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*Review Article*

# A Network Map of FGF-1/FGFR Signaling System

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Fibroblast growth factor-1 (FGF-1) is a well characterized growth factor among the 22 members of the FGF superfamily in humans. It binds to all the four known FGF receptors and regulates a plethora of functions including cell growth, proliferation, migration, differentiation, and survival in different cell types. FGF-1 is involved in the regulation of diverse physiological processes such as development, angiogenesis, wound healing, adipogenesis, and neurogenesis. Deregulation of FGF-1 signaling is not only implicated in tumorigenesis but also is associated with tumor invasion and metastasis. Given the biomedical significance of FGFs and the fact that individual FGFs have different roles in diverse physiological processes, the analysis of signaling pathways induced by the binding of specific FGFs to their cognate receptors demands more focused efforts. Currently, there are no resources in the public domain that facilitate the analysis of signaling pathways induced by individual FGFs in the FGF/FGFR signaling system. Towards this, we have developed a resource of signaling reactions triggered by FGF-1/FGFR system in various cell types/tissues. The pathway data and the reaction map are made available for download in different community standard data exchange formats through NetPath and NetSlim signaling pathway resources.

## 1. Introduction

Fibroblast growth factor (FGF) superfamily consists of structurally related polypeptides most of which function through its high affinity fibroblast growth factor receptors (FGFRs). In addition to FGFRs, they also bind to heparan sulfate proteoglycans (HPSGs) and their analog, heparin. These interactions influence the stability of FGFs in the extracellular matrix and also regulate their binding and activation of FGFRs [1–9]. In humans, FGFs are encoded by 22 genes, FGF-1-14 and FGF-16-23, and are divided into 7 subfamilies. FGFs 1–10 and 16–23 are FGFR ligands, while FGFs 11–14 are intracellular FGF homologous factors which act in a receptor-independent fashion [10]. Knock-out mice of different FGFs exhibit diverse developmental and physiological disorders [11]. For instance, FGF-9 is involved in the development of lung and testes [12, 13], FGF-3 is critical for inner ear development [14], and FGF-18 is important in bone and lung development [15–17]. Moreover, knock-out of FGFs 4, 8, 9, 10, 15, 18, or 23 was found to be lethal in mice [18]. FGFs are also involved in wound healing, tissue repair [19, 20], and angiogenesis [21]. Facilitating cell proliferation, migration,

and differentiation [16, 22–26], FGFs are implicated in diverse pathological conditions including cancer [27] as well as metabolic and developmental disorders [18].

Most FGFs have an N-terminal signal peptide and are thus secreted. FGFs 1, 2, 9, 16, and 20 do not have signal peptides. FGFs 9, 16, and 20 may be released through classical secretory pathway; however, FGF-1 and FGF-2 are released from damaged cells or through endoplasmic reticulum-golgi independent exocytotic pathway [10]. FGF-1 along with FGF-2 was initially isolated from bovine pituitary extracts based on their ability to induce proliferation in 3T3 fibroblasts [28, 29]. Also known as acidic FGF, FGF-1 is a 155 amino acid long non-glycosylated polypeptide. FGF-1 is not released from the cells under normal physiological conditions, but it was secreted in response to stress conditions such as heat shock, hypoxia [30, 31], serum starvation [32], and exposure to low-density lipoproteins [33]. Stress induces the release of inactive disulfide bond-linked homodimeric form of FGF-1, which is dependent on p40-Syt1, S100A13, and $Cu^{2+}$ ions [34–37]. FGF-1 has been shown to reduce apoptosis in vascular injury [38–40]. Administration of FGF-1 has shown promise as a therapeutic strategy against human cervical spinal cord injury [41] and ischemic conditions [42–44]. Increased expression of FGF-1 was observed in ovarian [45] and prostate cancers [46]. Taken together, FGF1 is involved in different cellular functions that are mediated through its interaction with the four FGF receptors [47, 48]. A pathway resource representing these diverse functions and the underlying mechanisms that regulate these processes would be immensely useful.

Curated pathway maps are invaluable resources for scientific community. Such comprehensive pathway datasets are being increasingly used in bioinformatics efforts directed towards analysis of high-throughput datasets from various disease contexts. Repositories including Pathway Interaction Database of the National Cancer Institute (http://pid.nci.nih.gov/), Database of Cell Signaling (http://stke.sciencemag.org/cm/), KEGG Pathway Database (http://www.genome.jp/kegg/pathway.html), and INOH Pathway Database (http://inoh.org/) have cataloged basic components of FGF signaling. We have expanded the scope of this by providing a comprehensive representation of FGF1 signaling pathway and its diverse roles in regulating various cellular processes.

## 2. Methodology

Documentation of specific pathway reactions scattered in the literature into an organized, user-friendly, query-enabled platform is primary to the analysis of signaling pathways. We used NCBI PubMed database to carry out an extensive literature search to retrieve research articles where molecular events triggered by the FGF-1/FGFR signaling system were studied. Specific molecular events screened include (a) physical associations between proteins, (b) posttranslational modifications (PTMs), (c) change in subcellular localization of proteins, (d) activation or inhibition of specific proteins, and (e) regulation of gene expression. Relevant information from research articles were manually documented using the curation tool, PathBuilder. To streamline and organize data collection from literature, we followed the previously described criteria for the inclusion/exclusion of pathway specific reactions [49, 50]. The data accumulated was submitted to the NetPath signaling pathway resource developed by our group [51]. We then generated a signaling map for this pathway using PathVisio pathway visualization software. We also applied additional criteria to filter out low confidence reactions from the gathered data [52] and generated a NetSlim map. In addition to curation of molecular level information, we have also cataloged physiological effects brought about by FGF-1 in different cell types/tissues.

## 3. Results and Discussion

Canonical FGF/FGFR signaling reactions have been documented in a few public repositories and review articles. Vast amount of literature in the last few years have revealed several novel pathway intermediates of FGF/FGFR signaling system. In order to generate a comprehensive view of FGF/FGFR signaling pathway, we carried out extensive literature search on PubMed for articles pertaining to FGF-1 signaling. Of a total of 3275 articles that were screened, 237 of them had molecular reactions reported downstream of FGF-1 in various cell types/tissues. Manual curation from these research articles revealed 109 molecules involved in FGF-1 induced physical associations, modulation by PTMs, activity, and subcellular or cell surface translocation events. Of the 42 physical associations that were cataloged, 29 were "binary" and 13 were "complex" interactions inclusive of the ligand/receptor interactors. We could record a total of 87 catalysis events, 15 activation/inhibition, and 21 translocation events. The 87 catalysis events include 19 events, where the enzymes directly catalyzing the reactions were studied and reported, and 68 events for which the enzymes which post-translationally modified the proteins are not studied under FGF-1 stimulation. Apart from these molecular reactions, we have also cataloged 117 genes whose expression is reported to be either upregulated or downregulated by FGF-1 treatment. However, only a total of 25 genes were reported to be differentially regulated at mRNA level by FGF-1 stimulation in different human cell types. A list of genes reported to be regulated by FGF-1 in different mammalian systems at the mRNA and/or the protein level is provided in Table 1. After the annotation process, all the entries were reviewed and approved by internal reviewers. Internally reviewed pathways were further reviewed and approved by an external pathway authority (LC, who is an author in this paper).

*3.1. Signaling Modules Activated by FGF-1.* Signaling modules comprise a well-characterized group of molecules and their interactions downstream of activation of a receptor. We documented the following signaling modules to be activated upon stimulation with FGF-1.

*3.1.1. Ras/Raf/Mek/Erk Pathway.* The Ras/Raf/Mek/Erk pathway has been implicated in cellular processes including cell

Table 1: List of genes that are reported to be transcriptionally and translationally regulated by FGF-1 in humans and other mammals.

| | Gene symbol | Up-/down regulation | mRNA/Protein | Experiment | Organism | Tissue/cell line/type | PubMed ID | Transcriptional regulator | Regulator Gene ID | PubMed ID |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | APOE | Up | mRNA and protein | RT-PCR, Western blot | Rat | Astrocytes | 18216067, 19229075, 17548887, 15627653 | | | |
| 2 | BAMBI | Down | mRNA and protein | RT-PCR, Western blot | Human | Preadipocytes | 22187378 | | | |
| 3 | CCND1 | Up | mRNA and protein | Gene chip array, Western blot | Human, rat | MG63 osteoblastic cells, Rat Wister bladder tumor cells (NBT-II) | 15572039, 18189245 | | | |
| 4 | CDK5R1 | Up | mRNA and protein | Q-PCR, Western blot | Rat | PC12 cells | 19249349 | | | |
| 5 | CDKN1A | Up | mRNA and protein | RT-PCR, Western blot | Human, mouse, rat | Chondrocytes, REtsAF cells | 16091747, 16153144, 11779141, 10364154 | STAT1 | 6772 | 11779141, 10364154 |
| 6 | CEBPA | Up | mRNA and protein | RT-PCR, Western blot | Human, mouse | Preadipocytes, 3T3-L1 cells | 17068114 | | | |
| 7 | CEBPB | Up | mRNA and protein | RT-PCR, Western blot | Human, mouse | Preadipocytes, 3T3-L1 cells | 17068114 | | | |
| 8 | COX2 | Up | mRNA and protein | Northern blot, ELISA | Human, rabbit | Cardiac muscle microvessel endothelial cells | 8790580, 2107185 | | | |
| 9 | EGR1 | Up | mRNA and protein | Q-PCR, Western blot | Mouse, rat | PC12 cells, Hippocampal neuronal cell line HT22, human periodontal ligament cells | 19249349, 20649566, 18179472, 24396070 | STAT3, SP1 | 6774, 6667 | 24396070 |
| 10 | FOS | Up | mRNA and protein | RT-PCR, northern blot (mouse and rat), Immunohisto-chemistry, Western blot | Mouse, rat, human | 3T3 cells, Adipocytes, ENU1564 cell, Astrocytes of periventricular zone of third ventricle, SUM-52PE cells | 16309174, 2507555, 18041768, 11172932, 20388777 | | | |
| 11 | JUN | Up | mRNA and protein | RT-PCR, Western blot | Rat | ENU1564 cells | 18041768 | | | |
| 12 | JUNB | Up | mRNA and protein | Gene chip array (Rat), Western blot | Rat, human | Rat Wister bladder tumor cells (NBT-II), SUM-52PE cells | 18189245, 20388777 | | | |
| 13 | MDM2 | Up | mRNA and protein | RT-PCR, Western blot | Rat | REtsAF cells | 16091747 | | | |

Table 1: Continued.

| | Gene symbol | Up-/down regulation | mRNA/Protein | Experiment | Organism | Tissue/cell line/type | PubMed ID | Transcriptional regulator | Regulator Gene ID | PubMed ID |
|---|---|---|---|---|---|---|---|---|---|---|
| 14 | MMP14 | Up | mRNA and protein | Northern blot, Gene chip array, Western blot | Human, rat | Prostate cancer cell line, LNCaP, Rat Wister bladder tumor cells (NBT-II) | 14673954, 18189245 | STAT3 | 6774 | 14673954 |
| 15 | MMP9 | Up | mRNA and protein | RT-PCR, Gene chip array, Western blot | Rat | ENU1564 cells, Rat Wister bladder tumor cells (NBT-II) | 18041768, 18189245 | RELA, JUN, FOS | 5970, 3725, 2353 | 18041768 |
| 16 | MYC | Up | mRNA and protein | Northern blot (Mouse), Western blot | Mouse, human | 3T3 cells, SUM-52PE cells | 16309174, 20388777 | | | |
| 17 | NOS2 | Up | mRNA and protein | RT-PCR, Western blot | Rat | Astrocytes | 16524372 | | | |
| 18 | PLAU | Up | mRNA and protein | RT-PCR, ELISA | Human | Fibroblasts | 12008951 | | | |
| 19 | PPARG | Up | mRNA and protein | RT-PCR, Western blot | Human, mouse | Preadipocytes, 3T3-L1 cells | 17068114, 22187378 | | | |
| 20 | SLC2A4 | Up | mRNA and protein | RT-PCR, Western blot | Human, mouse | Preadipocytes, 3T3-L1 cells | 22187378, 17068114 | | | |
| 21 | THY1 | Up | mRNA and protein | Northern blot, Western blot | Rat | PC12 cell lines | 11084019 | | | |
| 22 | TNFRSF12A | Up | mRNA and protein | RT-PCR, Immunoblot | Rat | Cardiomyocytes | 19629561 | | | |
| 23 | NGF | Up | mRNA and Protein | RT-PCR, Enzyme Immuno assay | Rat | Hippocampal astrocytes, skin fibroblasts, Primary spinal cord astrocyte | 1377078, 15773903 | | | |
| 24 | VEGFA | Up | mRNA and protein | Real time PCR, ELISA | Human | Primary human airway smooth muscle cells | 22205500 | | | |
| 25 | ACPL2 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 26 | ARG1 | Up | mRNA | Gene chip array, Q-PCR | Rat | Rat Wister bladder tumor cells (NBT-II) | 18189245 | | | |
| 27 | ATP2A2 | Up | mRNA | RNA gel blot | Mouse | NIH 3T3 cells | 7506544 | | | |
| 28 | AXIN2 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 29 | BGLAP | Up | mRNA | *in situ* hybridization | Mouse | Mouse calvaria cells (coronal sutures) | 12674336 | | | |
| 30 | CTSC | Up | mRNA | Gene chip array | Rat | Rat wister bladder tumor cells (NBT-II) | 18189245 | | | |
| 31 | DKK3 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 32 | DLL1 | Down | mRNA | Northern blot | Mouse | Neuroepithelial precursor (E10) | 11466430 | | | |
| 33 | DUSP1 | Up | mRNA | Gene chip array | Rat | Rat Wister bladder tumor cells (NBT-II) | 18189245 | | | |

Table 1: Continued.

| | Gene symbol | Up-/down regulation | mRNA/Protein | Experiment | Organism | Tissue/cell line/type | PubMed ID | Transcriptional regulator | Regulator Gene ID | PubMed ID |
|---|---|---|---|---|---|---|---|---|---|---|
| 34 | DYNC2LI1 | Up | mRNA | Gene chip array | Rat | Rat Wister bladder tumor cells (NBT-II) | 18189245 | | | |
| 35 | EDNRA | Up | mRNA | Northern blot | Rat | Arterial smooth muscle cells | 12851419 | | | |
| 36 | EFNB1 | Up | mRNA | Gene chip array | Rat | Rat Wister bladder tumor cells (NBT-II) | 18189245 | | | |
| 37 | ELF4 | Up | mRNA | Gene chip array | Rat | Rat Wister bladder tumor cells (NBT-II) | 18189245 | | | |
| 38 | FASN | Up | mRNA | RNA gel blot | Mouse | NIH 3T3 cells | 7506544 | | | |
| 39 | FGF1 | Up | mRNA | RT-PCR | Rat | Pheochromocytoma cells | 8576258 | | | |
| 40 | FGF7 | Up | mRNA | RT-PCR | Mouse | Embryonic lung mesenchymal cells | 10446271 | | | |
| 41 | FN1 | Up | mRNA | Gene chip array | Rat | Rat Wister bladder tumor cells (NBT-II) | 18189245 | | | |
| 42 | FZD1 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 43 | FZD2 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 44 | FZD7 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 45 | FZD8 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 46 | F3 | Down | mRNA | Northern blot | Human | Human umbilical vein endothelial cells | 9157959 | | | |
| 47 | GADD45A | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 48 | HBEGF | Up | mRNA | Gene chip array | Rat | Rat Wister bladder tumor cells (NBT-II) | 18189245 | | | |
| 49 | HMGA2 | Down | mRNA | Northern blot | Rat | 3T3-L1 cells | 10490844 | | | |
| 50 | IBSP | Up | mRNA | *in situ* hybridization | Mouse | Mouse calvaria cells (coronal sutures) | 12674336 | | | |
| 51 | IGF1 | Down | mRNA | RT-PCR | Human | Fibroblasts | 12008951 | | | |
| 52 | IGF2 | Down | mRNA | RT-PCR | Human | Fibroblasts | 12008951 | | | |
| 53 | IGF1R | Down | mRNA | RT-PCR | Human | Fibroblasts | 12008951 | | | |
| 54 | IGF2R | Down | mRNA | RT-PCR | Human | Fibroblasts | 12008951 | | | |
| 55 | IGFBP4 | Down | mRNA | RT-PCR | Human | Fibroblasts | 12008951 | | | |
| 56 | IL4 | Up | mRNA | Q-PCR | Rat | Transected spinal cord tissue | 21411654 | | | |
| 57 | IRS1 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 58 | LAMA3 | Up | mRNA | Gene chip array | Rat | Rat Wister bladder tumor cells (NBT-II) | 18189245 | | | |
| 59 | LRRC17 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 60 | MITF | Up | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 61 | MMP13 | Up | mRNA | Gene chip array, Q-PCR | Rat | Rat Wister bladder tumor cells (NBT-II) | 18189245 | | | |
| 62 | MMP3 | Up | mRNA | Northern blot | Rat | PC12 cell lines | 11084019 | | | |
| 63 | MSH6 | Up | mRNA | RNA gel blot | Mouse | NIH 3T3 cells | 8870641 | | | |

Table 1: Continued.

| | Gene symbol | Up-/down regulation | mRNA/Protein | Experiment | Organism | Tissue/cell line/type | PubMed ID | Transcriptional regulator | Regulator Gene ID | PubMed ID |
|---|---|---|---|---|---|---|---|---|---|---|
| 64 | MSX2 | Up | mRNA | *in situ* hybridization | Mouse | Mouse calvaria cells | 12674336 | | | |
| 65 | NID2 | Up | mRNA | Gene chip array | Rat | Rat Wister bladder tumor cells (NBT-II) | 18189245 | | | |
| 66 | NOTCH1 | Up | mRNA | Northern blot, Gene chip array, Q-PCR | Mouse, rat | Neuroepithelial precursor (E10), bladder tumor cells (NBT-II) | 11466430, 18189245 | | | |
| 67 | NR1H3 | Up | mRNA | RT-PCR | Rat | Astrocytes | 19229075 | | | |
| 68 | ODC1 | Up | mRNA | Northern blot | Mouse | NIH 3T3 cells | 9223379 | | | |
| 69 | PDGFA | Up | mRNA | RNA gel blot | Human | HUVE cells | 1689299 | | | |
| 70 | PFKL | Up | mRNA | RNA gel blot | Mouse | NIH 3T3 cells | 7506544 | | | |
| 71 | PLAT | Up | mRNA | RT-PCR | Human | Fibroblasts | 12008951 | | | |
| 72 | PLAUR | Up | mRNA | RT-PCR | Human | Fibroblasts | 12008951 | | | |
| 73 | PLF | Up | mRNA | Northern blot | Mouse | NIH 3T3 cells | 9223379 | | | |
| 74 | PMEPA1 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 75 | PNRC1 | Up | mRNA | Gene chip array | Rat | Rat Wister bladder tumor cells (NBT-II) | 18189245 | | | |
| 76 | POSTN | Up | mRNA | Northern blot | Rat | Pulmonary arterial smooth muscle cells | 15121739 | | | |
| 77 | PPIA | Up | mRNA | Northern blot | Rat | PC12 cell lines | 11084019 | | | |
| 78 | PRICKLE1 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 79 | PRPH | Up | mRNA | Northern blot | Rat | PC12 cell lines | 11084019 | | | |
| 80 | PTPRE | Up | mRNA | Gene chip array | Rat | Rat Wister bladder tumor cells (NBT-II) | 18189245 | | | |
| 81 | RUNX2 | Up | mRNA | *in situ* hybridization | Mouse | Mouse calvaria cells (coronal sutures) | 12674336 | | | |
| 82 | SCGB1A1 | Up | mRNA | RT-PCR | Mouse | Mouse lung epithelium | 12242715 | | | |
| 83 | SDC1 | Up | mRNA | Gene chip array | Rat | Rat Wister bladder tumor cells (NBT-II) | 18189245 | | | |
| 84 | SERPINB1 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 85 | SERPINB2 | Up | mRNA | RT-PCR | Human | Fibroblasts | 12008951 | | | |
| 86 | SERPINE1 | Up | mRNA | RT-PCR | Human | Fibroblasts | 12008951 | | | |
| 87 | SFRP1 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 88 | SFTPC | Up | mRNA | RT-PCR | Mouse | Mouse lung epithelium, Embryonic stem cell (mESC) line E14-Tg2a | 12242715, 20497026 | | | |
| 89 | SOCS1 | Up | mRNA | Northern blot | Rat | Mouse lens epithelium | 14985304 | | | |
| 90 | SOCS3 | Up | mRNA | Northern blot | Rat | Mouse lens epithelium | 14985304 | | | |
| 91 | SOX2 | Up | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |

Table 1: Continued.

| | Gene symbol | Up-/down regulation | mRNA/Protein | Experiment | Organism | Tissue/cell line/type | PubMed ID | Transcriptional regulator | Regulator Gene ID | PubMed ID |
|---|---|---|---|---|---|---|---|---|---|---|
| 92 | SPP1 | Up | mRNA | Quantitative northern blot | Rat | Pulmonary arterial smooth muscle cells | 15121739 | | | |
| 93 | SPRY1 | Up | mRNA | RNA gel blot | Mouse | MC3T3-E1 osteoblasts | 16604287 | | | |
| 94 | SPRY2 | Up | mRNA | RNA gel blot | Mouse | MC3T3-E1 osteoblasts | 16604287 | | | |
| 95 | SPRY4 | Up | mRNA | RNA gel blot | Mouse | MC3T3-E1 osteoblasts | 16604287 | | | |
| 96 | S1PR3 | Up | mRNA | Northern blot | Human | Human umbilical vein endothelial cells | 9315732 | | | |
| 97 | TCF3 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 98 | TCF4 | Down | mRNA | RT-PCR | Human | Preadipocytes | 22187378 | | | |
| 99 | TGFA | Up | mRNA | Northern blot | Mouse | Cultured keratinocytes | 7535082 | | | |
| 100 | TGFB2 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 101 | TGFBR3 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 102 | THBS1 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 103 | THBS1 | Up | mRNA | Northern blot | Mouse | NIH 3T3 cells | 9223379 | | | |
| 104 | TIMP1 | Up | mRNA | Gene chip array | Rat | Rat Wister bladder tumor cells (NBT-II) | 18189245 | | | |
| 105 | TIMP3 | Down | mRNA | Microarray | Mouse | Osteoblast cells | 18505824 | | | |
| 106 | VIM | Up | mRNA | Gene chip array | Rat | Rat Wister bladder tumor cells (NBT-II) | 18189245 | | | |
| 107 | ADIPOQ | Up | Protein | Radioimmunoassay | Human | Preadipocytes | 17068114 | | | |
| 108 | CCNE1 | Up | Protein | Western blot | Human | MG63 osteoblastic cells | 15572039 | | | |
| 109 | CTNNB1 | Down | Protein | Western blot | Human | Simpson Golabi Behmel syndrome (SGBS), Preadipocytes | 22187378 | | | |
| 110 | HMOX1 | Up | Protein | Western blot | Human | Spinal cord astrocytes | 16524372 | | | |
| 111 | MMP7 | Up | Protein | ELISA | Human | LNCaP cells | 11922392 | STAT3 | 6774 | 11922392 |
| 112 | PKMYT1 | Up | Protein | Immunoblot | Rat | Chondrosarcoma cells | 21051949 | | | |
| 113 | PLIN1 | Up | Protein | Western blot | Human, mouse | Preadipocytes, 3T3-L1 cells | 17068114 | | | |
| 114 | PTGIS | Down | Protein | ELISA | Human | Endothelial cells | 2107185 | | | |
| 115 | PTGS2 | Down | Protein | ELISA | Human | Endothelial cells | 2107185 | | | |
| 116 | RELA | Up | Protein | Western blot | Rat | ENU1564 cells | 18041768 | | | |
| 117 | RHOA | Up | Protein | Immunoblot | Rat | Cardiomyocytes | 19629561 | | | |
| 118 | SOX9 | Up | Protein | Western blot | Mouse | Costal chondrocytes | 10655493 | | | |
| 119 | WEE1 | Up | Protein | Immunoblot | Rat | Chondrosarcoma cells | 21051949 | | | |
| 120 | CDH2 | Up | Protein | Western blot | Rat | PC12 cells | 24396070 | STAT3, SP1 | 6774, 6667 | 24396070 |
| 121 | GAP43 | Up | Protein | Western blot | Rat | PC12 cells | 24396070 | STAT3 | 6774 | 24396070 |

growth, proliferation, and migration. Stimulation of different cell types with FGF-1 resulted in the formation of multiple complexes involving FRS2, GAB1, SOS1, PTPN11, SHC1, SH2B1, and GRB2 [53–60]. These complexes are critical to the subsequent activation of Ras [53, 56]. Association of Ras with Raf kinase [53] induces autophosphorylation and activation of Raf. Activation of Raf leads to phosphorylation dependent activation of Map kinases 1/2 (MAP2K1/2) and subsequently Erk2/1 (MAPK1/3) [60–62]. In the context of FGF-1 signaling, this module was reported to be involved in a number of processes including neurogenesis, adipocyte differentiation, cell proliferation, cholesterogenesis, cardioprotection, and tumor invasion and metastasis [62–67].

*3.1.2. Pi3k/Akt Pathway.* The complexes mentioned above also lead to the activation of Pi3k/Akt pathway, another signaling module that regulates various processes including cell growth, survival, cell proliferation, and cell migration [68]. A number of studies have shown FGF-1 induced phosphorylation of Akt [63, 64, 69]. Pi3k inhibitor-based functional assays also proved the involvement of FGF-1 pathway in diverse physiological conditions including angiogenesis [70], lung development [71], maintenance of neuronal phenotype [72], neuroprotection [73], and ApoE-HDL secretion [69].

*3.1.3. Jnk and p38 Mapk Pathway.* The c-jun N-terminal kinase (Jnk) pathway is implicated in the regulation of cell cycle, cell survival and apoptosis. FGF-1 stimulates the phosphorylation of p38 Mapk (MAPK14) as well as Jnk1/2 (MAPK8/9). The Jnk1/2 was also found to be crucial to neurogenesis and vascular remodeling [63, 74]. The specific functions of FGF-1 signaling mediated by p38 Mapk include growth arrest, promotion of apoptosis in response to oxidative stress, and formation of actin stress fibers [75–77].

*3.1.4. STAT3 and Nf-kb Pathway.* FGF-1 also stimulates STATs (STAT1 and STAT3) and Nf-kB signaling modules. FGFR signaling is reported to be regulated through several downstream molecules including JAK2, SRC, SH2B1, MAPK1/3, MAPK8/9, and STAT3. This signaling axis is known to regulate various cellular processes including neurite outgrowth, cell proliferation, and increased cancer cell invasion [78–80]. In addition, FGF-1 is also reported to induce MMP9 expression in mammary adenocarcinoma cells through the Nf-kb pathway [81].

*3.2. Physiological Effects Mediated by FGF-1.* FGF-1 was found to be involved in a number of biological processes. It is associated with the development of heart [82], lens [83], lung, and liver [84–86]. Its crucial roles in neurogenesis as well as adipogenesis [65, 87, 88] have also been reported. FGF-1 induces growth arrest and differentiation in chondrocytes [89–92]. It is implicated in angiogenesis [93–95] and wound healing [95–99]. Multiple studies have also shown the role of FGF-1 in cardioprotection [99–101] and neuroprotection [22, 102]. FGF-1 also induces migration [103–105] and proliferation [106–108] in different types of cancer cells. It is also involved in the regulation of epithelial-to-mesenchymal transition [109, 110], and tumorigenesis [111] as well as invasion and metastasis [64, 112]. A list of functional effects of FGF-1 studied in different cell types/tissues is provided in Table 2.

*3.3. Pathway Visualization, Data Formats, and Availability.* User-friendly visualization of pathways is an important aspect to provide a concise view. A number of tools are available for visualization and analysis of pathway data including Cytoscape [113], ChisioBioPAX Editor (ChiBE) [114], visualization and layout services for BioPAX pathway models (VISIBIOweb) [115], and ingenuity pathway analysis. These tools use pathway and molecular interaction data in different XML-based community standard data exchange formats as input. These standard formats, which include Proteomics Standards Initiative for Molecular Interaction (PSI-MI version 2.5), Biological Pathway eXchange (BioPAX level 3), and Systems Biology Markup Language (SBML version 2.1), enable easy data exchange and interoperability with multiple software. We have provided the annotated pathway data in the standard formats mentioned above. This data can be downloaded and used from NetPath [51], an open source resource for signal transduction pathways developed by our group (http://www.netpath.org/index.html). Additionally, we have drawn a map of FGF-1/FGFR signaling using the data accumulated in NetPath. This network map represents the molecules and their reactions organized by topology and excludes the molecules identified through phosphoproteomics approaches for which topology could not be assigned (Figure 1). The map was manually drawn using freely available software, PathVisio [116]. The topology of the molecules and their reactions in the pathway was arranged based on (i) inhibitor-based assays, (ii) mutation-based assays, (iii) knock-out studies, (iv) prior knowledge of canonical modules, and/or (v) with reference to multiple review articles. Another map, which incorporated high confidence reactions in accordance with NetSlim criteria [52], is submitted to the NetSlim database. These maps can be visualized and downloaded in gpml, GenMAPP, png, and pdf formats from http://www.netpath.org/netslim/FGF-1_pathway.html. Each node in the map is linked to their molecule page in NetPath, thereby to other pathways in NetPath, and to HPRD [117] and RefSeq protein accessions. In the "map with citation" option, the edges connecting the nodes are linked to the corresponding articles in PubMed that report the FGF-1 stimulated reaction(s). Direct reactions are represented by solid edges. Indirect reactions are represented with dashed edges. The edges which represent the protein-protein interactions, enzyme-substrate reactions and translocation events are distinguished by different colors.

## 4. Conclusions

Availability of specific ligand-receptor mediated signaling data in community approved formats is crucial to the understanding of proteins and their reactions in diverse biological processes. Analysis of high-throughput data obtained from

Table 2: Functions of FGF-1 identified in diverse cell/tissue types of human and other mammalian origins.

| Function | PubMed ID | Cell type/tissue | Organism |
|---|---|---|---|
| Adipogenesis | 22187378, 17068114 | Preadipocytes | Human |
| | 20657013 | Hepatoma cells, HEK293 cells | Human |
| Apoptosis | 15773903 | Motor neuron | Rat |
| | 9681989 | Peroxynitrite-induced apoptosis in PC12 cells | Rat |
| Cell cycle arrest | 16153144 | cells | Human |
| Cell migration | 9108375 | Skin fibroblasts | Human |
| | 11019781 | Fibroblasts | Mouse |
| | 9182757 | Embryo fibroblasts | Rat |
| | 2441696 | Arterial smooth muscle cells | Human |
| | 14966081 | AT2 alveolar cells | Human |
| | 15094393 | Human long-bone growth plate chondrocytes | Human |
| | 1699952 | Umbilical vein endothelial ceils | Human |
| | 15767480 | Y79 cells | Human |
| | 2303528 | Epidermal keratinocytes (BALB-MK1) | Mouse |
| | 2303528 | Keratinocytes (BALB/MK-1) | Mouse |
| | 2383402 | Leydig cells (TM3) | Mouse |
| | 1379845 | Megakaryocyte progenitor cells | Mouse |
| | 1379845 | Megakaryocytes | Mouse |
| | 14985304 | Murine lens epithelial cell lines CRLE2, 1AMLE6, TN4-1 and NKR11 | Mouse |
| Cell proliferation | 15574884 | NIH-3T3 cells | Mouse |
| | 3272188 | Adrenal chromaffin cells | Rat |
| | 2566605 | Astroblasts | Rat |
| | 1377078 | Hippocampal astrocytes | Rat |
| | 2153969 | Rat bladder carcinoma cell line (NBT-II) | Rat |
| | 8622701 | PC12 cells | Rat |
| | 8732667 | Prostate cancer cells | Rat |
| | 1638984 | Retinal cells | Rat |
| | 1377078 | Skin fibroblasts | Rat |
| | 12907464 | Aortic smooth muscle cells | Human, rat |
| | 1638984 | Retinal cells | Rats |
| | 22108586 | Periodontal fibroblasts | Rat |
| | 3272188 | Adrenal chromaffin cells | Rat |
| | 22108586 | Periodontal ligament fibroblasts | Rat |
| | 20388777 | SUM-52PE cells | Human |
| Cell rounding, growth inhibition | 11779141 | ATDC5 cells, chondroprogenitor cell lines | Mouse |
| | 19713443 | Mouse fibroblasts and rat astrocytes | Mouse, rat |
| Cholesterol biosynthesis | 19229075 | Astrocytes | Rat |
| | 18216067 | Astrocytes | Rat |
| | 17548887 | Astrocytes | Rat |
| Differentiation | 20497026 | Embryonic stem cell (mESC) line E14-Tg2a | Mouse |
| Epithelial-mesenchymal transition | 2153969 | NBT-II cells (Rat bladder carcinoma cell line) | Rat |
| | 7593195 | NBT-II | Rat |
| | 2153969 | NBT-II | Rat |
| Fiber cell differentiation | 7539358 | Lens epithelial cells | Mouse |
| G0/G1 arrest | 21051949 | Chondrosarcoma cells | Rat |
| G2 arrest | 21051949 | Chondrosarcoma cells | Rat |
| G2/M transition | 20044603 | Breast cancer cells | Human |
| Growth arrest | 14593093 | Rat chondrosarcoma (RCS) cells | Rat |
| Inhibition of apoptosis | 16524372 | Astrocytes | Rat |
| | 17473910, 16091747 | PC12 and RetsAF cells | Rat |
| Inhibition of cell growth | 17363592 | TAKA-1 cells | Hamster |

Table 2: Continued.

| Function | PubMed ID | Cell type/tissue | Organism |
|---|---|---|---|
| Inhibition of neurogenesis | 11466430 | NEP cells | Mouse |
| Inhibition of proliferation | 10364154 | Chondrosarcoma cells (RCS) | Rat |
| Membrane ruffling | 7534069 | Human ductal breast epithelial tumor cell line (T47D) | Human |
| Neurite outgrowth | 20175207 | TREX 293 cells | Human |
| | 3272188 | Adrenal chromaffin cells | Rat |
| | 8764646 | PC12 cells | Rat |
| | 19249349 | PC12 cells | Rat |
| | 3316527, 8576258 | PC12 cells | Rat |
| | 12127979, 9182757, 2157719 | PC12 cells | Rat |
| Neuronal differentiation | 16716298 | Primary astrocyte from human fetal brain | Human |
| | 7514169, 8622701, 2157719 | PC12 cells | Rat |
| Osteoblast proliferation | 18041768 | ENU1564 cells | Rat |
| Osteoblast differentiation | 18505824 | Osteoblasts | Mouse |
| Osteogenic differentiation | 12674336 | Sutural mesenchyme in mouse calvaria | Mouse |
| Protection from apoptosis | 19765618, 8576258 | PC12 cells | Rat |
| Repression of myogenic differentiation | 1379245 | Skeletal muscle myoblasts (MM14) | Mouse |
| Retinal cell proliferation | 15978261 | Retinal cells | Mouse |
| Skeletal muscle development | 8601591 | Skeletal muscle myoblasts (MM14) | Mouse |
| Synaptic plasticity | 20649566 | Hippocampal neuronal cell line HT22 | Mouse |
| Tumorigenesis | 20889570 | JMSU1 urothelial carcinoma cell lines | Human |
| | 9038374 | NBD-II | Rat |
| Vascular remodeling | 15121739 | Pulmonary arterial smooth muscle cells (PASMCs) | Rat |
| | 22205500 | ASM (Airway Smooth Muscle cells) | Human |
| Regeneration | 3353388 | Retinal ganglion cells | Rat |
| Astrocyte activation | 15773903 | Primary spinal cord astrocyte | Rat |
| Neurogenesis | 20429889 | Embryonic stem cells | Mouse |
| Wound healing | 9036931 | | Mouse |
| Cord Formation | 16631103 | | Rat |
| Decrease in food intake | 7692459 | | Rat |
| Facilitation of memory | 7692459 | | Rat |
| Increase in sleep duration | 8985960 | | Rabbit |
| Maintenance of the integrity of the organ of corti, initiation of protective recovery and repair processes following damaging auditory stimuli | 7568115 | | Rat |
| Arteriole dilation | 8853345 | | Rat |
| Feeding suppressor function | 11172932 | | Rat |
| Hair-cell innervation during the terminal development of the sensory epithelium | 12792312 | | Rat |
| Lens regeneration | 3792708 | | Bovine |
| Lung morphogenesis and differentiation | 12242715 | | Rat |
| Metastasis | 1707175 | | Rat |
| Muscle regeneration | 1384586 | | Mouse |
| Myocardial remodeling | 19629561 | | Rat |
| Neuroprotection | 12095987 | | Rat |
| Prevention of premature angiogenesis and inflammatory responses | 17643421 | | Mouse |
| Protection against hypoxic-ischemic injury | 16635575 | | Rat |
| Spinal cord injury repair | 21411654 | | Rat |
| Cardioprotection | 15337227, 12176126 | | Mouse |

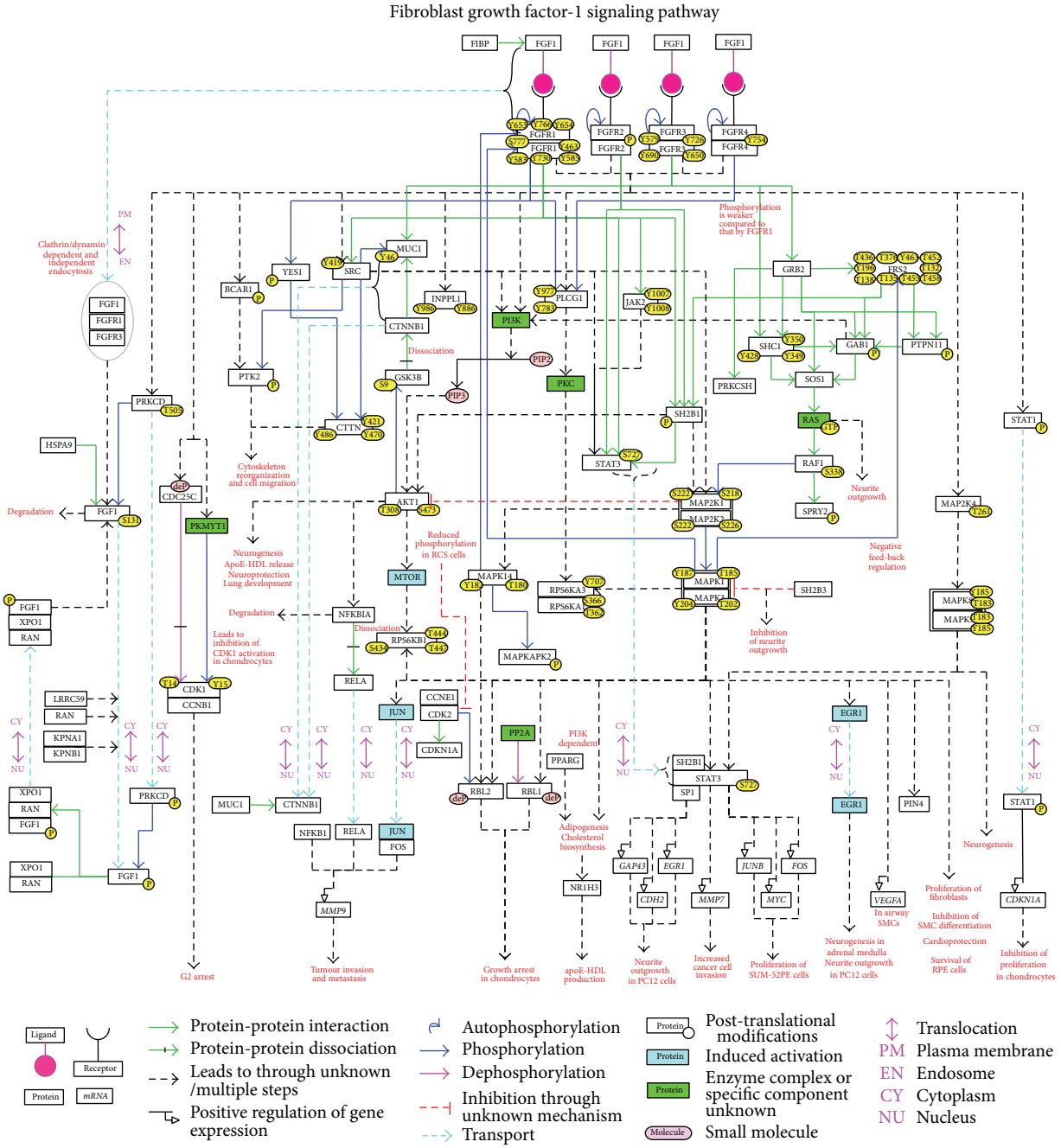


FIGURE 1: Network map of FGF-1 signaling. This map manually drawn using PathVisio [112] represents the reactions induced by FGF-1 through their receptors. Each node represents the molecules and the post-translationally modified states of proteins are also represented. Distinguished by color and continuous/dashed lines, the edges represent the specific information such as protein-protein interactions, enzyme-substrate reactions, reactions mediated through unknown/multiple steps, and protein translocations as provided in the legend. The biological processes that FGF-1 regulates through multiple signaling modules are also represented. A NetSlim [52] version of this map can be obtained from http://www.netpath.org/netslim/FGF-1_pathway.html.

microarray- and mass spectrometry-based platforms essentially relies on enrichment of biological function or signaling pathways available in databases to obtain insights into their physiological functions. Although some resources have cataloged FGF signaling in general, this is the first attempt to provide a comprehensive view of FGF-1 signaling. This will be extended to other FGF ligands and/or specific FGFRs in the future to facilitate the analysis of differences between different FGFs and/or FGFRs. The pathway information has been made available through NetPath and NetSlim resources in multiple community standard data formats. The FGF-1 signaling pathway data will be periodically updated in NetPath. We have cataloged multiple signaling modules that are activated upon activation of FGFR and their implications

in diverse physiological and pathophysiological processes. We believe that the data presented here will boost further research in this area and will help identify novel therapeutically important molecules that could be targeted in pathological conditions involving aberrant FGF-1 signaling.

## Abbreviations

S100A13: S100 calcium binding protein A13
FRS2: Fibroblast growth factor receptor substrate 2
GAB1: GRB2-associated binding protein 1
SOS1: Son of sevenless homolog 1
PTPN11: Protein tyrosine phosphatase, non-receptor type 11
SHC1: Src homology 2 domain containing transforming protein 1
GRB2: Growth factor receptor-bound protein 2
Mapk: Mitogen activated protein kinase
Pi3k: Phosphatidylinositide 3-kinase
Akt: v-akt murine thymoma viral oncogene homolog
HDL: High density lipoprotein
Jnk: Jun N-terminal kinase
STAT3: Signal transducer and activator of transcription 3.

## Conflict of Interests

The authors have no conflict of interests.

## Authors' Contribution

Shyam Mohan Palapetta, Varot K. Sandhya, and Apeksha Sahu contributed equally to the paper.

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