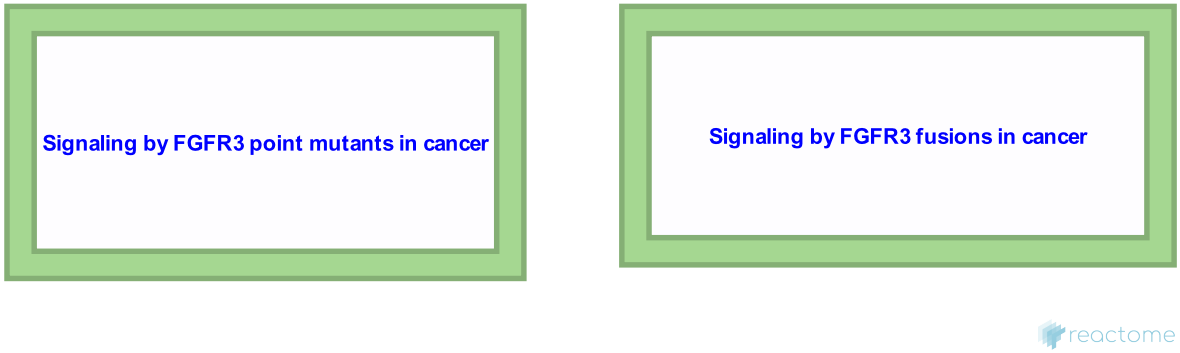
Signaling by FGFR3 in disease



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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

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

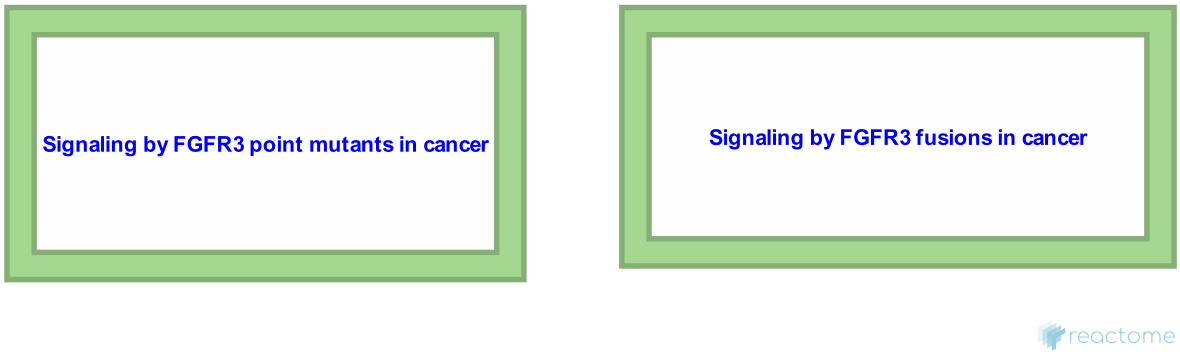
Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Signaling by FGFR3 in disease ↗

Stable identifier: R-HSA-5655332

Diseases: cancer, bone development disease



The FGFR3 gene has been shown to be subject to activating mutations and gene amplification leading to a variety of proliferative and developmental disorders depending on whether these events occur in the germline or arise somatically.

Activating mutations in FGFR3 are associated with the development of a range of skeletal dysplasias that result in dwarfism (reviewed in Webster and Donoghue, 1997; Burke et al, 1998; Harada et al, 2009). The most common form of human dwarfism is achondroplasia (ACH), which is caused by mutations G380R and G375C in the transmembrane domain of FGFR3 that are thought to promote ligand-independent dimerization (Rousseau et al, 1994; Shiang et al, 1994; Bellus et al, 1995a) Hypochondroplasia (HCH) is a milder form dwarfism that is the result of mutations in the tyrosine kinase domain of FGFR3 (Bellus et al, 1995b). Two neonatal lethal conditions, thanatophoric dysplasia type I and II (TDI and TDII) are also the result of mutations in FGFR3; TDI arises from a range of mutations that either result in the formation of unpaired cysteine residues in the extracellular region that promote aberrant ligand-independent dimerization or by mutations that introduce stop codons (Rousseau et al, 1995; Rousseau et al, 1996, D'Avis et al,1998). A single mutation, K650E in the second tyrosine kinase domain of FGFR3 is responsible for all identified cases of TDII (Tavormina et al, 1995a, b). Other missense mutations at the same K650 residue give rise to Severe Achondroplasia with Developmental Disorders and Acanthosis Nigricans (SADDAN) syndrome (Tavormina et al, 1999; Bellus et al, 1999). The severity of the phenotype arising from many of the activating FGFR3 mutations has recently been shown to correlate with the extent to which the mutations activate the receptor (Naski et al, 1996; Bellus et al, 2000)

In addition to mutations that cause dwarfism syndromes, a Pro250Arg mutation in the conserved dipeptide between the IgII and IgIII domains has been identified in an atypical craniosynostosis condition (Bellus et al, 1996; Reardon et al, 1997). This mutation, which is paralogous to mutations seen in FGFR1 and 2 in Pfeiffer and Apert Syndrome, respectively, results in an increase in ligand-binding affinity for the receptor (Ibrahimi et al, 2004b).

Of all the FGF receptors, FGFR3 has perhaps the best established link to the development in cancer. 50% of bladder cancers have somatic mutations in the coding sequence of FGFR3; of these, more than half occur in the extracellular region at a single position (S249C) (Cappellen et al, 1999; Naski et al, 1996; di Martino et al, 2009, Sibley et al, 2001). Activating mutations are also seen in the juxta- and trans-membrane domains, as well as in the kinase domain (reviewed in Weshe et al, 2011). As is the case for the other receptors, many of the activating mutations that are seen in FGFR3-related cancers mimic the germline FGFR3 mutations that give rise to autosomal skeletal disorders and include both ligand-dependent and inde-

pendent mechanisms (reviewed in Webster and Donoghue, 1997; Burke et al, 1998). In addition to activating mutations, the FGFR3 gene is subject to a translocation event in 15% of multiple myelomas (Avet-Loiseau et al, 1998; Chesi et al, 1997). This chromosomal rearrangement puts the FGFR3 gene under the control of the highly active IGH promoter and promotes overexpression and constitutive activation of FGFR3. In a small proportion of multiple myelomas, the translocation event is accompanied by activating mutations in the FGFR3 coding sequence (Chesi et al, 1997).

More recently, a number of fusion proteins of FGFR3 have been identified in various cancers (Singh et al, 2012; Williams et al, 2013; Parker et al, 2013; Wu et al, 2013; Wang et al, 2014; Yuan et al, 2014; reviewed in Parker et al, 2014). The most common fusion protein is TACC3, a coiled coil protein involved in mitotic spindle assembly. FGFR3 fusion proteins are constitutively active and appear to contribute to proliferation and tumorigenesis through activation of the ERK and AKT signaling pathways (reviewed in Parker et al, 2014).

Literature references

Bellus, GA., Spector, EB., Speiser, PW., Weaver, CA., Garber, AT., Bryke, CR. et al. (2000). Distinct missense mutations of the FGFR3 lys650 codon modulate receptor kinase activation and the severity of the skeletal dysplasia phenotype. *Am J Hum Genet, 67*, 1411-21. ↗

Rousseau, F., Bonaventure, J., Legeai-Mallet, L., Pelet, A., Rozet, JM., Maroteaux, P. et al. (1994). Mutations in the gene encoding fibroblast growth factor receptor-3 in achondroplasia. *Nature, 371*, 252-4. ↗

Harada, D., Yamanaka, Y., Ueda, K., Tanaka, H., Seino, Y. (2009). FGFR3-related dwarfism and cell signaling. *J Bone Miner Metab, 27*, 9-15. ↗

Avet-Loiseau, H., Li, JY., Facon, T., Brigaudeau, C., Morineau, N., Maloisel, F. et al. (1998). High incidence of translocations t(11;14)(q13;q32) and t(4;14)(p16;q32) in patients with plasma cell malignancies. *Cancer Res, 58*, 5640-5. ↗

Singh, P., Thomas, GE., Gireesh, KK., Manna, TK. (2014). TACC3 protein regulates microtubule nucleation by affecting γ-tubulin ring complexes. *J. Biol. Chem., 289*, 31719-35. ↗

Editions

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2014-11-20	Authored	Rothfels, K.
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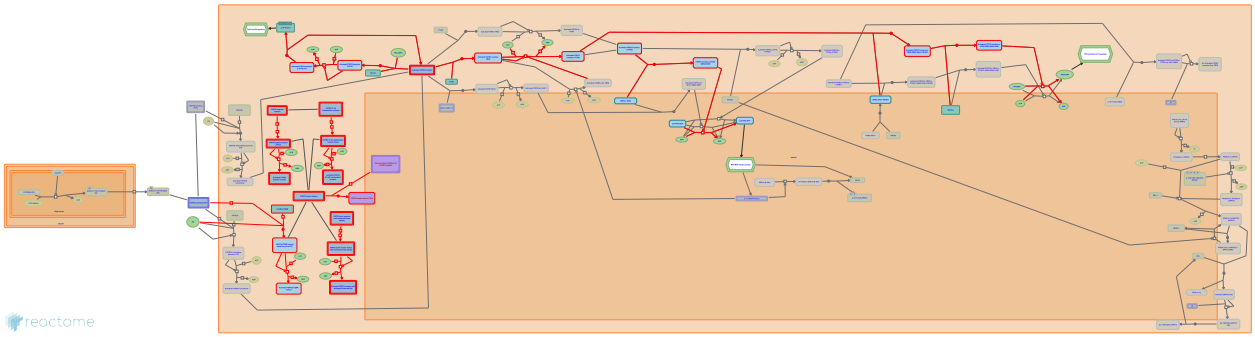
Signaling by FGFR3 point mutants in cancer ↗

Location: Signaling by FGFR3 in disease

Stable identifier: R-HSA-8853338

Diseases: cancer



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Literature references

Webster, MK., Donoghue, DJ. (1997). FGFR activation in skeletal disorders: too much of a good thing. *Trends Genet, 13* , 178-82. ↗

Burke, D., Wilkes, D., Blundell, TL., Malcolm, S. (1998). Fibroblast growth factor receptors: lessons from the genes. *Trends Biochem Sci, 23*, 59-62. ↗

Harada, D., Yamanaka, Y., Ueda, K., Tanaka, H., Seino, Y. (2009). FGFR3-related dwarfism and cell signaling. *J Bone Miner Metab, 27*, 9-15. ↗

Avet-Loiseau, H., Li, JY., Facon, T., Brigaudeau, C., Morineau, N., Maloisel, F. et al. (1998). High incidence of translocations t(11;14)(q13;q32) and t(4;14)(p16;q32) in patients with plasma cell malignancies. *Cancer Res, 58*, 5640-5. ↗

Rousseau, F., El Ghouzzi, V., Delezoide, AL., Legeai-Mallet, L., Le Merrer, M., Munnich, A. et al. (1996). Missense FGFR3 mutations create cysteine residues in thanatophoric dwarfism type I (TD1). *Hum Mol Genet, 5*, 509-12. ↗

Editions

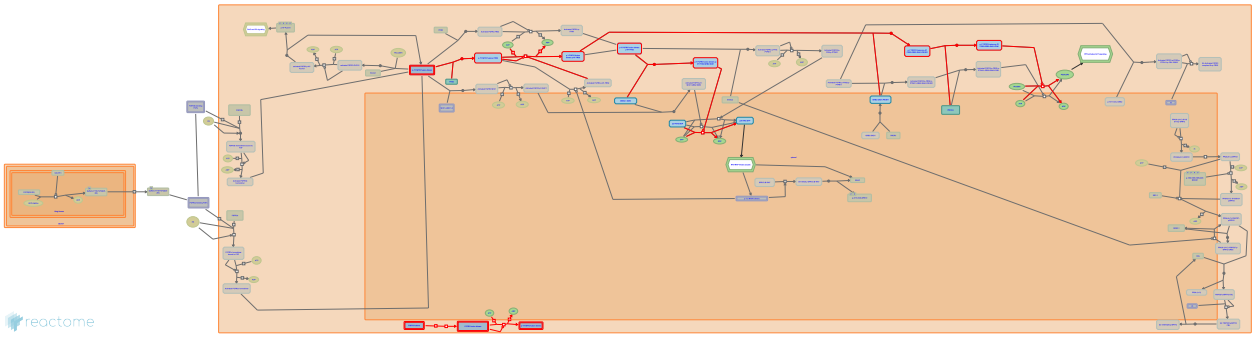
2012-02-09	Authored, Edited	Rothfels, K.
2012-05-15	Reviewed	Ezzat, S.

Signaling by FGFR3 fusions in cancer ↗

Location: Signaling by FGFR3 in disease

Stable identifier: R-HSA-8853334

Diseases: cancer



In recent years, recurrent fusions of FGFR3 have been identified in a number of cancers, including glioblastoma and cancers of the lung and bladder, among others (Singh et al, 2012; Parker et al, 2013; Williams et al, 2013; Wu et al, 2013; Capelletti et al, 2014; Yuan et al, 2014; Wang et al, 2014; Carneiro et al, 2015; reviewed in Parker et al, 2014). The most common fusion partner of FGFR3 is TACC3 (transforming acidic coiled coil protein 3), a protein involved in mitotic spindle assembly and chromosome segregation (Lin et al, 2010; Burgess et al, 2015). FGFR3 fusions are constitutively active and may form oligomers in a ligand-independent manner based on dimerization domains provided by the fusion partner (Singh et al, 2012; Williams et al, 2013; Parker et al, 2013; reviewed in Parker et al, 2014). Transformation and proliferation appear to be promoted through activation of the ERK and AKT signaling pathways. In contrast, PLC gamma signaling is not stimulated downstream of FGFR3 fusions, as the PLC gamma docking site is not present in the fusion. FGFR3 fusions are sensitive to protein kinase inhibitors, suggesting their potential as therapeutic targets (Singh et al, 2012; Williams et al, 2013; Wu et al, 2013; reviewed in Parker et al, 2014).

Literature references

Singh, D., Chan, JM., Zoppoli, P., Niola, F., Sullivan, R., Castano, A. et al. (2012). Transforming fusions of FGFR and TACC genes in human glioblastoma. *Science, 337*, 1231-5. ↗

Parker, BC., Annala, MJ., Cogdell, DE., Granberg, KJ., Sun, Y., Ji, P. et al. (2013). The tumorigenic FGFR3-TACC3 gene fusion escapes miR-99a regulation in glioblastoma. *J. Clin. Invest., 123*, 855-65. ↗

Williams, SV., Hurst, CD., Knowles, MA. (2013). Oncogenic FGFR3 gene fusions in bladder cancer. *Hum. Mol. Genet., 22*, 795-803. ↗

Wu, YM., Su, F., Kalyana-Sundaram, S., Khazanov, N., Ateeq, B., Cao, X. et al. (2013). Identification of targetable FGFR gene fusions in diverse cancers. *Cancer Discov, 3*, 636-47. ↗

Wang, R., Wang, L., Li, Y., Hu, H., Shen, L., Shen, X. et al. (2014). FGFR1/3 tyrosine kinase fusions define a unique molecular subtype of non-small cell lung cancer. *Clin. Cancer Res., 20*, 4107-14. ↗

Editions

2016-01-08	Authored, Edited	Rothfels, K.
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