Crosstalk of the cell surface receptors

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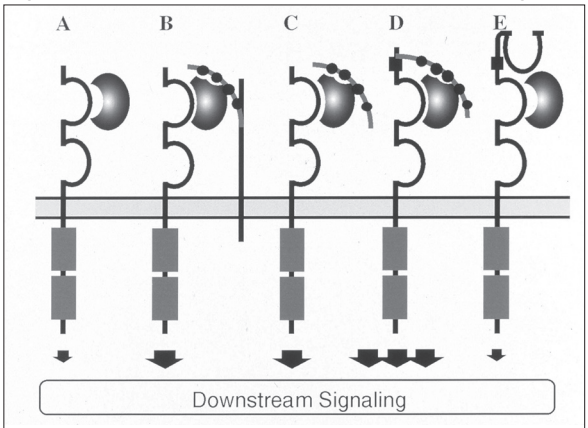
Cell surface receptors receive extracellular signals via interaction with a specific ligand, and transduce the signals from the cell membrane to other parts of the cell. Many types of receptors have been identified through molecular cloning, and most of their functions have been clarified. For intracellular signal transduction, cytoplasmic signaling molecules are required. These molecules relay signals to downstream via conformational change and/or phosphorylation, resulting in a change in cell metabolism, cytoskeletal modulation, up- or down-regulation of gene transcription, etc.

We have so far focused on several receptors and biological systems to investigate how the receptors interact with each other to fulfill their functions. The first focus is on fibroblast growth factor receptor (FGFR) and heparan sulfate proteoglycan. Using a parathyroid cell line model, we were among the first groups that proved heparan sulfate is required for FGFR to bind to FGF and be properly activated (**Fig.1**) [1)-4)]. We further identified one of the FGFR2 isoforms as a form of proteoglycan, and studied molecular mechanisms that regulate the covalent glycosaminoglycan modification [5)].

The next focus is on FGFR and EphA4. We screened for binding partners of the FGFR cytoplasmic domain using the yeast two-hybrid screening system, and identified EphA4 as one of such partners. Both FGFR and Eph belong to a superfamily of receptor tyrosine kinases. We found that the EphA4-FGFR interaction upregulates two pathways (**Fig.2**); (1) an FRS2α (fibroblast growth factor receptor substrate 2α; a docking protein)-mediated signal transduction pathway that culminates in proliferation and self-

Fig.1 FGF Receptor and Heparan Sulfate Proteoglycan



A, The 2-loop FGFR isoform without heparan sulfate; B, The 2-loop FGFR isoform interacting with the external heparan sulfate proteoglycan; C, The 2-loop FGFR isoform interacting with heparin; D, The 2-loop FGFR isoform interacting with its own heparan sulfate moiety; E, The 3-loop FGFR isoform.

renewal of neural stem cells, and (2) another pathway via ephexin1, a guanine nucleotide exchange factor, that regulates Rho family small G proteins for cytoskeletal modulation [6)-9)].

The final focus of this presentation is concerned with growth hormone receptor (GHR) and EphA4. GH is regarded as an essential hormone for postnatal body growth that mainly works through IGF1 production in liver and other tissues, and the whole signaling process is named GH-IGF1 axis. We identified EphA4 as an essential binding partner of GHR (**Fig.3**). EphA4 binds to GHR and augments activation of the JAK2/STAT5B pathway. In addition, EphA4 directly binds to and phosphorylates STAT5B. Through these interactions, EphA4 transcriptionally enhances IGF1 production in liver cells as well as in others. *Epha4* KO mice show short stature in an *Epha4* gene dose-dependent fashion, and respond well to IGF1 but not to GH treatment [10)]. Thus, we conclude that crosstalk of the cell surface receptors is one of the essential signaling processes that affect many biological phenomena, fine-tuning and sometimes regulating the function of individual receptors.

Fig.2 Signal transduction through the FGFR/EphA4 complex

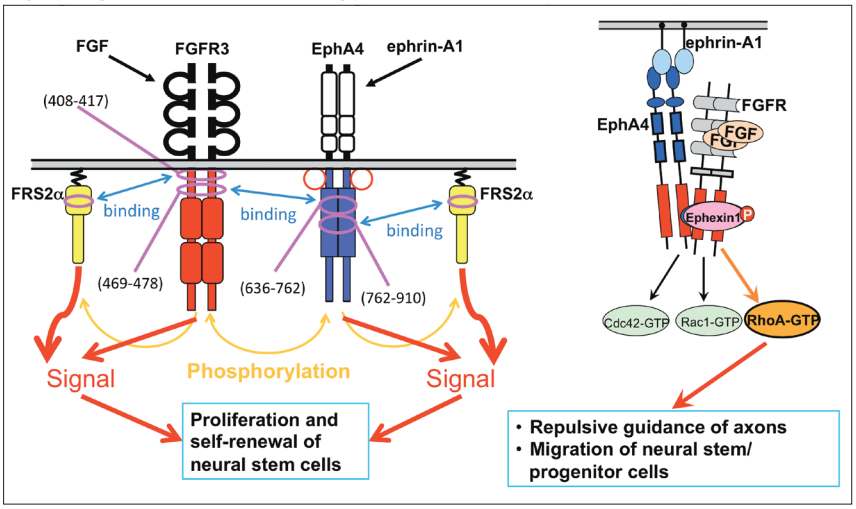
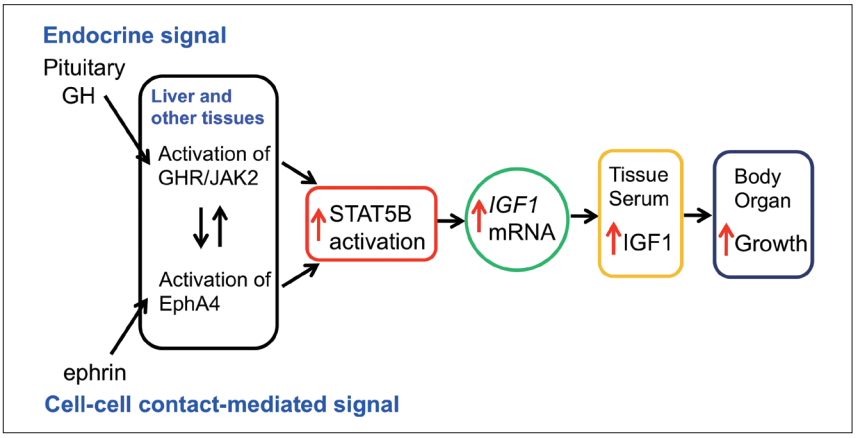


Fig.3 Interaction of the GH/GHR and the ephrin/EphA4 signals



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