Diseases of signal transduction by growth factor receptors and second messengers


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10/03/2021
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: 75

This document contains 13 pathways (see Table of Contents)
Diseases of signal transduction by growth factor receptors and second messengers

Stable identifier: R-HSA-5663202

Signaling processes are central to human physiology (e.g., Pires-da Silva & Sommer 2003), and their disruption by either germ-line and somatic mutation can lead to serious disease. Here, the molecular consequences of mutations affecting visual signal transduction and signaling by diverse growth factors are annotated.

**Literature references**

The pathway "Signaling by EGFR in Cancer" shows signaling by constitutively active EGFR cancer variants in the context of "Signaling by EGFR", allowing users to compare cancer events with the wild-type EGFR events. Red lines emphasize cancer related events and physical entities, while wild-type entities and events are shaded. Please refer to "Signaling by Ligand-Responsive EGFR Variants in Cancer", "Signaling by EGFRvIII in Cancer" and "Signaling by Overexpressed Wild-Type EGFR in Cancer" for detailed pathway summations.

**Editions**

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A number of skeletal and developmental diseases have been shown to arise as a result of mutations in the FGFR1, 2 and 3 genes. These include dwarfism syndromes (achondroplasia, hypochondroplasia and the neonatal lethal disorders thanatophoric dysplasia I and II), as well as craniosynostosis disorders such as Pfeiffer, Apert, Crouzon, Jackson-Weiss and Muenke syndromes (reviewed in Webster and Donoghue 1997; Burke, 1998, Cunningham, 2007; Harada, 2009). These mutations fall into four general regions of the receptor: a) the immunoglobulin (Ig)-like domain II-III linker region, b) the alternatively spliced second half of the Ig III domain, c) the transmembrane domain and d) the tyrosine kinase domain (reviewed in Webster and Donoghue, 1997). With the exception of mutations in class b), which affect only the relevant splice variant, these mutations may be present in either the 'b' or 'c' isoforms. These activating mutations affect FGFR function by altering or expanding the ligand-binding range of the receptors (see for instance Ibrahimi, 2004a), by promoting ligand-independent dimerization (for instance, Galvin, 1996; Neilson and Friesel, 1996; d’Avis, 1998) or by increasing the activity of the kinase domain (for instance, Webster, 1996; Naski, 1996; Tavormina, 1999; Bellus, 2000). Thus, a number of the point mutations found in FGFR receptors alter their activity without altering their intrinsic kinase activity. Many of the mutations that promote constitutive dimerization do so by creating or removing cysteine residues; the presence of an unpaired cysteine in the receptor is believed to promote dimerization through the formation of intramolecular disulphide bonds (Galvin, 1996; Robertson, 1998). Paralogous mutations at equivalent positions have been identified in more than one FGF receptor, sometimes giving rise to different diseases. For instance, mutation of the highly conserved FGFR2 Ser252-Pro253 dipeptide in the region between the second and third Ig domain is responsible for virtually all cases of Apert Syndrome (Wilkie, 1995), while paralogous mutations in FGFR1 (S252R) and FGFR3 (P250R) are associated with Pfeiffer and Crouzon syndromes, respectively (Bellus, 1996). FGFR4 is unique in that mutations of this gene are not known to be associated with any developmental disorders.

Recently, many of the same activating mutations in the FGFR genes that have been characterized in skeletal and developmental disorders have begun to be identified in a range of cancers (reviewed in Turner and Gross, 2010; Greulich and Pollock, 2011; Wesche, 2011). The best established link between a somatic mutation of an FGFR and the development of cancer is in the case of FGFR3, where 50% of bladder cancers have mutations in the FGFR3 coding sequence. Of these mutations, which largely match the activating mutations seen in thanatophoric dysplasias, over half occur at a single residue (S249C) (Cappellen, 1999; van Rhijn, 2002). Activating mutations have also been identified in the coding sequences of FGFR1, 2 and 4 (for review, see Wesche, 2011).

In addition to activating point mutations, the FGFR1, 2 and 3 genes are subject to misregulation in cancer through gene amplification and translocation events, which are thought to lead to overexpression and ligand-independent dimerization (Weiss, 2010; Turner, 2010; Kunii, 2008; Takeda, 2007; Chesi, 1997; Avet-Loiseau, 1998; Ronchetti, 2001). It is important to note, however, that in each of these cases, the amplification or translocation involve large genomic regions encompassing additional genes, and the definit-
ive roles of the FGFR genes in promoting oncogenesis has not been totally established. In the case of FGFR1, translocation events also give rise to FGFR1 fusion proteins that contain the intracellular kinase domain of the receptor fused to a dimerization domain from the partner gene. These fusions, which are expressed in a pre-leukemic myeloproliferative syndrome, dimerize constitutively based on the dimerization domain provided by the fusion partner and are constitutively active (reviewed in Jackson, 2010).

**Literature references**


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Gene amplification of the ERBB2 (HER2) oncogene is observed across various different cancer types. In addition to HER2 gene amplification, sequencing of tumour samples have revealed HER2 mutations, which fall within three major regions: the extracellular domain (ECD), transmembrane domain/juxtamembrane domain (TMD/JMD) and kinase domain (KD). Based on the functional studies of their catalytic activity, signaling and drug sensitivity, as well as their time of occurrence with respect to treatment, these mutation can be classified as primary mutations, that can be activating or silent, and may confer drug resistance, and secondary mutations, associated with development of drug resistance upon initial response to targeted therapy.

Overexpression of ERBB2 (HER2) protein, usually as a consequence of ERBB2 gene amplification, leads to formation of constitutively active, growth factor independent, ERBB2 homodimers, which are sensitive to the therapeutic antibody trastuzumab (herceptin) (Pickl and Ries 2009).

Co-overexpression of ERBB2 and its dimerization partner ERBB3 leads to formation of both ERBB2 homodimers and ERRB2:ERBB3 heterodimers and is associated with chemotherapy resistance and reduced relapse-free and overall survival (Spears et al. 2012).

Sensitivity to tyrosine kinase inhibitors (TKIs) and the therapeutic antibody trastuzumab (herceptin) differs between different ERBB2 KD mutants (Bose et al. 2013, Rexer et al. 2013, Nagano et al. 2018).

ERBB2 extracellular domain (ECD) mutants harbor missense mutations that lead to substitutions of amino acid residues in the heterodimerization arm contact surface, involved in formation of ERBB2 heterodimers (Greulich et al. 2012).

Recurrent missense mutations in regions encoding the transmembrane domain (TMD) and the juxtamembrane domain (JMD) are frequently reported in cancer. TMD and JMD mutations can activate ERBB2 signaling by improving the active dimer interface or by stabilizing the active conformation (Ou et al. 2017, Pahuja et al. 2018).

ERBB2 TMD/JMD mutants differ in their sensitivity to the therapeutic antibody pertuzumab, which blocks ligand-driven heterodimerization of ERBB2 (Pahuja et al. 2018).

**Literature references**


Class IA PI3K is a heterodimer of a p85 regulatory subunit (encoded by PIK3R1, PIK3R2 or PIK3R3) and a p110 catalytic subunit (encoded by PIK3CA, PIK3CB or PIK3CD). In the absence of activating signals, the regulatory subunit stabilizes the catalytic subunit while inhibiting its activity. The complex becomes activated when extracellular signals stimulate the phosphorylation of the cytoplasmic domains of transmembrane receptors or receptor-associated proteins. The p85 regulatory subunit binds phosphorylated motifs of activator proteins, which induces a conformational change that relieves p85-mediated inhibition of the p110 catalytic subunit and enables PI3K to phosphorylate PIP2 to form PIP3. The phosphoinositide kinase activity of PI3K is opposed by the phosphoinositide phosphatase activity of PTEN.

PI3K/AKT Signaling in Cancer

**Location:** Diseases of signal transduction by growth factor receptors and second messengers

**Stable identifier:** R-HSA-2219528

**Diseases:** cancer

PI3K acts as a messenger that recruits PDPK1 (PDK1) and AKT (AKT1, AKT2 or AKT3) to the plasma membrane. PDPK1 also possesses a low affinity for PIP2, so small amounts of PDPK1 are always present at the membrane. Binding of AKT to PI3P3 induces a conformational change that enables TORC2 complex to phosphorylate AKT at a conserved serine residue (S473 in AKT1). Phosphorylation at the serine residue enables AKT to bind to PDK1 and exposes a conserved threonine residue (T308) that is phosphorylated by PDK1. AKT phosphorylated at both serine and threonine residues dissociates from the plasma membrane and acts as a serine/threonine kinase that phosphorylates a number of cytosolic and nuclear targets involved in regulation of cell metabolism, survival and gene expression. For a recent review, please refer to Manning and Cantley, 2007.

Signaling by PI3K/AKT is frequently constitutively activated in cancer. This activation can be via gain-of-function mutations in PI3KCA (encoding catalytic subunit p110alpha), PIK3R1 (encoding regulatory subunit p85alpha) and AKT1. The PI3K/AKT pathway can also be constitutively activated by loss-of-function mutations in tumor suppressor genes such as PTEN.

Gain-of-function mutations activate PI3K signaling by diverse mechanisms. Mutations affecting the helic-
al domain of PIK3CA and mutations affecting nSH2 and iSH2 domains of PIK3R1 impair inhibitory interactions between these two subunits while preserving their association. Mutations in the catalytic domain of PIK3CA enable the kinase to achieve an active conformation. PI3K complexes with gain-of-function mutations therefore produce PIP3 and activate downstream AKT in the absence of growth factors (Huang et al. 2007, Zhao et al. 2005, Miled et al. 2007, Horn et al. 2008, Sun et al. 2010, Jaiswal et al. 2009, Zhao and Vogt 2010, Urick et al. 2011). While AKT1 gene copy number, expression level and phosphorylation are often increased in cancer, only one low frequency point mutation has been repeatedly reported in cancer and functionally studied. This mutation represents a substitution of a glutamic acid residue with lysine at position 17 of AKT1, and acts by enabling AKT1 to bind PIP2. PIP2-bound AKT1 is phosphorylated by TORC2 complex and by PDPK1 that is always present at the plasma membrane, due to low affinity for PIP2. Therefore, E17K substitution abrogates the need for PI3K in AKT1 activation (Carpten et al. 2007, Landgraf et al. 2008).

Loss-of-function mutations affecting the phosphatase domain of PTEN are frequently found in sporadic cancers (Kong et al. 1997, Lee et al. 1999, Han et al. 2000), as well as in PTEN hamartoma tumor syndromes (PHTS) (Marsh et al. 1998). PTEN can also be inactivated by gene deletion or epigenetic silencing, or indirectly by overexpression of microRNAs that target PTEN mRNA (Huse et al. 2009). Cells with deficient PTEN function have increased levels of PIP3, and therefore increased AKT activity. For a recent review, please refer to Hollander et al. 2011.

Because of their clear involvement in human cancers, PI3K and AKT are targets of considerable interest in the development of small molecule inhibitors. Although none of the currently available inhibitors display preference for mutant variants of PIK3CA or AKT, several inhibitors targeting the wild-type kinases are undergoing clinical trials. These include dual PI3K/mTOR inhibitors, class I PI3K inhibitors, pan-PI3K inhibitors, and pan-AKT inhibitors. While none have yet been approved for clinical use, these agents show promise for future therapeutics. In addition, isoform-specific PI3K and AKT inhibitors are currently being developed, and may provide more specific treatments along with reduced side-effects. For a recent review, please refer to Liu et al. 2009.

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Human NOTCH1 was cloned as a chromosome 9 gene, translocated to the T-cell beta receptor (TCBR) promoter on chromosome 7 in T-cell acute lymphoblastic leukemia (T-ALL) (Ellisen et al. 1991). This translocation, present in only a small percentage of T-ALL patients, results in the overexpression of a truncated NOTCH1 receptor, which lacks almost the entire extracellular domain, in T lymphocytes. Oncogenic NOTCH1 mutations were subsequently found to be present in >50% of T-ALL patients, with hotspots in the heterodimerization domain (HD domain) and PEST domain of NOTCH1 (Weng et al. 2004).

Normal NOTCH1 becomes activated by binding DLL (DLL1 or DLL4) or JAG (JAG1 or JAG2) ligands expressed on the surface of a neighboring cell, which leads to proteolytic cleavage of NOTCH1 by ADAM10/17 and gamma-secretase, and release of the NOTCH1 intracellular domain (NICD1) which regulates expression of genes that play important roles in the development of T lymphocytes (Washburn et al. 1997. Radtke et al. 1999, Maillard et al. 2004, Sambandam et al. 2005, Tan et al. 2005). Mutations in the HD domain, responsible for association of NOTCH1 extracellular and transmembrane regions after furin-mediated cleavage of NOTCH1 precursor, as well as the truncation of the NOTCH1 extracellular domain by the rare T-ALL translocation, enable constitutive production of NICD1, in the absence of ligand binding (Malecki et al. 2006, Ellisen et al. 1991).

Mutations in the NOTCH1 PEST domain interfere with FBXW7 (FBW7)-mediated ubiquitination and degradation of NICD1, resulting in prolonged half-life and increased transcriptional activity of NICD1, which promotes growth and division of T-lymphocytes (Weng et al. 2004, Thompson et al. 2007, O'Neil et al. 2007).
Mutations in the HD domain and PEST domain of NOTCH1 are frequently found in cis in T-ALL. While HD mutations alone result in up to ~10-fold increase in NOTCH1 transcriptional activity and PEST domain mutations alone result in up to ~2-fold increase in NOTCH1 transcriptional activity, in cis mutations of HD and PEST domains act synergistically, increasing NOTCH1 transcriptional activity up to ~40-fold (Weng et al. 2004).

FBXW7 (FBW7), a component of the SCF (SKP1, CUL1, and F-box protein) ubiquitin ligase complex SCF-FBW7 involved in the degradation of NOTCH1 (Oberg et al. 2001, Wu et al. 2001, Fryer et al. 2004), is subject to loss of function mutations in T-ALL (Akhoondi et al. 2007, Thompson et al. 2007, O'Neil et al. 2007) which are mutually exclusive with NOTCH1 PEST domain mutations (Thompson et al. 2007, O'Neil et al. 2007).

Although gamma-secretase inhibitors (GSIs) are successfully used in vitro to inhibit NOTCH1 signaling in T-ALL cell lines, the gamma-secretase complex has many other substrates besides NOTCH. The specificity of GSIs is therefore limited and, as they are not considered to be particularly promising drugs for the clinical treatment of T-ALL (reviewed by Purow, 2012), they have not been annotated.

For a recent review of NOTCH1 signaling in cancer, please refer to Grabher et al. 2006.

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Signaling by TGF-beta Receptor Complex in Cancer

Location: Diseases of signal transduction by growth factor receptors and second messengers

Stable identifier: R-HSA-3304351

Diseases: cancer


In advanced cancer, signaling by TGF-beta may be tumor promoting, as it induces epithelial-to-mesenchymal transition (EMT), thereby increasing invasiveness (Cui et al. 1996, Guasch et al. 2007, reviewed by Heldin et al. 2012).

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Signaling by WNT in cancer

Location: Diseases of signal transduction by growth factor receptors and second messengers

Stable identifier: R-HSA-4791275

Compartments: cytosol

Diseases: cancer

The WNT signaling pathway has been linked with cancer ever since the identification of the first WNT as a gene activated by integration of mouse mammary tumor virus proviral DNA in virally-induced breast tumors (Nusse et al, 1984). The most well known example of aberrant WNT signaling in cancer is in colorectal cancer, where an activating mutation in a WNT pathway component is seen in 90% of sporadic cases. Inappropriate WNT pathway activation has also been implicated in most other solid human cancers but is not always associated with mutations in WNT pathway components (reviewed in Polakis, 2012).

Both tumor suppressors and oncogenes have been identified in the so-called canonical WNT pathway, which regulates WNT-dependent transcription by promoting the degradation of beta-catenin in the absence of ligand (reviewed in Polakis, 2012). Loss-of-function mutations in the destruction complex components APC, Axin and AMER1 and gain-of-function mutations in beta-catenin itself cause constitutive signaling and are found in cancers of the intestine, kidney, liver and stomach, among others (Polakis, 1995; Segiditsas and Tomlinson, 2006; Peifer and Polakis, 2000; Laurent-Puig et al, 2001; Liu et al, 2000; Satoh et al, 2000; Major et al, 2007; Ruteshouser et al, 2008). WNTs and WNT pathway components are also frequently over- or under-expressed in various cancers, and these changes are correlated with epigenetic regulation of promoter activity. In some contexts, both the canonical and non-canonical WNT signaling, which governs processes such as cell polarity and morphogenesis, may also contribute to tumor formation by promoting cell migration, invasiveness and metastasis.

Literature references


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Hh mutants abrogate ligand secretion

**Location:** Diseases of signal transduction by growth factor receptors and second messengers

**Stable identifier:** R-HSA-5387390

**Diseases:** holoprosencephaly

Hh signaling is required for a number of developmental processes, and mutations that disrupt the normal processing and biogenesis of Hh ligand can result in neonatal abnormalities. SHH is one of a number of genes that have been associated with the congenital disorder holoprosencephaly, which causes abnormalities in brain and craniofacial development (Roessler et al, 2009; reviewed in Roessler and Muenke, 2011). SHH variants associated with the condition affect the autocatalytic processing of the precursor and dramatically impair the production of the secreted active Hh-Np, abrogating signaling (reviewed in Pan et al, 2013). Aberrant Hh signaling is also associated with gondal dysgenesis syndromes in which palmitoylation of DHH is abrogated by mutation of the acyltransferase HHAT (Callier et al, 2014).

**Literature references**


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The importance of the RAS/RAF/MAPK cascade in regulating cellular proliferation, differentiation and survival is highlighted by the fact that components of the pathway are mutated with high frequency in a large number of human cancers. Activating mutations in RAS are found in approximately one third of human cancers, while ~8% of tumors express an activated form of BRAF. RAS pathway activation is also achieved in a smaller subset of cancers by loss-of-function mutations in negative regulators of RAS signaling, such as the RAS GAP NF1 (reviewed in Prior et al, 2012; Pylayeva-Gupta et al, 2011; Stephen et al, 2014; Lavoie and Therrien, 2015; Lito et al, 2013; Samatar and Poulikakos, 2014; Maertens and Cichowski, 2014).

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**Signaling by KIT in disease**

**Location:** Diseases of signal transduction by growth factor receptors and second messengers

**Stable identifier:** R-HSA-9669938

**Diseases:** cancer

KIT signaling is important in several processes including stem cell maintenance, erythropoiesis, mast cell development, lymphopoiesis, melanogenesis and maintenance of interstitial cell of Cajal (Hirota et al, 1998; Chi et al, 2010). Gain-of-function mutations in KIT have been identified at low frequency in a number of diseases, including AML, melanoma and mast and germ cell tumors, and at higher frequency in gastrointestinal stromal tumors (reviewed in Lennartsson and Roonstrand, 2012; Abbaspour Babaei et al, 2016; Roskoski, 2018).

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PDGFRA and PDGFRB are type III receptor tyrosine kinases that promote development and maintenance of mesenchymal tissues, including vascular smooth muscle, kidney, intestine, skin and lung, among others (reviewed in Tallquist and Kazlauskas, 2004; reviewed in Wang et al, 2016). Signaling through PDGF receptors stimulates cell proliferation and survival through activation of downstream signaling pathways including the RAS-MAP kinase cascade, PI3K signaling and STAT signaling (reviewed in Roskoski, 2018). Aberrant signaling through PDGF receptors is implicated in a number of human diseases. Point mutations in PDGFRA and, to a lesser extent, PDGFRB are implicated in a number of cancers, such as gastrointestinal stromal tumors (GIST; 5-10% mutation frequency in PDGFRA) and haematological cancers (Corless et al, 2005; Wang et al, 2016; reviewed in Klug et al, 2018). In addition, amplified signaling through the PDGF pathway can arise through gene fusion events or overexpression of ligand or receptor through gene amplification (Ozawa et al, 2010; Verhaak et al, 2010; reviewed in Appiah-Kubi et al, 2017).

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FLT3 signaling in disease

**Location:** Diseases of signal transduction by growth factor receptors and second messengers

**Stable identifier:** R-HSA-9682385

**Diseases:** cancer

FLT3 is a type III receptor tyrosine kinase (RTK). The extracellular domain consists of 5 immunoglobulin (Ig) domains that contribute to dimerization and ligand binding. The intracellular region has a juxtamembrane domain that plays a role in autoinhibiting the receptor in the absence of ligand, and a bilobed kinase region with an activation loop and the catalytic cleft (reviewed in Klug et al, 2018). Signaling through FLT3 occurs after ligand-induced dimerization and transautophosphorylation, and promotes signaling through the MAP kinase, PI3K and STAT5 pathways, among others. FLT3 signaling promotes cellular proliferation and differentiation and contributes to haematopoiesis. FLT3 is mutated in up to 30% of acute myeloid leukemias. ~25% of the FLT3 mutations in AML cases occur as internal tandem duplications (ITDs) either in the juxtamembrane domain region encoded by exon 14 or the tyrosine kinase domain (TKD), while ~7-10% of AML cases contain FLT3 missense mutations in the TKD (reviewed in Klug et al, 2018; Daver et al, 2019). These mutations all support ligand-independent activation of the receptor and result in constitutive activation and signaling (Zheng et al, 2004; reviewed in Klug et al, 2018; Kazi and Roonstrand, 2019). In rare cases, the FLT3 locus is also subject to translocations that generate constitutively active fusion proteins (reviewed in Kazi and Roonstrand, 2019). Oncogenic FLT3 activity can be targeted with tyrosine kinase inhibitors, although resistance often arises due to secondary mutations or activation of bypass pathways (reviewed in Staude et al, 2018; Daver et al, 2019).

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# Table of Contents

## Introduction 1

- Diseases of signal transduction by growth factor receptors and second messengers 2
  - Signaling by EGFR in Cancer 3
  - Signaling by FGFR in disease 4
  - Signaling by ERBB2 in Cancer 6
  - PI3K/AKT Signaling in Cancer 8
  - Signaling by NOTCH1 in Cancer 10
  - Signaling by TGF-beta Receptor Complex in Cancer 12
  - Signaling by WNT in cancer 14
  - Hh mutants abrogate ligand secretion 16
  - Oncogenic MAPK signaling 18
  - Signaling by KIT in disease 19
  - Signaling by PDGFR in disease 21
  - FLT3 signaling in disease 23

## Table of Contents 25