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## Supplemental Information

# Cell Signaling by Receptor Tyrosine Kinases

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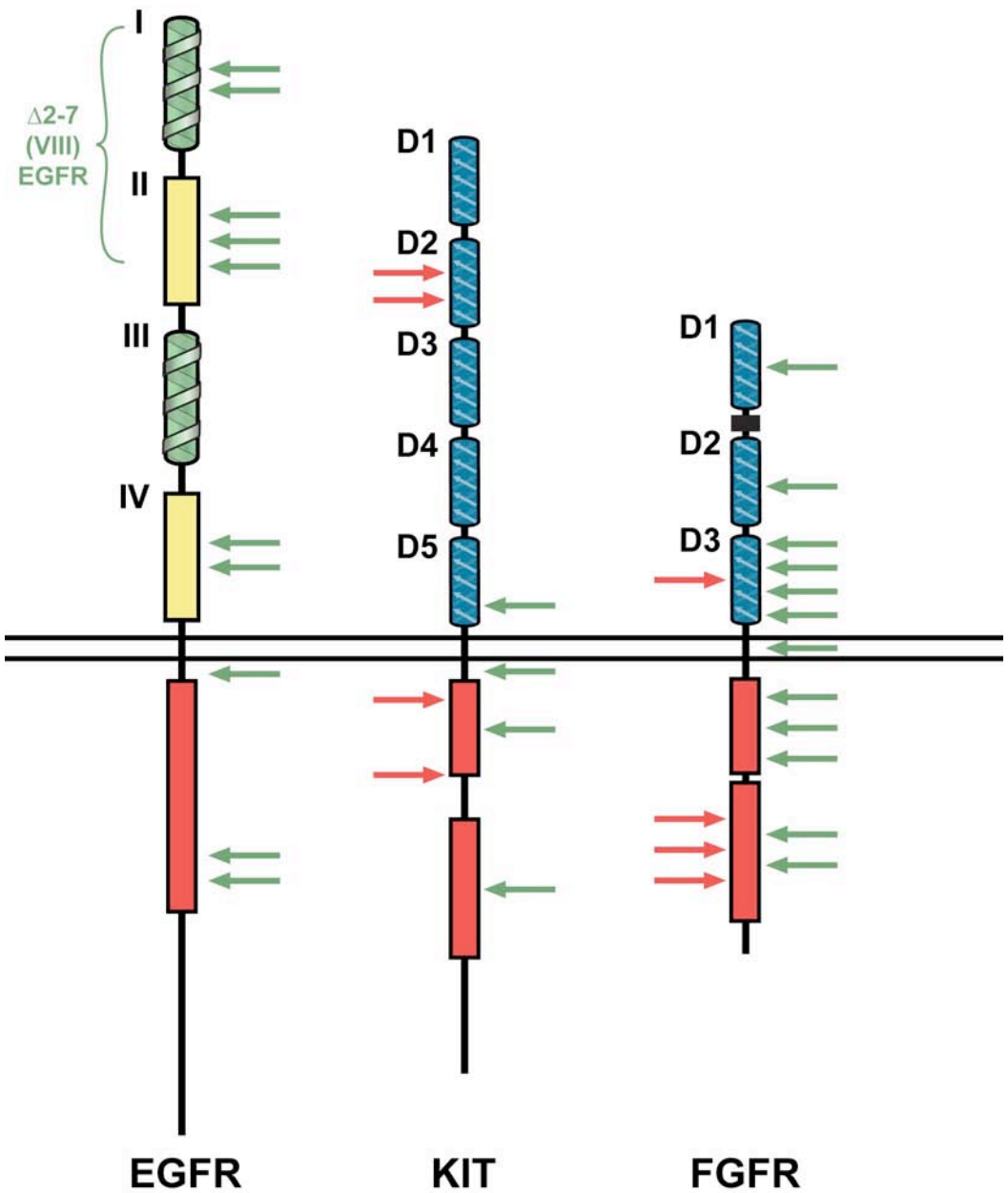
I
Δ2-7
(VIII)
EGFR
II
III
IV
D1
D2
D3
D4
D5
D1
D2
D3
EGFR
KIT
FGFR

**Figure S1. RTK Mutations in Diseases**

Locations of gain-of-function (green arrows) and loss of function (red arrows) mutations in epidermal growth factor receptor (EGFR) (left), KIT (middle), and fibroblast growth factor receptor (FGFR) (right). Receptors are depicted as in Figure 1.

**EGFR** Mutations in the EGFR tyrosine kinase domain (TKD) relieve autoinhibitory interactions and constitutively elevate kinase activity. These mutations were identified in patients with non-small cell lung carcinoma (Sharma et al., 2007). Additional activating mutations are found in the juxtamembrane region (Red Brewer et al., 2009). Point mutations in Domains I, II and III of the extracellular region were also identified in glioblastoma patients (Libermann et al., 1985; Pedersen et al., 2001). In addition, variant III (vIII) or Δ2-7 EGFR, which lacks Domain I and the majority of Domain II was identified in glioblastoma patients.

**KIT** Gain-of-function mutations in KIT have been identified in gastrointestinal stromal tumors (GIST), acute myeloid leukemia (AML) and in melanoma. Activating mutations in the juxtamembrane region release the autoinhibitory constraints and constitutively elevate tyrosine kinase activity. The oncogenic mutations in the KIT D5 extracellular region enhance contacts between neighboring KIT molecules, resulting in enhanced tyrosine kinase activity. Loss-of-function mutations in KIT give rise to the disorder Piebaldism. Examples include point mutations in the catalytic domain that impair tyrosine kinase activity and point mutations in D2 of the extracellular region that compromise stem cell factor binding.

**FGFRs** Gain-of-function FGFR1, FGFR2 and FGFR3 have been identified in severe skeletal dysplasias such as Crouzon, Jackson-Weiss, Apert and Pfeiffer Syndromes. Similar activating mutations were identified in bladder cancer, cervical carcinoma and in multiple myeloma among other cancers. Activating mutations in the extracellular region are primarily seen in D3 of FGFR2; these result in aberrantly disulfide-linked and activated FGFR2 dimers. Other point mutations in the FGFR2 extracellular region enhance fibroblast growth factor (FGF) binding or alter FGF selectivity. Activating mutations in the cytoplasmic domain enhance tyrosine kinase activity of FGFR2 and FGFR3. Loss-of-function FGFR2 mutations in the TKD were identified in Lacrimo-Auriculo-Dento-Digital Syndrome. A loss-of-function point mutation in D3 of FGFR1C that impairs its ability to bind FGF8 was also shown to be responsible for the autosomal dominant Kallmann Syndrome.

Table S1. FDA-Approved Small-Molecule Inhibitors and Monoclonal Antibodies against RTKs for Cancer Therapy

| Small Molecule | Mab | Target | Disease | Year of approval |
|---|---|---|---|---|
| Imatinib (Gleevec) | | PDGFR, KIT, Abl, Arg | CML, GIST | 2001 |
| Gefitinib (Iressa) | | EGFR | Esophageal cancer, Glioma | 2003 |
| Erlotinib (Tarceva) | | EGFR | Esophageal cancer, Glioma | 2004 |
| Sorafenib (Nexavar) | | Raf, VEGFR, PDGFR, Flt3, KIT | Renal cell carcinoma | 2005 |
| Sunitinib (Sutent) | | KIT, VEGFR, PDGFR, Flt3 | Renal cell carcinoma, GIST, Endocrine pancreatic cancer | 2006 |
| Desatinib (Sprycel) | | Abl, Arg, KIT, PDGFR, Src | Gleevec-resistant CML | 2007 |
| Nilotinib (Tasigna) | | Abl, Arg, KIT, PDGFR | Gleevec-resistant CML | 2007 |
| Lapatinib (Tykerb) | | EGFR, ErbB2 | Mammary carcinoma | 2007 |
| | Trastuzumab (Herceptin) | ErbB2 | Mammary carcinoma | 1998 |
| | Cetuximab (Erbitux) | EGFR | Colorectal cancer, Head and neck cancer | 2004 |
| | Bevacizumab (Avastin) | VEGF | Lung cancer, Colorectal cancer | 2004 |
| | Panitumumab (Vectibix) | EGFR | Colorectal cancer | 2006 |

Table S2. Protein Modules that Mediate Intracellular Signaling Pathways Downstream of RTKs and the Targets They Recognize (Li, 2005; Schlessinger and Lemmon, 2003; Seet et al., 2006)

| **Receptor Tyrosine Kinase Module** | **Target**[a] |
|---|---|
| SH2 | **pYXXX** |
| PTB | **NPXpY peptides** |
| FHA | **pTXXD** |
| 14-3-3 | **SXpSXP** |
| SH3 | **PXXP** |
| WW | **PXPX** |
| CH | F-actin |
| LIM | Protein-protein |
| SAM | Homotypic oligomerization |
| PDZ | C-terminal valine |
| FERM | Membrane and cytoskeleton |
| PX | Phosphoinositides |
| C1 | Membrane |
| C2 | Membrane and calcium |
| PH | Phosphoinositides |
| FYVE | PtdIns3*P* |
| UIM | Ubiquitin |
| UBA | Ubiquitin |

[a] Protein sequence motifs are shown in bold.

## Supplemental References


Li, S.S. (2005). Specificity and versatility of SH3 and other proline-recognition domains: structural basis and implications for cellular signal transduction. Biochem. J. 390, 641–653.

Schlessinger, J., and Lemmon, M.A. (2003). SH2 and PTB domains in tyrosine kinase signaling. Sci. STKE 191, RE12.

Seet, B.T., Dikic, I., Zhou, M.M., and Pawson, T. (2006). Reading protein modifications with interaction domains. Nat. Rev. Mol. Cell Biol. 7, 473–483.