune function, brain function, and aging. GH also has insulin-like effects such as stimulating amino acid transport, protein synthesis, glucose transport, and lipogenesis. The growth hormone receptor (GHR) is a member of the cytokine receptor family. When the dimeric receptor binds GH it undergoes a conformational change which leads to phosphorylation of key tyrosine residues in its cytoplasmic domains and activation of associated tyrosine kinase JAK2. This leads to recruitment of signaling molecules such as STAT5 and Src family kinases such as Lyn leading to ERK activation. The signal is attenuated by association of Suppressor of Cytokine Signaling (SOCS) proteins and SHP phosphatases which bind to or dephosphorylate specific phosphorylated tyrosines on GHR/JAK. The availability of GHR on the cell surface is regulated by at least two processes; internalization and cleavage from the surface by metalloproteases.

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Prolactin (PRL) is a hormone secreted mainly by the anterior pituitary gland. It was originally identified by its ability to stimulate the development of the mammary gland and lactation, but is now known to have numerous and varied functions (Bole-Feyset et al. 1998). Despite this, few pathologies have been associated with abnormalities in prolactin receptor (PRLR) signaling, though roles in various forms of cancer and certain autoimmune disorders have been suggested (Goffin et al. 2002). A vast body of literature suggests effects of PRL in immune cells (Matera 1996) but PRLR KO mice have unaltered immune system development and function (Bouchard et al. 1999). In addition to the pituitary, numerous other tissues produce PRL, including the decidua and myometrium, certain cells of the immune system, brain, skin and exocrine glands such as the mammary, sweat and lacrimal glands (Ben-Jonathan et al. 1996). Pituitary PRL secretion is negatively regulated by inhibitory factors originating from the hypothalamus, the most important of which is dopamine, acting through the D2 subclass of dopamine receptors present in lactotrophs (Freeman et al. 2000). PRL-binding sites or receptors have been identified in numerous cells and tissues of adult mammals. Various forms of PRLR, generated by alternative splicing, have been reported in several species including humans (Kelly et al. 1991, Clevenger et al. 2003).

PRLR is a member of the cytokine receptor superfamily. Like many other members of this family, the first step in receptor activation was generally believed to be ligand-induced dimerization whereby one molecule of PRL bound to two molecules of receptor (Elkins et al. 2000). Recent reports suggest that PRLR pre-assembles at the plasma membrane in the absence of ligand (Gadd & Clevenger 2006, Tallet et al. 2011), suggesting that ligand-induced activation involves conformational changes in preformed PRLR dimers (Broutin et al. 2010).

PRLR has no intrinsic kinase activity but associates (Lebrun et al. 1994, 1995) with Janus kinase 2 (JAK2)
which is activated following receptor activation (Campbell et al. 1994, Rui et al. 1994, Carter-Su et al. 2000, Barua et al. 2009). JAK2-dependent activation of JAK1 has also been reported (Neilson et al. 2007). It is generally accepted that activation of JAK2 occurs by transphosphorylation upon ligand-induced receptor activation, based on JAK activation by chimeric receptors in which various extracellular domains of cytokine or tyrosine kinase receptors were fused to the IL-2 receptor beta chain (see Ihle et al. 1994). This activation step involves the tyrosine phosphorylation of JAK2, which in turn phosphorylates PRLR on specific intracellular tyrosine residues leading to STAT5 recruitment and signaling, considered to be the most important signaling cascade for PRLR. STAT1 and STAT3 activation have also been reported (DaSilva et al. 1996) as have many other signaling pathways; signaling through MAP kinases (Shc/SOS/Grb2/Ras/Raf/MAPK) has been reported as a consequence of PRL stimulation in many different cellular systems (see Bole-Feysot et al. 1998) though it is not clear how this signal is propagated. Other cascades non exhaustively include Src kinases, Focal adhesion kinase, phospholipase C gamma, PI3 kinase/Akt and Nek3 (Clevenger et al. 2003, Miller et al. 2007). The protein tyrosine phosphatase SHP2 is recruited to the C terminal tyrosine of PRLR and may have a regulatory role (Ali & Ali 2000). PRLR phosphotyrosines can recruit insulin receptor substrates (IRS) and other adaptor proteins to the receptor complex (Bole-Feysot et al. 1998).

Female homozygous PRLR knockout mice are completely infertile and show a lack of mammary development (Ormandy et al. 1997). Hemizogotes are unable to lactate following their first pregnancy and depending on the genetic background, this phenotype can persist through subsequent pregnancies (Kelly et al. 2001).

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Tumor necrosis factor-alpha (TNFA) exerts a wide range of biological effects through TNF receptor 1 (TNFR1) and TNF receptor 2 (TNFR2). Under normal physiological conditions TNFR2 exhibits more restricted expression, being found on certain subpopulation of immune cells and few other cell types (Grell et al. 1995). TNFR1 mediated signalling pathways have been very well characterized but, TNFR2 has been much less well studied. TNFR1 upon activation by TNFA activates apoptosis through two pathways, involving the adaptor proteins TNFR1-associated death domain (TRADD) and fas-associated death domain (FADD). In contrast, TNFR2 signalling especially in highly activated T cells, induces cell survival pathways that can result in cell proliferation by activating transcription factor NF-kB (nuclear factor-kB) via the alternative non-canonical route. TNFR2 signalling seems to play an important role, in particular for the function of regulatory T cells. It offers protective roles in several disorders, including autoimmune diseases, heart diseases, demyelinating and neurodegenerative disorders and infectious diseases (Faustman & Davis 2010).

Activation of the non-canonical pathway by TNFR2 is mediated through a signalling complex that includes TNF receptor-associated factor (TRAF2 and TRAF3), cellular inhibitor of apoptosis (cIAP1 and cIAP2), and NF-kb-inducing kinase (NIK). In this complex TRAF3 functions as a bridging factor between the cIAP1/2:TRAF2 complex and NIK. In resting cells cIAP1/2 in the signalling complex mediates K48-linked polyubiquitination of NIK and subsequent proteasomal degradation making NIK levels invisible. Upon TNFR2 stimulation, TRAF2 is recruited to the intracellular TRAF binding motif and this also indirectly recruits TRAF1 and cIAP1/2, as well as TRAF3 and NIK which are already bound to TRAF2 in unstimulated cells. TRAF2 mediates K63-linked ubiquitination of cIAP1/2 and this in turn mediates cIAP dependent K48-linked ubiquitination of TRAF3 leading to the proteasome-dependent degradation of the latter. As TRAF3 is degraded, NIK can no longer interact with TRAF1/2: cIAP complex. As a result NIK concentration in the cytosol increases and NIK gets stabilised and activated. Activated NIK phosphorylates IKKalpha, which in turn phosphorylates p100 (NFkB2) subunit. Phosphorylated p100 is also ubiquitinated by the SCF-beta-TRCP ubiquitin ligase complex and is subsequently processed by the proteasome to p52, which is a transcriptionally competent NF-kb subunit in conjunction with RelB (Petrus et al. 2011, Sun 2011, Vallabhapurapu & Karin 2009).
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Feline McDonough Sarcoma-like tyrosine kinase (FLT3) (also known as FLK2 (fetal liver tyrosine kinase 2), STK-1 (stem cell tyrosine kinase 1) or CD135) is a member of the class III receptor tyrosine kinase family involved in the differentiation, proliferation and survival of hematopoietic progenitor cells and of dendritic cells. Upon FLT3 ligand (FL) binding, the receptor forms dimers and is phosphorylated. Consequently, adapter and signaling molecules bind with the active receptor and trigger the activation of various pathways downstream including PI3K/Akt and MAPK cascades (Grafone T et al. 2012).

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</table>
Table of Contents

Introduction 1

- Cytokine Signaling in Immune system 2
- Interferon Signaling 3
- Signaling by Interleukins 5
- Growth hormone receptor signaling 6
- Prolactin receptor signaling 8
- TNFR2 non-canonical NF-kB pathway 10
- FLT3 Signaling 12

Table of Contents 13