reactome

Pathway Analysis Report

This report contains the pathway analysis results for the submitted sample ". Analysis was performed against Reactome version 69 on 18/07/2019. The web link to these results is:

https://reactome.org/PathwayBrowser/#/ANALYSIS=MjAxOTA3MTUxMDMzMzRfMTEyMg%3D%3D

Please keep in mind that analysis results are temporarily stored on our server. The storage period depends on usage of the service but is at least 7 days. As a result, please note that this URL is only valid for a limited time period and it might have expired.

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1. Introduction

Reactome is a curated database of pathways and reactions in human biology. Reactions can be considered as pathway 'steps'. Reactome defines a 'reaction' as any event in biology that changes the state of a biological molecule. Binding, activation, translocation, degradation and classical biochemical events involving a catalyst are all reactions. Information in the database is authored by expert biologists, entered and maintained by Reactome's team of curators and editorial staff. Reactome content frequently cross-references other resources e.g. NCBI, Ensembl, UniProt, KEGG (Gene and Compound), ChEBI, PubMed and GO. Orthologous reactions inferred from annotation for Homo sapiens are available for 17 non-human species including mouse, rat, chicken, puffer fish, worm, fly, yeast, rice, and Arabidopsis. Pathways are represented by simple diagrams following an SBGN-like format.

Reactome's annotated data describe reactions possible if all annotated proteins and small molecules were present and active simultaneously in a cell. By overlaying an experimental dataset on these annotations, a user can perform a pathway over-representation analysis. By overlaying quantitative expression data or time series, a user can visualize the extent of change in affected pathways and its progression. A binomial test is used to calculate the probability shown for each result, and the p-values are corrected for the multiple testing (Benjamini–Hochberg procedure) that arises from evaluating the submitted list of identifiers against every pathway.

To learn more about our Pathway Analysis, please have a look at our relevant publications:

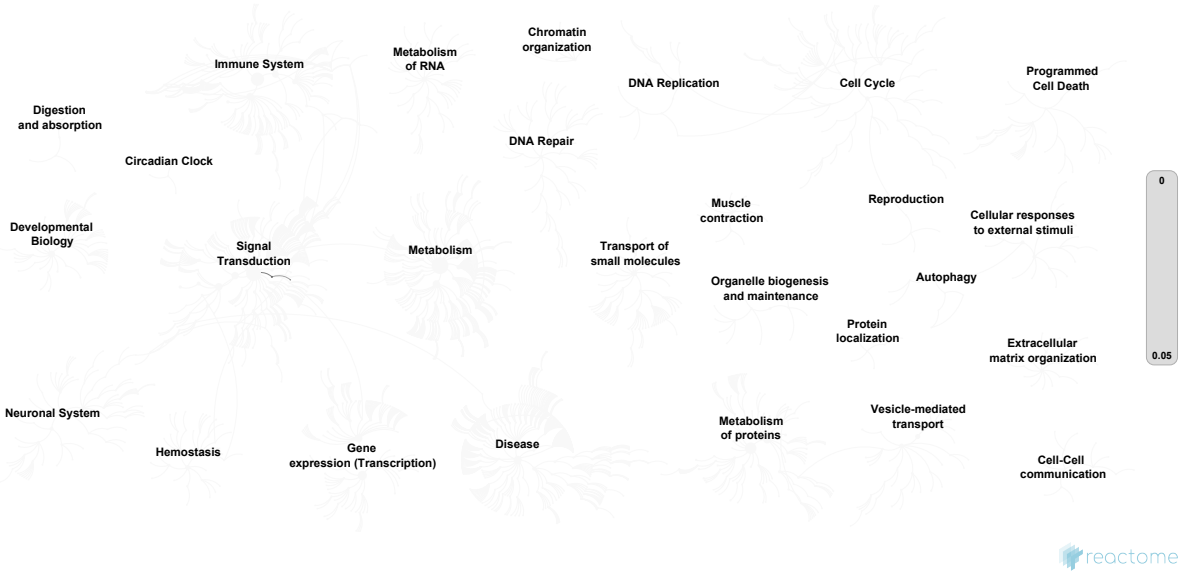
Fabregat A, Sidiropoulos K, Garapati P, Gillespie M, Hausmann K, Haw R, … D'Eustachio P (2016). The reactome pathway knowledgebase. Nucleic Acids Research, 44(D1), D481–D487. https://doi.org/10.1093/nar/gkv1351.

Fabregat A, Sidiropoulos K, Viteri G, Forner O, Marin-Garcia P, Arnau V, … Hermjakob H (2017). Reactome pathway analysis: a high-performance in-memory approach. BMC Bioinformatics, 18.

2. Properties

- This is an **overrepresentation** analysis: A statistical (hypergeometric distribution) test that determines whether certain Reactome pathways are over-represented (enriched) in the submitted data. It answers the question 'Does my list contain more proteins for pathway X than would be expected by chance?' This test produces a probability score, which is corrected for false discovery rate using the Benjamani-Hochberg method.
- 1 out of 2 identifiers in the sample were found in Reactome, where 3 pathways were hit by at least one of them.
- All non-human identifiers have been converted to their human equivalent.
- This report is filtered to show only results for species 'Homo sapiens' and resource 'UniProt'.
- The unique ID for this analysis (token) is MjAxOTA3MTUxMDMzMzRfMTEyMg%3D%3D. This ID is valid for at least 7 days in Reactome's server. Use it to access Reactome services with your data.

3. Genome-wide overview



This figure shows a genome-wide overview of the results of your pathway analysis. Reactome pathways are arranged in a hierarchy. The center of each of the circular "bursts" is the root of one top-level pathway, for example "DNA Repair". Each step away from the center represents the next level lower in the pathway hierarchy. The color code denotes over-representation of that pathway in your input dataset. Light grey signifies pathways which are not significantly over-represented.

4. Most significant pathways

The following table shows the 3 most relevant pathways sorted by p-value.

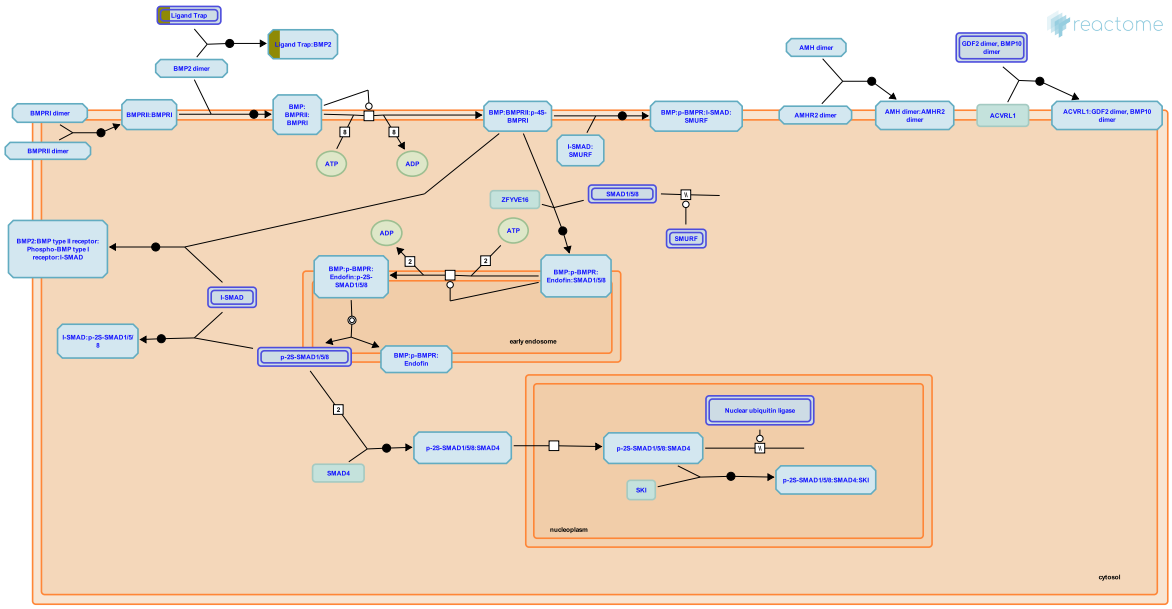
Pathway name	Entities				Reactions	
	found	ratio	p-value	FDR*	found	ratio
Signaling by BMP	1 / 28	0.003	0.005	0.015	1 / 17	0.001
Signaling by TGF-beta family members	1 / 102	0.009	0.018	0.018	1 / 107	0.009
Signal Transduction	1 / 2,768	0.248	0.435	0.435	1 / 2,230	0.183

* False Discovery Rate

5. Pathways details

For every pathway of the most significant pathways, we present its diagram, as well as a short summary, its bibliography and the list of inputs found in it.

1. Signaling by BMP (R-HSA-201451)



Bone morphogenetic proteins (BMPs) have many biological activities in various tissues, including bone, cartilage, blood vessels, heart, kidney, neurons, liver and lung. They are members of the Transforming growth factor-Beta (TGFB) family. They bind to type II and type I serine-threonine kinase receptors, which transduce signals through SMAD and non-SMAD signalling pathways. BMP signalling is linked to a wide variety of clinical disorders, including vascular diseases, skeletal diseases and cancer. BMPs typically activate BMP type I receptors and signal via SMAD1, 5 and 8. They can be classified into several subgroups, including the BMP2/4 group, the BMP5-8 osteogenic protein-1 (OP1) group, the growth and differentiation factor (GDF) 5-7 group and the BMP9/10 group. Most of the proteins of the BMP2/4, OP1 and BMP9/10 groups induce formation of bone and cartilage tissues in vivo, while the GDF5-7 group induce cartilage and tendon-like, but not bone-like, tissues (Miyazono et al. 2010). Members of the TGFB family bind to two types of serine-threonine kinase receptors, type I and type II (Massagué 2012). BMPs can bind type I receptors in the absence of type II receptors, but both types are required for signal transduction. The presence of both types dramatically increases binding affinity (Rozenweig et al. 1995). The type II receptor kinase transphosphorylates the type I receptor, which transmits specific intracellular signals. Type I and type II receptors share similar structural properties, comprised of a relatively short extracellular domain, a single membrane-spanning domain and an intracellular domain containing a serine-threonine kinase domain. Seven receptors, collectively referred to as the Activin receptor-like kinases (ALK), have been identified as type I receptors for the TGFB family in mammals. ALKs are classified into three groups based on their structure and function, the BMPRI group (Bone morphogenetic protein receptor type-1A, ALK3, BMPR1A and Bone morphogenetic protein receptor type-1B, ALK6, BMPR1B), the ALK1 group (Serine/threonine-protein kinase receptor R3, ALK1, ACVRL1 and Activin receptor type-1, ALK2, ACVR1) and the TBetaR1 group (Activin receptor type-1B, ALK4, ACVR1B and TGF-beta receptor type-1, ALK5, TGFBR1 and Activin receptor type-1C, ALK7, ACVR1C)

(Kawabata et al. 1998). ALK1 group and BMPRI group activate SMAD1/5/8 and transduce similar intracellular signals. The TBetaR1 group activate SMAD2/3. BMPR1A and ACVR1 are widely expressed. BMPR1B shows a more restricted expression profile. ACVRL1 is limited to endothelial cells and a few other cell types. The binding specificities of BMPs to type I receptors is affected by the type II receptors that are present (Yu et al. 2005). Typically, BMP2 and BMP4 bind to BMPR1A and BMPR1B (ten Dijke et al. 1994). BMP6 and BMP7 bind strongly to ACVR1 and weakly to BMPR1B. Growth/differentiation factor 5 (BMP14, GDF5) preferentially binds to BMPR1B, but not to other type I receptors (Nishitoh et al. 1995). BMP9 and BMP10 bind to ACVRL1 and ACVRL (Scharpfenecker et al. 2007). BMP type I receptors are shared by other members of the TGFB family. Three receptors, Bone morphogenetic protein receptor type-2 (BMPR2), Activin receptor type-2A (ACVR2A) and Activin receptor type-2B (ACVR2B) are the type II receptors for mammalian BMPs. They are widely expressed in various tissues. BMPR2 is specific for BMPs, whereas ACVR2A and ACVR2B are shared with activins and myostatin. BMP binding and signalling can be affected by coreceptors. Glycosylphosphatidylinositol (GPI)-anchored proteins of the repulsive guidance molecule (RGM) family, including RGMA, RGMB (DRAGON) and Hemojuvelin (HFE2, RGMC) are coreceptors for BMP2 and BMP4, enhancing signaling (Samad et al. 2005, Babitt et al. 2005, 2006). They interact with BMP type I and/or type II receptors and bind BMP2 and BMP4, but not BMP7 or TGFB1. BMP2/4 signalling normally involves BMPR2, not ACVR2A or ACVR2B. Cells transfected with RGMA use both BMPR2 and ACVR2A for BMP-2/4 signalling, suggesting that RGMA facilitates the use of ACVR2A by BMP2/4 (Xia et al. 2007). Endoglin (ENG) is a transmembrane protein expressed in proliferating endothelial cells. It binds various ligands including TGFB1/3, Activin-A and BMP2/7 (Barbara et al. 1999). It inhibits TGFB-induced responses and enhances BMP7-induced responses (Scherner et al. 2007). Mutations in ENG result in hereditary haemorrhagic telangiectasia (HHT1), also known as OslerWeberRendu disease, while mutations in ACVRL1 lead to HHT2, suggesting that they act in a common signalling pathway (McAllister et al. 1994, Johnson et al. 1996). BMP2 is a dimeric protein, having two receptor-binding motifs. One is a high-affinity binding site for BMPR1A, the other is a low-affinity binding site for BMPR2 (Kirsch et al. 2000). In the absence of ligand stimulation, small fractions of type II and type I receptors are present as preexisting homodimers and heterodimers on the cell surface. Ligand-binding increases oligomerization. The intracellular domains of type I receptors have a characteristic GS domain (glycine and serine-rich domain) located N-terminal to the serine-threonine kinase domains. Type II receptor kinases are constitutively active in the absence of ligand. Upon ligand binding, the type II receptor kinase phosphorylates the GS domain of the type I receptor, a critical event in signal transduction by the serine/threonine kinase receptors (Miyazono et al. 2010). Activation of the TGFBR1 receptor has been studied in detail. The inactive conformation is maintained by interaction between the GS domain, the N-terminal lobe and the activation loop of the kinase (Huse et al. 1999). When the GS domain is phosphorylated by the type II receptor kinase, the TGFBR1 kinase is converted to an active conformation. Mutations of Thr-204 in TGFBR1 and the corresponding Gln in BMP type I receptors lead to their constitutive activation. The L45 loop, in the kinase domain of type I receptors, specifically interacts with receptor-regulated Smads (R-Smads). Neurotrophic tyrosine kinase receptor type 3 (NT-3 growth factor receptor, TrkC, NTRK3) directly binds BMPR2, interfereing with its interaction with BMPR1A, which inhibits downstream signalling (Jin et al. 2007). Tyrosine-protein kinase transmembrane receptor ROR2 and BMPR1B form a heteromeric complex in a ligand independent fashion that modulatesGDF5-BMPR1B signalling by inhibition of Smad1/5 signalling (Sammar et al. 2004). Type I receptor kinases activated by the type II receptor kinases, phosphorylate R-Smads. R-Smads then form a complex with common-partner Smad (co-Smad) and translocate to the nucleus. The oligomeric Smad complexes regulate the transcription of target genes through interaction with

various transcription factors and transcriptional coactivators or corepressors. Inhibitory Smads (I-Smads) negatively regulate the action of R-Smads and/or co-Smads. Eight different Smads have been identified in mammals. Smad1, Smad5 and Smad8 are R-Smads in BMP signalling pathways (BMP-specific R-Smads). Smad2 and Smad3 are R-Smads in TGFB/activin

signalling pathways. BMP receptors can phosphorylate Smad2 in certain types of cells (Murakami et al. 2009). Smad1, Smad5 and Smad8 are structurally highly similar to each other. The functional differences between them are largely unknown. Smad4 is the only co-Smad in mammals, shared by both BMP and TGFB/activin signalling pathways. Smad6 and Smad7 are I-Smads.

References

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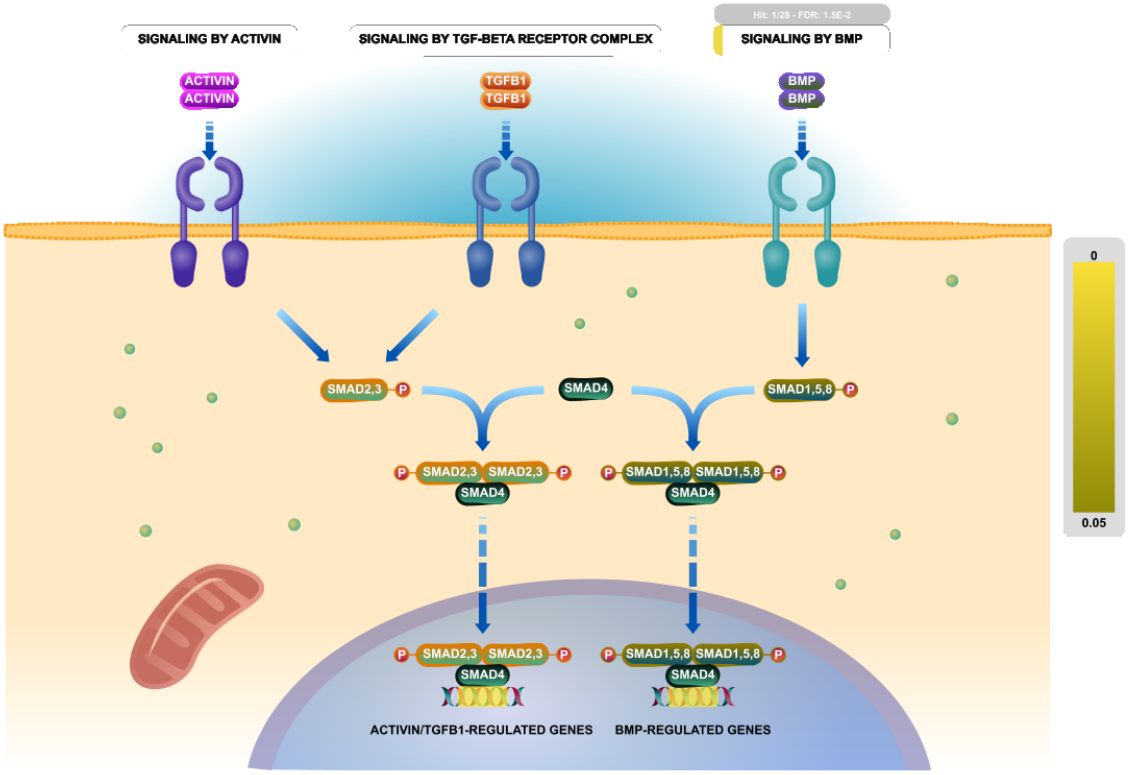
Edit history

Date	Action	Author
2007-08-13	Created	Jassal B
2007-11-07	Authored	Moustakas A, Huminiecki L
2007-11-12	Reviewed	Heldin CH
2019-05-17	Modified	Weiser D

Entities found in this pathway (1)

Input	UniProt Id
NOG	Q13253

2. Signaling by TGF-beta family members (R-HSA-9006936)



The human genome encodes 33 TGF-beta family members, including TGF-beta itself, as well as bone morphogenetic protein (BMP), activin, nodal and growth and differentiation factors (GDFs). This superfamily of ligands generally binds as dimers to hetero-tetrameric cell-surface receptor serine/threonine kinases to activate SMAD-dependent and SMAD-independent signaling (reviewed in Morikawa et al, 2016; Budi et al, 2017).

Signaling by the TGF-beta receptor complex is initiated by TGF-beta. TGF-beta (TGFB1), secreted as a homodimer, binds to TGF-beta receptor II (TGFBR2), inducing its dimerization and formation of a stable hetero-tetrameric complex with TGF-beta receptor I homodimer (TGFBR1). TGFBR2-mediated phosphorylation of TGFBR1 triggers internalization of the heterotetrameric TGF beta receptor complex (TGFBR) into clathrin coated endocytic vesicles and recruitment of cytosolic SMAD2 and SMAD3, which act as R-SMADs for TGF beta receptor complex. TGFBR1 phosphorylates SMAD2 and SMAD3, promoting their association with SMAD4 (known as Co-SMAD). In the nucleus, the SMAD2/3:SMAD4 heterotrimer binds target DNA elements and, in cooperation with other transcription factors, regulates expression of genes involved in cell differentiation. For a review of TGF-beta receptor signaling, please refer to Kang et al. 2009.

Signaling by BMP is triggered by bone morphogenetic proteins (BMPs). BMPs can bind type I receptors in the absence of type II receptors, but the presence of both types dramatically increases binding affinity. The type II receptor kinase transphosphorylates the type I receptor, leading to recruitment and phosphorylation of SMAD1, SMAD5 and SMAD8, which function as R-SMADs in BMP signalling pathways. Phosphorylated SMAD1, SMAD5 and SMAD8 form heterotrimeric complexes with SMAD4, the only Co-SMAD in mammals. The SMAD1/5/8:SMAD4 heterotrimer regulates transcription of genes involved in development of many tissues, including bone, cartilage, blood vessels, heart, kidney, neurons, liver and lung. For review of BMP signaling, please refer to Miyazono et al. 2010.

Signaling by activin is triggered when an activin dimer (activin A, activin AB or activin B) binds the type II receptor (ACVR2A, ACVR2B). This complex then interacts with the type I receptor (ACVR1B, ACVR1C) and phosphorylates it. The phosphorylated type I receptor phosphorylates SMAD2 and SMAD3. Dimers of phosphorylated SMAD2/3 bind SMAD4 and the resulting ternary complex enters the nucleus and activates target genes. For a review of activin signaling, please refer to Chen et al. 2006.

References

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Morikawa M, Derynck R & Miyazono K (2016). TGF- and the TGF- Family: Context-Dependent Roles in Cell and Tissue Physiology. Cold Spring Harb Perspect Biol, 8.

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Chen YG, Wang Q, Lin SL, Chang CD, Chuang J, Chung J & Ying SY (2006). Activin signaling and its role in regulation of cell proliferation, apoptosis, and carcinogenesis. Exp. Biol. Med. (Maywood), 231, 534-44.

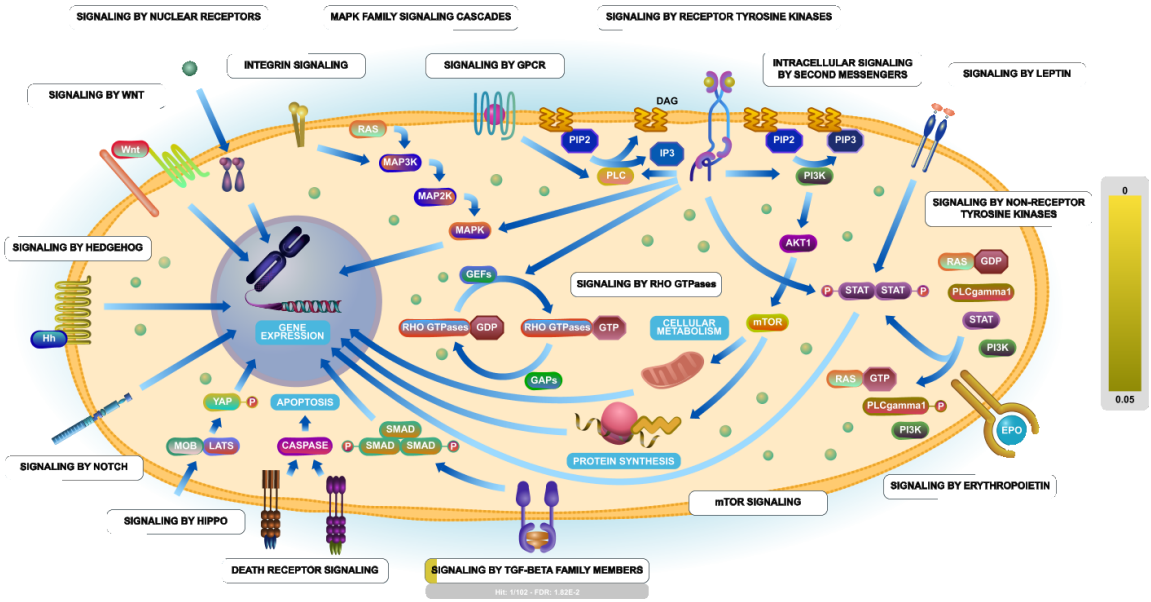
Edit history

Date	Action	Author
2017-05-24	Edited	Rothfels K
2017-05-24	Authored	Rothfels K
2017-05-24	Created	Rothfels K
2017-06-22	Reviewed	D'Eustachio P
2019-05-17	Modified	Weiser D

Entities found in this pathway (1)

Input	UniProt Id
NOG	Q13253

3. Signal Transduction (R-HSA-162582)



Signal transduction is a process in which extracellular signals elicit changes in cell state and activity. Transmembrane receptors sense changes in the cellular environment by binding ligands, such as hormones and growth factors, or reacting to other types of stimuli, such as light. Stimulation of transmembrane receptors leads to their conformational change which propagates the signal to the intracellular environment by activating downstream signaling cascades. Depending on the cellular context, this may impact cellular proliferation, differentiation, and survival. On the organism level, signal transduction regulates overall growth and behavior.

Receptor tyrosine kinases (RTKs) transmit extracellular signals by phosphorylating their protein partners on conserved tyrosine residues. Some of the best studied RTKs are EGFR (reviewed in Avraham and Yarden, 2011), FGFR (reviewed in Eswarakumar et al, 2005), insulin receptor (reviewed in Saltiel and Kahn, 2001), NGF (reviewed in Reichardt, 2006), PDGF (reviewed in Andrae et al, 2008) and VEGF (reviewed in Xie et al, 2004). RTKs frequently activate downstream signaling through RAF/MAP kinases (reviewed in McKay and Morrison, 2007 and Wellbrock et al 2004), AKT (reviewed in Manning and Cantley, 2007) and PLC- gamma (reviewed in Patterson et al, 2005), which ultimately results in changes in gene expression and cellular metabolism.

Receptor serine/threonine kinases of the TGF-beta family, such as TGF-beta receptors (reviewed in Kang et al. 2009) and BMP receptors (reviewed in Miyazono et al. 2009), transmit extracellular signals by phosphorylating regulatory SMAD proteins on conserved serine and threonine residues. This leads to formation of complexes of regulatory SMADs and SMAD4, which translocate to the nucleus where they act as transcription factors.

WNT receptors transmit their signal through beta-catenin. In the absence of ligand, beta-catenin is constitutively degraded in a ubiquitin-dependent manner. WNT receptor stimulation releases beta-catenin from the destruction complex, allowing it to translocate to the nucleus where it acts as a transcriptional regulator (reviewed in MacDonald et al, 2009 and Angers and Moon, 2009). WNT receptors were originally classified as G-protein coupled receptors (GPCRs). Although they are structurally related, GPCRs primarily transmit their signals through G-proteins, which are trimers of alpha, beta and gamma subunits. When a GPCR is activated, it acts as a guanine nucleotide exchange factor, catalyzing GDP to GTP exchange on the G-alpha subunit of the G protein and its dissociation from the gamma-beta heterodimer. The G-alpha subunit regulates the activity of adenylate cyclase, while the gamma-beta heterodimer can activate AKT and PLC signaling (reviewed in Rosenbaum et al. 2009, Oldham and Hamm 2008, Ritter and Hall 2009).

NOTCH receptors are activated by transmembrane ligands expressed on neighboring cells, which results in cleavage of NOTCH receptor and release of its intracellular domain. NOTCH intracellular domain translocates to the nucleus where it acts as a transcription factor (reviewed in Kopan and Ilagan, 2009).

Integrins are activated by extracellular matrix components, such as fibronectin and collagen, leading to conformational change and clustering of integrins on the cell surface. This results in activation of integrin-linked kinase and other cytosolic kinases and, in co-operation with RTK signaling, regulates survival, proliferation and cell shape and adhesion (reviewed in Hehlgans et al, 2007) .

Besides inducing changes in gene expression and cellular metabolism, extracellular signals that trigger the activation of Rho GTP-ases can trigger changes in the organization of cytoskeleton, thereby regulating cell polarity and cell-cell junctions (reviewed in Citi et al, 2011).

References

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Avraham R & Yarden Y (2011). Feedback regulation of EGFR signalling: decision making by early and delayed loops. Nat Rev Mol Cell Biol, 12, 104-17.

Edit history

Date	Action	Author
2005-04-01	Created	Joshi-Tope G
2005-05-06	Authored	Joshi-Tope G, Charalambous M, Gopinathrao G, Rothfels K, Bevan AP et al.
2019-05-10	Reviewed	Barroso I, Joutel A, Rush MG, Stanley FM
2019-05-17	Modified	Weiser D

Entities found in this pathway (1)

Input	UniProt Id
NOG	Q13253

6. Identifiers found

Below is a list of the input identifiers that have been found or mapped to an equivalent element in Reactome, classified by resource.

Entities (1)

Input	UniProt Id
NOG	Q13253

7. Identifiers not found

These 1 identifiers were not found neither mapped to any entity in Reactome.

ASCL5