Cellular/Molecular

Anosmin-1 Modulates Fibroblast Growth Factor Receptor 1 Signaling in Human Gonadotropin-Releasing Hormone Olfactory Neuroblasts through a Heparan Sulfate-Dependent Mechanism

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Defects of either anosmin-1 or fibroblast growth factor receptor 1 (FGFR1) are known to underlie hereditary Kallmann's syndrome (KS), a human disorder of olfactory and gonadotropin-releasing hormone (GnRH) neuronal ontogeny. Here, we report a functional interaction between anosmin-1 and the FGFR1–FGF2–heparan sulfate complex, leading to amplified responses in the FGFR1 signaling pathway. In human embryonic GnRH olfactory neuroblasts, wild-type anosmin-1, but not proteins with loss-of-function KS mutations, induces neurite outgrowth and cytoskeletal rearrangements through FGFR1-dependent mechanisms involving p42/44 and p38 mitogen-activated protein kinases and Cdc42/Rac1 activation. Furthermore, anosmin-1 enhances FGF2 signaling specifically through FGFR1 IIIc in heterologous BaF3 lymphoid cells in a heparan sulfate-dependent manner. Our study provides compelling evidence for anosmin-1 as an isoform-specific co-ligand modulator of FGFR signaling that amplifies and specifies FGFR1 signaling responses during human nervous system development and defines a mechanism underlying the link between autosomal and X-linked KS.

Key words: FGFR1; GnRH; anosmin-1; heparan sulfate proteoglycans; Kallmann's syndrome; MAPKs