Asian Journal of Pediatric Research

Volume 14, Issue 4, Page 20-27, 2024; Article no.AJPR.114843
ISSN: 2582-2950

The Role of Fibroblast Growth Factor-Receptor Pathway Aberrations in Pediatric Diseases

Stefan Bittmann [a,b++*], Elisabeth Luchter [b] and Elena Moschüring-Alieva [b]

[a] Shangluo Vocational and Technical College, Shangluo, 726000, Shaanxi, China.
[b] Ped Mind Institute (PMI), Department of Pediatrics, Hindenburgring 4, D-48599 Gronau, Germany.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/AJPR/2024/v14i4337

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/114843

Mini Review Article

Received: 17/01/2024
Accepted: 23/03/2024
Published: 01/04/2024

ABSTRACT

The fibroblast growth factor receptors play a crucial role in binding to fibroblast growth factor and are involved in various pathological conditions. These receptors consist of an extracellular ligand domain, a transmembrane helix domain, and an intracellular domain with tyrosine kinase activity. There are over 48 different isoforms of FGFR. Each FGF receptor in ligand-binding properties and kinase domains. The FGF/FGFR signaling pathway is implicated in various pediatric cancers and therefore are both non-selective and selective FGFR inhibitors available. Additionally, there are five distinct membrane FGF receptors dentified in vertebrates. All belonging to the tyrosine kinase superfamily. In this manuscript, the focus is based on an analysis of the role of FGF receptor signaling pathways and aberrations especially in pediatric diseases. Erk 1 and Erk 2 seem to have an important role as a mediator of FGF signaling in

[++] Visiting Professor;
**Corresponding author: Email: stefanbittmann@gmx.de;*

different biological and developmental processes. FGF signaling plays an important role in conserved developmental functions in skeletal growth, palate closure, ear development, cranial suture ossification and neuronal development in the child. Aberrant FGF signaling causes different congenital disorders and different forms of cancer in childhood. Modulating FGF signaling is of great importance for the treatment of rare diseases in childhood.

Keywords: FGF; receptor; signaling pathway; aberration; pediatric, disease.

1. INTRODUCTION

The fibroblast growth factors are a group of growth factors known as the FGF family. A total of 23 members of the FGF group are known to date: FGF-1 to FGF-23. FGFs are single-chain polypeptides with a mass usually between 16 and 22 kDalton. They are signaling proteins that are important and potent regulators of cell growth and differentiation. They play a key role in embryonic development. Accordingly, disturbances of FGF functions lead to severe developmental disorders in the embryonic period. In the adult organism, FGFs control tissue repair processes and are actively involved in the processes of wound healing and the formation of new blood vessels, as well as in the regeneration of nerves and cartilage tissue. FGFs have been detected in almost all tissues of the organism. FGFs control and alter or usually stimulate the proliferation, migration and differentiation of cells, especially endothelial cells, but also smooth muscle cells and fibroblasts. The complex process of angiogenesis is essentially controlled and influenced by growth factors of the FGF family. Prototypes of the FGF family are FGF-1 (acidic-FGF) and FGF-2 (basic-FGF). FGF molecules bind to their specific receptors (FGFR = FGF receptor) on the cell surface. FGFRs are receptor tyrosine kinases which -after binding the ligand FGF-are activated by autophosphorylation and initiate an intracellular signaling cascade with subsequent gene activation. FGFRs consist of an extracellular region containing three immunoglobulin-like (IG-like) protein domains (D1-D3), a single transmembrane helix, and an intracellular protein domain with tyrosine kinase activity. There are four FGFRs: FGFR1, FGFR2, FGFR3, FGFR4. Alternative mRNA splicing of the FGFR1-3 receptors results in additional forms of FGFRs (a total of seven FGFRs are known), which are designated "b" and "c". FGF-1 is the only ligand that binds to all seven cell surface receptors. The actual signaling complex formed at the cell membrane after binding of FGF and FGFR is called a ternary complex, which consists of two identical FGF ligands, two identical FGF receptor units and either one or two heparan sulfate chains. A special feature of the mechanism of action of FGFs is that it is significantly enhanced by the particularly high affinity of FGFs for proteoglycans, heparan sulphates and heparin (glycosaminoglycan). This is why the growth factors of the FGF family were previously also referred to as heparin-binding growth factors (HBGFs).

2. 23 FIBROBLAST GROWTH FACTORS AND CO-factors

FGF-1 is the most active growth factor of the FGF family [1-53]. It consists of 141 amino acids [1-52]. The FGF-1-encoding gene is located on chromosome 5. Due to its comprehensive binding capacity with all FGF receptors, the biological, mitogenic cell effects are particularly pronounced and characterized by the initiation of cell proliferation, migration and differentiation. FGF-1 has a particular effect on endothelial cells, but also on many other cell types. Due to the particularly pronounced angiogenic activity of FGF-1, FGF-1 has recently been studied more intensively in clinical research and used in various clinical studies in human medicine [1-53]. The plasma half-life of FGF-1 after intramyocardial injection is between 0.4 and 4.6 hours. High purification of FGF-1 by SDS-polyacryamide gel electrophoresis. *FGF-2 (b-FGF)* has a similar molar mass to FGF-1; its structure is more than 50 % identical to that of FGF-1. The FGF-2 coding gene is localized on chromosome 4. The effects of FGF-2 are similar to those of FGF-1, but not quite as pronounced. It is also produced by adipocytes and influences bone metabolism.

FGF-3 consists of 240 amino acids, its structure is approximately 40 % homologous with FGF-1; the coding gene is located on chromosome 11 [1,6,7]. The physiological effects of FGF-3 are still poorly understood, but it is possible that FGF-3 may be particularly important during embryonic development. *FGF-4 (formerly K-FGF or hst1)* consists of 206 amino acids, is 40 % homologous with the structure of FGF-1-3, and the coding gene is located on chromosome 11.

FGF-4 is frequently found in tumors, especially in gastric tumors. In healthy adult tissues, FGF-4 is only present in low concentrations. FGF-5 consists of 251 amino acids, the coding gene is located on chromosome 4. *FGF-5* apparently plays an important role during embryonic development, but in adult tissues, FGF-5 is only present in very low concentrations. *FGF-6* is 70 % homologous with FGF-4. The coding gene is located on chromosome 12. Little is known about its effects, but FGF-6 may play a role in wound healing. *FGF-7* was first called keratinocyte growth factor; it has a specific proliferative effect on epithelial cells. The coding gene is located on chromosome 15. *FGF-8* (gene localization on chromosome 10) may play a key role in the formation of the extremities during embryonic development. *FGF-9*, initially referred to as glioma-derived growth factor (GDGF), stimulates in particular the proliferation and activation of glial cells in the brain. *FGF-10 to FGF-22*: Although the structures and amino acid sequences of these growth factors have been described, little is known about the detailed functions of these proteins. FGF-18 stimulates the formation of cartilage in model organisms when injected intraarticularly. A recombinantly produced human FGF-18 is currently undergoing clinical trials. *FGF-23* is secreted by osteocytes and is an important regulator of the phosphate and vitamin D balance. FGF-23 stimulates the excretion of phosphate by the kidneys. The task of FGF-23 is to keep phosphate levels in the blood constant despite varying phosphate intake with food. Increased blood levels of FGF-23 lead to a drop in the phosphate level in the blood (hypophosphatemia), reduced production of 1,25 (OH)2 vitamin D and rickets or bone softening. Reduced blood levels of FGF-23 lead to increased phosphate levels in the blood (hyperphosphatemia), increased production of 1,25 (OH)2 vitamin D, soft tissue calcification, excessive bone formation (hyperostosis) and reduced life expectancy. In kidney patients who have to start dialysis treatment, increased FGF-23 levels are associated with increased mortality. FGF-23 binds to the FGF receptor 1c and the co-receptor Klotho. Activation of this receptor complex in the proximal tubule in the nephron of the kidney inhibits the reabsorption of phosphate from the primary urine and thus has a phos-Activation of this receptor complex in the proximal tubule in the nephron of the kidney inhibits the reabsorption of phosphate from the primary urine and thus has a phos-Activation of this receptor complex in the proximal tubule in the nephron of the kidney inhibits the reabsorption of phosphate from the primary urine and thus has a phosphoric effect.

3. CO-FACTORS

Eight factors belonging to the fibroblast growth factor family are known [1-53]. These are acidic FGF (aFGE), basic FGF (bFGF), int-2, Kaposi sarcoma FGF (K. FGF), also known as the product of hst-l oncogene, FGF5, FGF6, keratinocyte growth factor (KGF) and androgen induced growth factor (AIGT). These polypeptides are 35-55% identical in their amino acid sequence and the aquainted genes have similar exon- intron structures. In contrast to the other members of the family, aFGF and bEGF lack a signal sequence, and the mechanism of their secretion is not yet fully understood. The most widely studied FGEs, aFGf and bFGE, appear to elicit very similar biological responses in most target cell types. These two factors have effects in vito on a wide variety of cells of mesodermal, neutroectodermal as well as endodermal origin. They support the survival of neural cells and stimulate the proliferation of many cell types including fibroblasts, endothelial cells, smooth muscle cells, hepatocytes and skeletal myoblasts. aFGF and bFGE can also affect cellular differentiation: both factors stimulate the outgrowth by Polz rat pheochromocytoma cells and are capable of blocking myoblasts of the skelet differentiation. In addition, bFGF has been claimed to enhance the cloning efficiency of hematopoietic progenitor celis. Other PGEs may have more specific functions. The mitogenic activity of KGF seems to be restricted to epithelial cell lines. In vitro bFGE has been implicated in mesoderm induction in Xenopus embryos. Disruption of the FGF signaling by expression of a dominant negative mutant of the Xenopus FGF receptor has recently been shown to inhibit the formation of mesodermal tissues. Other members of the FGF l family also seem to function in developmental processes. In addition to inducing proliferation and migration of endothelial cells in culture, bFGF and aFGF also induce neovascular structures in vivo. It was recently claimed that the progression and neovascularization of fibro sarcomas of transgenic mice carrying the bovine papillomavirus genome is correlated with enhanced secretion of bFGF.

4. LIGAND BINDING SPECIFICITY

The ligand binding represents the first step in activating the FGFR signaling cascade. FGFR`s

are based on three immunoglobulin-like domains (IgI-III) [48]. The ligand binding specificity depends on splicing of the C terminus of the Ig III domain, which will be encoded by exon 8 and 9 to produce FGFRb or FRGFRc isoforms, which correlate to receptors of epithelial or mesenchymal tissues [48].

5. INTRACELLULAR SIGNALING WITH PROTEIN INTERACTIONS (MODULATORS) OF FGFR 1-4

Known intracellular protein interactions of FGFR1-4 are Frs2 and 3, CrkL and II, Shb, SH2, Grb14, Stat1 and 3, Src, SH2, SH3 and p85 protein [48]. Some interactions depend on additional FGFR1-4 mutations [48]. FGF signaling seems to be the major driver of Erk1 and 2 activation in many different developmental processes. For example, FGF4-Erk 1 and 2 regulate the primitive endoderm specification. Erk 1 and 2 signaling is necessary for primitive endoderm formation [48]. FGF-Erk1/2 signaling regulates epithelial-mesenchymal interactions in the limb [48]. Genetic disruption of FGF-10 or FGFR2b results in complete agenesis of the limbs [49]. Conditional disruption of FGF8 and FGF4 or FGFR2 in epithelial tissue causes complete agenesis of the hindlimb [50]. FGFR3 functions through Erk1/2 for inhibiting chondrocyte hypertrophic differentiation [48]. Loss of FGFR3 function causes long bone overgrowth, activated mutations in FGFR3 cause skeletal dwarfism like achondroplasia in childhood [48]. Erk1/2 and STAT 1 seem to regulate FGFR3 mediated inhibition of chondrocyte proliferation [51,52]. FGFR1 is part of complex binding with FGF23 and Klotho in X-linked hypophosphatemia [53]. *Klotho-FGFR1-FGF23 trimeric complex signaling* plays an important role in X-linked hypophosphatemia in childhood and inhibition of this complex could diminish the level of FGF in the kidney in this disease [53].

6. CHEMICAL STRUCTURES OF FGFs

The first FGFs were discovered and their chemical structures are described in the 1970s [1-53]. Initially, it was assumed that they acted exclusively on fibroblasts. However, it was later discovered that FGFs have much more general functions - especially proliferation and differentiation - and can act on almost all cells. Today, even FGFs are known that there is no effect on fibroblasts, FGF-7 and FGF-9. FGF-1 and FGF-2 were initially obtained and isolated from the brain of cattle, and later the structures of the human growth factors FGF-1 and FGF-2 were also described. The enhancing effect of heparin and heparan sulphates on the function of FGFs was recognized early on. To date, 23 different sub-types of the FGF family have been described. The different FGF types have intensive mitogenic activities and are of great importance for organ differentiation and development in the embryonic period. They regulate cell proliferation, migration and differentiation. Regular cell and tissue differentiation is not possible without FGFs. In adult tissues and organs, FGFs - especially FGF-1 - have an extremely intensive activity on the induction of angiogenesis. This property of FGFs has recently aroused the interest of medical research, as angiogenesis can be used as a therapeutic principle in disease states and disorders in which arterial blood flow is impaired, coronary heart disease (CHD) and peripheral artery disease (PAD). Coronary heart disease (CHD) and peripheral arterial occlusive disease (PAD). Hypoxia and ischemia trigger the secretion of FGF-1 and FGF-2, resulting in an up-regulation of FGF receptors in the tissue. Hypoxia and ischemia trigger the secretion of FGF-1 and FGF-2, resulting in an up-regulation of FGF receptors in the tissue. Clinical studies with patients suffering from severe coronary heart disease have demonstrated FGF-1-induced new vessels in the human heart muscle, as well as a local increase in blood flow with a reduction in angina pectoris symptoms. FGFs, especially FGF-1, also have a wound healing-promoting effect in cases of wound healing disorders. FGFR signaling can also lead to the activation of various downstream effectors, such as cell, survival, migration, and differentiation [8,25,51]. These functions are essential for normal development and tissue homeostasis. Dysregulation of FGFR signaling can lead to various diseases, including cancer, skeletal dysplasia, and developmental disorders [1,4,7,9]. Understanding the complex functions of FGFR signaling is crucial for developing targeted therapies for different pediatric diseases in the future [1-53].

7. CONCLUSION

The fibroblast growth factor family plays a key role in various developmental processes such as brain patterning, branching morphogenesis, and limb development. Researchers are currently exploring the therapeutic potential of FGFs in promoting cell growth, protecting cells, and

stimulating blood vessel formation. Recent studies have highlighted the important functions of the endocrine-acting FGF19 subfamily in regulating bile acid, glucose, and phosphate levels, leading to increased interest in the potential medical applications of these molecules. There is a potential in treating metabolic syndromes, skeletal dysplasia, cancer and hypophosphatemic disorders in childhood by altering fibroplast growth factor signaling pathways.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Liu G, Chen T, Ding Z, Wang Y, Wei Y, Wei X. Inhibition of FGF-FGFR and VEGF-VEGFR signalling in cancer treatment. Cell Prolif. 2021 Apr;54(4):e13009.
   DOI: 10.1111/cpr.13009. Epub 2021 Mar 2.
   PMID: 33655556
   PMCID: PMC8016646
2. Uehara Y, Ikeda S, Kim KH, Lim HJ, Adashek JJ, Persha HE, Okamura R, Lee S, Sicklick JK, Kato S, Kurzrock R. Targeting the FGF/FGFR axis and its co-alteration allies. ESMO Open. 2022 Dec; 7(6):100647.
   DOI: 10.1016/j.esmoop.2022.100647. Epub 2022 Nov 29.
   PMID: 36455506
   PMCID: PMC9808461
3. Taguchi M, Takeuchi Y. FGF receptor and FGF signaling pathways. Nihon Rinsho. 2005 Oct;63 Suppl 10:480-5.
   PMID: 16279686
4. Daniele G, Corral J, Molife LR, de Bono JS. FGF receptor inhibitors: Role in cancer therapy. Curr Oncol Rep. 2012 Apr;14 (2):111-9.
   DOI: 10.1007/s11912-012-0225-0
   PMID: 22311684
5. Jin M, Du X, Chen L. Cross-talk between FGF and other cytokine signalling pathways during endochondral bone development. Cell Biol Int. 2012 Aug 1;36(8):691-6.
   DOI: 10.1042/CBI20110352
   PMID: 22803513
6. Sbiera I, Kircher S, Altieri B, Lenz K, Hantel C, Fassnacht M, Sbiera S, Kroiss M. Role of FGF receptors and their pathways in adrenocortical tumors and possible therapeutic implications. Front Endocrinol (Lausanne). 2021 Dec 9;12: 795116.
   DOI: 10.3389/fendo.2021.795116
   PMID: 34956100
   PMCID: PMC8699171
7. Ahmad I, Iwata T, Leung HY. Mechanisms of FGFR-mediated carcinogenesis. Biochim Biophys Acta. 2012 Apr;1823(4): 850-60.
   DOI: 10.1016/j.bbamcr.2012.01.004. Epub 2012 Jan 18.
   PMID: 22273505
8. Mahapatra S, Jonniya NA, Koirala S, Ursal KD, Kar P. The FGF/FGFR signalling mediated anti-cancer drug resistance and therapeutic intervention. J Biomol Struct Dyn. 2023;41(22):13509-13533.
   DOI: 10.1080/07391102.2023.2191721. Epub 2023 Mar 30
   PMID: 36995019
9. Dabney RS, Khalife M, Shahid K, Phan AT. Molecular pathways and targeted therapy in cholangiocarcinoma. Clin Adv Hematol Oncol. 2019 Nov;17(11):630-637.
   PMID: 31851165
10. Tanner Y, Grose RP. Dysregulated FGF signalling in neoplastic disorders. Semin Cell Dev Biol. 2016 May;53:126-35.
    DOI: 10.1016/j.semcdb.2015.10.012. Epub 2015 Oct 19
    PMID: 26463732
11. Tanner Y, Grose RP. Dysregulated FGF signalling in neoplastic disorders. Semin Cell Dev Biol. 2016 May;53:126-35.
    DOI: 10.1016/j.semcdb.2015.10.012. Epub 2015 Oct 19
    PMID: 26463732
12. Furusho M, Ishii A, Bansal R. Signaling by FGF receptor 2, not FGF receptor 1, regulates myelin thickness through activation of ERK1/2-MAPK, which promotes mTORC1 activity in an akt-independent manner. J Neurosci. 2017 Mar 15;37(11):2931-2946.
    DOI: 10.1523/JNEUROSCI.3316-16.2017. Epub 2017 Feb 13
    PMID: 28193689
    PMCID: PMC5354334
13. Pérez Piñero C, Giulianelli S, Lamb CA, Lanari C. New Insights in the Interaction of FGF/FGFR and steroid receptor signaling

in breast cancer. Endocrinology. 2022 Feb 1;163(2):bqab265.
DOI: 10.1210/endocr/bqab265
PMID: 34977930

14. Ferguson HR, Smith MP, Francavilla C. Fibroblast growth factor receptors (FGFRs) and noncanonical partners in cancer signaling. Cells. 2021 May 14;10(5):1201.
DOI: 10.3390/cells10051201
PMID: 34068954
PMCID: PMC8156822
15. Marie PJ, Miraoui H, Sévère N. FGF/FGFR signaling in bone formation: progress and perspectives. Growth Factors. 2012 Apr;30 (2):117-23.
DOI: 10.3109/08977194.2012.656761. Epub 2012 Feb 1
PMID: 22292523
16. Kumar SB, Narasu L, Gundla R, Dayam R, JARPS. Fibroblast growth factor receptor inhibitors. Curr Pharm Des. 2013;19 (4): 687-701.
PMID: 23016864
17. Ornitz DM, Marie PJ. FGF signaling pathways in endochondral and intramembranous bone development and human genetic disease. Genes Dev. 2002 Jun 15;16(12):1446-65.
DOI: 10.1101/gad.990702
PMID: 12080084
18. Ornitz DM, Herr AB, Nilsson M, Westman J, Svahn CM, Waksman G. FGF binding and FGF receptor activation by synthetic heparan-derived di- and trisaccharides. Science. 1995 Apr 21;268(5209):432-6.
DOI: 10.1126/science.7536345
PMID: 7536345
19. Agrawal S, Maity S, AlRaawi Z, Al-Ameer M, Kumar TKS. Targeting drugs against fibroblast growth factor(s)-induced cell signaling. Curr Drug Targets. 2021;22 (2): 214-240.
DOI: 10.2174/1389450121999201012201926
PMID: 33045958
20. Kono SA, Heasley LE, Doebele RC, Camidge DR. Adding to the mix: Fibroblast growth factor and platelet-derived growth factor receptor pathways as targets in non-small cell lung cancer. Curr Cancer Drug Targets. 2012 Feb;12(2):107-23.
DOI: 10.2174/156800912799095144
PMID: 22165970
PMCID: PMC3418220
21. Bao Y, Gabrielpillai J, Dietrich J, Zarbl R, Strieth S, Schröck F, Dietrich D. Fibroblast growth factor (FGF), FGF receptor (FGFR), and cyclin D1 (CCND1) DNA methylation in head and neck squamous cell carcinomas is associated with transcriptional activity, gene amplification, human papillomavirus (HPV) status, and sensitivity to tyrosine kinase inhibitors. Clin Epigenetics. 2021 Dec 21;13(1):228.
DOI: 10.1186/s13148-021-01212-4
PMID: 34933671
PMCID: PMC8693503
22. Hallinan N, Finn S, Cuffe S, Rafee S, O'Byrne K, Gately K. Targeting the fibroblast growth factor receptor family in cancer. Cancer Treat Rev. 2016 May;46: 51-62.
DOI: 10.1016/j.ctrv.2016.03.015. Epub 2016 Apr 12
PMID: 27109926
23. Astolfi A, Pantaleo MA, Indio V, Urbini M, Nannini M. The emerging role of the FGF/FGFR pathway in gastrointestinal stromal tumor. Int J Mol Sci. 2020 May 7;21(9):3313.
DOI: 10.3390/ijms21093313
PMID: 32392832
PMCID: PMC7246647
24. Chen H, Cui Y, Zhang D, Xie J, Zhou X. The role of fibroblast growth factor 8 in cartilage development and disease. J Cell Mol Med. 2022 Feb;26(4):990-999.
DOI: 10.1111/jcmm.17174. Epub 2022 Jan 9
PMID: 35001536
PMCID: PMC8831980
25. Dietrich D. FGFR-gerichtete therapie von kopf-hals-karzinomen FGFR-targeted therapy in head and neck carcinomas. HNO. 2021 Mar;69(3):172-184.
DOI: 10.1007/s00106-020-00893-2
PMID: 32519203
PMCID: PMC7902560
26. Sonpavde G, Willey CD, Sudarshan S. Fibroblast growth factor receptors as therapeutic targets in clear-cell renal cell carcinoma. Expert Opin Investig Drugs. 2014 Mar;23(3):305-15.
DOI: 10.1517/13543784.2014.871259. Epub 2014 Jan 3
PMID: 24387233
27. Szeb Belcheva MM, Haas PD, Tan Y, Heaton VM, Coscia CJ. The fibroblast growth factor receptor is at the site of convergence between mu-opioid receptor and growth factor signaling pathways in rat C6 glioma cells. J Pharmacol Exp Ther. 2002 Dec;303(3):909-18.
DOI: 10.1124/jpet.102.038554

PMID: 12438509.
Enyi G, Fallon JF. Fibroblast growth factors as multifunctional signaling factors. Int Rev Cytol. 1999;185:45-106.
DOI: 10.1016/s0074-7696(08)60149-7
PMID: 9750265

28. Brooks AN, Kilgour E, Smith PD. Molecular pathways: Fibroblast growth factor signaling: A new therapeutic opportunity in cancer. Clin Cancer Res. 2012 Apr 1;18(7):1855-62.
DOI: 10.1158/1078-0432.CCR-11-0699. Epub 2012 Mar 2
PMID: 22388515
29. Dianat-Moghadam H, Teimoori-Toolabi L. Implications of fibroblast growth factors (FGFs) in cancer: From prognostic to therapeutic applications. Curr Drug Targets. 2019;20(8):852-870.
DOI: 10.2174/1389450120666190112145409
PMID: 30648505
30. Dailey L, Ambrosetti D, Mansukhani A, Basilico C. Mechanisms underlying differential responses to FGF signaling. Cytokine Growth Factor Rev. 2005 Apr;16 (2):233-47.
DOI: 10.1016/j.cytogfr.2005.01.007. Epub 2005 Mar 5
PMID: 15863038
31. Goetz R, Mohammadi M. Exploring mechanisms of FGF signalling through the lens of structural biology. Nat Rev Mol Cell Biol. 2013 Mar;14(3):166-80.
DOI: 10.1038/nrm3528. Epub 2013 Feb 13
PMID: 23403721
PMCID: PMC3695728
32. Marek L, Ware KE, Fritzsche A, Hercule P, Helton WR, Smith JE, McDermott LA, Coldren CD, Nemenoff RA, Merrick DT, Helfrich BA, Bunn PA Jr, Heasley LE. Fibroblast growth factor (FGF) and FGF receptor-mediated autocrine signaling in non-small-cell lung cancer cells. Mol Pharmacol. 2009 Jan;75(1):196-207.
DOI: 10.1124/mol.108.049544. Epub 2008 Oct 10
PMID: 18849352
PMCID: PMC2669785
33. Xie X, Wang Z, Chen F, Yuan Y, Wang J, Liu R, Chen Q. Roles of FGFR in oral carcinogenesis. Cell Prolif. 2016 Jun;49(3):261-9.
DOI: 10.1111/cpr.12260
PMID: 27218663
PMCID: PMC6495773
34. Repetto M, Crimini E, Giugliano F, Morganti S, Belli C, Curigliano G. Selective FGFR/FGF pathway inhibitors: Inhibition strategies, clinical activities, resistance mutations, and future directions. Expert Rev Clin Pharmacol. 2021 Oct;14(10): 1233-1252.
DOI: 10.1080/17512433.2021.1947246
PMID: 34591728
35. Chmiel P, Gęca K, Rawicz-Pruszyński K, Polkowski WP, Skórzewska M. FGFR inhibitors in cholangiocarcinoma-a novel yet primary approach: Where do we stand now and where to head next in targeting this axis? Cells. 2022 Dec 5;11(23):3929.
DOI: 10.3390/cells11233929
PMID: 36497187
PMCID: PMC9737583
36. Marseglia G, Lodola A, Mor M, Castelli R. Fibroblast growth factor receptor inhibitors: Patent review (2015-2019). Expert Opin Ther Pat. 2019 Dec;29(12):965-977.
DOI: 10.1080/13543776.2019.1688300. Epub 2019 Nov 8
PMID: 31679402
37. Demo SD, Kikuchi A, Peters KG, MacNicol AM, Muslin AJ, Williams LT. Signaling molecules that mediate the actions of FGF. Princess Takamatsu Symp. 1994 ;24:243-9.
PMID: 8983079
38. Demo SD, Kikuchi A, Peters KG, MacNicol AM, Muslin AJ, Williams LT. Signaling molecules that mediate the actions of FGF. Princess Takamatsu Symp. 1994;24:243-9.
PMID: 8983079
39. Criscitiello C, Esposito A, De Placido S, Curigliano G. Targeting fibroblast growth factor receptor pathway in breast cancer. Curr Opin Oncol. 2015 Nov;27(6):452-6.
DOI: 10.1097/CCO.0000000000000224
PMID: 26397764
40. Coleman SJ, Bruce C, Chioni AM, Kocher HM, Grose RP. The ins and outs of fibroblast growth factor receptor signalling. Clin Sci (Lond). 2014 Aug;127(4):217-31.
DOI: 10.1042/CS20140100
PMID: 24780002
41. Yashiro M, Matsuoka T. Fibroblast growth factor receptor signaling as therapeutic targets in gastric cancer. World J Gastroenterol. 2016 Feb 28;22(8):2415-23.
DOI: 10.3748/wjg.v22.i8.2415
PMID: 26937130
PMCID: PMC4768188

42. Horton WA, Hall JG, Hecht JT. Achondroplasia. Lancet. 2007 Jul 14;370(9582):162-172.
DOI: 10.1016/S0140-6736(07)61090-3
PMID: 17630040

43. Haffner D, Leifheit-Nestler M. Extrarenal effects of FGF23. Pediatr Nephrol. 2017 May;32(5):753-765.
DOI: 10.1007/s00467-016-3505-3. Epub 2016 Oct 4
PMID: 27704252

44. Högler W, Ward LM. New developments in the management of achondroplasia. Wien Med Wochenschr. 2020 Apr;170(5-6):104-111.
DOI: 10.1007/s10354-020-00741-6. Epub 2020 Mar 6
PMID: 32144686
PMCID: PMC7098936

45. Laederich MB, Horton WA. FGFR3 targeting strategies for achondroplasia. Expert Rev Mol Med. 2012 Jan 19;14:e11.
DOI: 10.1017/erm.2012.4
PMID: 22559284

46. Brown LM, Ekert PG, Fleuren EDG. Biological and clinical implications of FGFR aberrations in paediatric and young adult cancers. Oncogene. 2023 Jun;42(23): 1875-1888.
DOI: 10.1038/s41388-023-02705-7. Epub 2023 May 2.
PMID: 37130917
PMCID: PMC10244177

47. Guthrie G, Vonderohe C, Burrin D. Fibroblast growth factor 15/19 expression, regulation, and function: An overview. Mol Cell Endocrinol. 2022 May 15;548:111617.
DOI: 10.1016/j.mce.2022.111617. Epub 2022 Mar 15
PMID: 35301051
PMCID: PMC9038700

48. Brewer JR, Mazot P, Soriano P. Genetic insights into the mechanisms of Fgf signaling. Genes Dev. 2016 Apr 1;30(7): 751-71.
DOI: 10.1101/gad.277137.115
PMID: 27036966
PMCID: PMC4826393

49. De Moerlooze L, Spencer-Dene B, Revest JM, Hajihosseini M, Rosewell I, Dickson C. An important role for the IIIb isoform of fibroblast growth factor receptor 2 (FGFR2) in mesenchymal-epithelial signalling during mouse organogenesis. Development. 2000 Feb;127(3):483-92.
DOI: 10.1242/dev.127.3.483
PMID: 10631169

50. Yu K, Ornitz DM. FGF signaling regulates mesenchymal differentiation and skeletal patterning along the limb bud proximodistal axis. Development. 2008 Feb;135(3):483-91.
DOI: 10.1242/dev.013268. Epub 2007 Dec 19
PMID: 18094024

51. Raucci A, Laplantine E, Mansukhani A, Basilico C. Activation of the ERK1/2 and p38 mitogen-activated protein kinase pathways mediates fibroblast growth factor-induced growth arrest of chondrocytes. J Biol Chem. 2004 Jan 16;279(3):1747-56.
DOI: 10.1074/jbc.M310384200. Epub 2003 Oct 30
PMID: 14593093

52. Krejci P, Prochazkova J, Bryja V, Jelinkova P, Pejchalova K, Kozubik A, Thompson LM, Wilcox WR. Fibroblast growth factor inhibits interferon gamma-STAT1 and interleukin 6-STAT3 signaling in chondrocytes. Cell Signal. 2009 Jan;21(1): 151-60.
DOI: 10.1016/j.cellsig.2008.10.006. Epub 2008 Oct 12
PMID: 18950705
PMCID: PMC2655766

53. Bittmann S, Moschuring-Alieva E, Luchter E, Villalon G. Current and future therapeutical aspects of x-linked hypophosphatemia in children with special attention to klotho/fibroblast growth factor 23 system. J Clin Med Res. 2022 Oct;14(10):436-439.
DOI: 10.14740/jocmr4820. Epub 2022 Oct 28
PMID: 36406946
PMCID: PMC9635803

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/114843