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Review article

# Feedback regulation of RTK signaling in development

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ABSTRACT

Precise regulation of the amplitude and duration of receptor tyrosine kinase (RTK) signaling is critical for the execution of cellular programs and behaviors. Understanding these control mechanisms has important implications for the field of developmental biology, and in recent years, the question of how augmentation or attenuation of RTK signaling via feedback loops modulates development has become of increasing interest. RTK feedback regulation is also important for human disease research; for example, germline mutations in genes that encode RTK signaling pathway components cause numerous human congenital syndromes, and somatic alterations contribute to the pathogenesis of diseases such as cancers. In this review, we survey regulators of RTK signaling that tune receptor activity and intracellular transduction cascades, with a focus on the roles of these genes in the developing embryo. We detail the diverse inhibitory mechanisms utilized by negative feedback regulators that, when lost or perturbed, lead to aberrant increases in RTK signaling. We also discuss recent biochemical and genetic insights into positive regulators of RTK signaling and how these proteins function in tandem with negative regulators to guide embryonic development.

## 1. Introduction

Receptor tyrosine kinases (RTKs) regulate virtually all aspects of embryonic development from early patterning to organogenesis (Lemmon and Schlessinger, 2010; Li and Hristova, 2006). The RTK superfamily encompasses 58 known receptors in humans which are classified into several multi-member subfamilies including, among others, fibroblast growth factor receptors (FGFRs), insulin and insulin-like growth factor receptors (IR and IGF-1R), platelet-derived growth factor receptors (PDGFRs), vascular endothelial growth factor receptors (VEGFRs), and epidermal growth factor receptors (EGFR/HER/ERBBs) (Lemmon and Schlessinger, 2010). Together, these receptors are involved in the entire spectrum of developmental processes. The intracellular signals initiated by RTK activation play pivotal roles in cell fate determination and morphogenesis, and many are highly conserved in evolution from the nematode *Caenorhabditis elegans* to humans (Pires-daSilva and Sommer, 2003). Furthermore, numerous diseases result from germline or somatic genetic changes that alter the activity, abundance, or cellular distribution of RTKs. Mutations in RTKs or proteins that facilitate their downstream signaling have been implicated in the onset and progression of a wide-range of diseases such as diabetes, inflammation, bone disorders, atherosclerosis, angiogenesis, and various cancers (Lemmon and Schlessinger, 2010).

RTK activation is triggered by binding of extracellular ligands, which leads to receptor oligomerization and auto-phosphorylation on tyrosine residues within the cytoplasmic domains. These phosphorylated residues create docking sites for phosphotyrosine-binding domain containing proteins that couple RTK activation to downstream signaling pathways (Hubbard, 2004; Hubbard and Miller, 2007; Schlessinger, 2000). Interestingly, a large number of RTKs induce a similar set of downstream effectors, in particular those coupled to activation of the RAS/MAP kinase (MAPK) and phosphatidylinositide-3 kinase (PI3K)/AKT pathways (Blume-Jensen and Hunter, 2001; Ledda and Paratcha, 2007). What distinguishes the signaling outputs between distinct RTKs is often the duration and extent of pathway activation. Feedback regulators play a major role in fine-tuning these variables by attenuating or amplifying the signaling output. They can be already present and act prior to or immediately after receptor activation (early attenuators and amplifiers) (Haglund et al., 2003; Thien and Langdon, 2001) or can be transcriptionally induced by the pathways on which they eventually act (late attenuators and amplifiers)

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**Table 1**
Classification of RTK signaling modulators according to their spatiotemporal feedback.

| Feedback | Modulator | Target/Pathway | Signaling output | Mechanism of action |
|---|---|---|---|---|
| Late, reversible | Anosmin 1 | FGFR | Amplification | FGF-FGFR signaling complex assembly and stabilization |
| | DUSP6 | FGF-MAPK | Attenuation | Dephosphorylation of ERK |
| | FLRT family | FGFR | Amplification | FGF-FGFR signaling complex activation |
| | MIG6 | ErbB receptor family | Attenuation | Inhibition of ErbB receptor family dimerization |
| | SEF | FGF-MAPK/ERK & FGF-PI3K/AKT | Attenuation | FGF-FGFR signaling complex assembly and activation |
| | SPRED | FGF-RAS/RAF | Attenuation | Inhibition of RAF activation |
| | Sprouty family | RAS/MAPK & RAS/PI3K | Attenuation | Inhibition of downstream effector signaling |
| Early, reversible | PTEN | PI3K/AKT | Attenuation | Dephosphorylation of $PIP_3$ |
| | RKIP | RAF/MEK | Attenuation | Inhibition of RAF1 and MEK interaction |
| | SHP2 | EGFR, FGF-MAPK/ERK, IR, & RET | Amplification | Dephosphorylation of inhibitory modulators of downstream effectors |
| Late, irreversible | CNPY1 | FGFR | Amplification | FGFR maturation |
| | LRIG family | ErbB receptor family, MET, & RET | Attenuation | Receptor ubiquitination and degradation |
| | SOCS family | c-KIT, EGFR, FLT3, IGF-1R, & IR | Attenuation | Receptor ubiquitination and degradation |
| Early, irreversible | CBL family | EGFR, MET, PDGFR, & RET | Attenuation | Receptor ubiquitination and degradation |
| | NEDD4 & NEDD4L | ErbB receptor family, FGFR, IGF-1R, IR, NRTK1, & VEGFR | Attenuation | Receptor ubiquitination and degradation |
| | NRDP1 | ERBB3 | Attenuation | ERBB3 trafficking and ubiquitination |
| | SHISA2 | FGFR | Attenuation | Receptor maturation and ubiquitination |

(Table 1) (Casci and Freeman, 1999; Fiorini et al., 2002; Ghiglione et al., 1999; Golembo et al., 1996; Korsensky and Ron, 2016; Tsang and Dawid, 2004).

One of the characteristic features of RTK signaling during embryonic development is establishing patterns of cell organization, proliferation, and migration through signaling output gradients. (Ashe and Briscoe, 2006). This gradation is traditionally thought to arise from a corresponding gradient in extracellular ligand concentration or receptor expression on the cell surface. However, there is growing evidence that strongly suggests RTK feedback regulators play a significant role in creating and maintaining these critical signaling output gradeints. Indeed, the heparin sulfate proteoglycans (HSPGs), which serve as an amplifier of many RTK signaling pathways, most notably FGFRs, can control morphogen gradient formation by regulating the diffusion rates of ligands (Yan and Lin, 2009). Another example of such a mechanism is the action of CBL, a well-characterized negative feedback regulator of multiple RTK pathways such as EGFR, MET, and RET. This protein regulates the distribution of the Egfr ligand Gurken during *Drosophila melanogaster* embryogenesis by mediating endocytosis and subsequent degradation of the Egfr-Gurken complex (Chang et al., 2008). In this manner, feedback regulators are essential for not only controlling the level of signal output but also for tuning their spatiotemporal localization.

Here, we review several modulators of RTK signaling with an emphasis on those with known roles in development (Supplemental Table 1) and contributions to human congenital disorders. Our discussion highlights the insights gained from *in vivo* work in model organisms that can be used to further our biochemical understanding of RTK regulation through feedback pathways. Several other excellent reviews cover feedback regulators in more molecular detail (Avraham and Yarden, 2011; Lemmon et al., 2016; Mohapatra et al., 2013).

### *1.1. Regulation of biosynthesis and maturation of RTKs*

Recent studies have revealed that modulation of RTKs' signaling outputs starts even prior to receptor arrival at the cell surface. A key aspect of this type of regulation occurs via quality control checks in the endoplasmic reticulum (ER) where newly synthesized receptors undergo folding and maturation by post-translational modification before being trafficked to the cell membrane. RTKs that are not properly synthesized, folded, or modified are degraded through a proteasome-dependent pathway. Several proteins, including the Canopy family, the Shisa family, and NRDP1, have been identified to regulate the strength of RTK-mediated signaling through interaction with and modification of receptors in the ER, consequently controlling the number of functional receptors at the cell surface.

The Canopy (*CNPY*) genes encode four putative ER-resident proteins hypothesized to be positive-feedback regulators of receptor maturation and trafficking (Do et al., 2012; Hart and Tapping, 2012; Hirate and Okamoto, 2006; Matsui et al., 2011), however, only a few studies to date have addressed their structure or function. In *Danio rerio* (zebrafish), *cnpy1* expression is restricted to the midbrain-hindbrain boundary and can be induced by exogenous Fgf8. Knockdown of *cnpy1* resulted in midbrain-hindbrain boundary defects with the appearance of an airplane "canopy" and impaired Fgf signaling in a cell-autonomous manner, indicating a positive-feedback relationship between *cnpy1* and *fgf8* (Hirate and Okamoto, 2006). *Cnpy1* was also shown to positively regulate Fgf signaling for proper formation of Kupffer's vesicle, which orchestrates left–right asymmetric body plan in zebrafish (Matsui et al., 2011). The closely-related CNPY2 protein has been linked to FGF signaling *in vitro*: in mouse macrophages and human hepatocytes, FGF21 enhanced expression of *Cnpy2*, which resulted in stabilized expression of low-density lipoprotein receptors (Do et al., 2012). More recent work has identified CNPY2 as a HIF-1α-regulated angiogenic secreted factor that stimulates cell proliferation, migration, and angiogenesis in mouse models of cardiovascular pathologies and cancer (Guo et al., 2015b, 2015c; Ito et al., 2014; Taniguchi et al., 2017; Yan et al., 2016). Although these processes are known to be mediated by FGF signaling, no genetic interactions between CNPY2 and FGFs have been reported *in vivo*. While the involvement of Canopy proteins in FGFR signaling is poorly understood, CNPY3 and CNPY4 have been shown to regulate toll-like receptors (TLRs), another class of single-pass transmembrane receptors. Co-expression of CNPY3 increased trafficking of exogenously expressed TLRs to the cell membrane via chaperone gp96, leading to elevated TLR-mediated signaling *in vitro* (Hart and Tapping, 2012). Interestingly, CNPY4 seems to exert an opposite effect and led to the downregulation of TLRs at the cell membrane, subsequently attenuating TLR-mediated signaling. It is possible that Canopy proteins may play a similar regulatory role on RTKs to control trafficking, as CNPY1 directly interacts with FGFR1 and modulates the extent of mature N-linked glycosylation of the receptor (Matsui et al., 2011), however, further studies will be necessary to understand how Canopy proteins interact with and modulate RTK-mediated signaling.

In a manner potentially similar to the Canopy proteins, the nine Shisa proteins in vertebrates represent a novel class of ER-associated proteins that antagonize FGF-mediated signaling in a cell-autonomous manner by regulating receptor maturation. The founding member of

the Shisa family, *shisa1*, was named based on its expression in the prospective head ectoderm and organizer in *Xenopus laevis* and in reference to a form of Japanese sculpture with a large head (Yamamoto et al., 2005). Misexpression of *shisa1* in *X. laevis* resulted in enlarged cement glands and anterior head structures due to expansion of *otx2* expression, which marks prospective forebrain and midbrain. Accordingly, morpholino knockdown of *shisa1* reduced Fgf-mediated *xbra* expression at the mid-gastrula, and embryos exhibited small eyes and cement glands, suggesting that Shisa1 directs anterior-posterior axis formation through Fgf activity (Yamamoto et al., 2005). Subsequent studies of *X. laevis, Gallus gallus* (chick), and *Mus musculus* (mouse) showed that *Shisa2* expression along the antero-posterior axis exerts negative regulatory effects on FGF signaling, suggesting that SHISA2 also plays a key role in the proper establishment of segmental patterning of the head (Supplemental Table 1) (Filipe et al., 2006; Furushima et al., 2007; Hedge and Mason, 2008; Nagano et al., 2006). Although the mechanism of action remains unclear, it has been suggested that the Shisa family members bind immature forms of receptors and utilize a conserved PY motif to interact with WW-domain-containing proteins such as the E3 ubiquitin ligase family of NEDD4 proteins, which are discussed below. In doing so, the Shisa proteins bring these ligases into proximity with immature forms of FGFR in the ER, resulting in ubiquitination of the receptor for retention and degradation (Pei and Grishin, 2012; Yamamoto et al., 2005).

Another example of a trafficking modulator is the ubiquitin ligase NRDP1 which regulates ERBB3, the catalytically inactive (pseudokinase) member of the ErbB receptor family (Qiu and Goldberg, 2002). In zebrafish, *nrdp1* is expressed in the neural crest, nervous system, and muscle during embryogenesis and significantly overlaps with expression of ERBB3, suggesting functional cooperation (Britsch et al., 1998; Lyons et al., 2005; Maddirevula et al., 2011). Knockdown of *nrdp1* resulted in decreased expression of melanoblast markers and caused a significant reduction in pigmentation of embryos, a process driven by ERRB3 signaling (Maddirevula et al., 2011). As a RING finger-type ubiquitin ligase, NRDP1 regulates ERBB3 by controlling the abundance of receptor trafficked to the cell surface through constitutive ubiquitination of newly synthesized ERBB3 in the ER (Fry et al., 2011). The mechanism by which the cell regulates NRDP1 activity to fine-tune the precise level of receptor at the membrane was recently found to involve RTNA4. This member of the reticulon family of proteins, which control curvature of ER membranes, counteracts the NRDP1-dependent degradation of ERBB3 by sequestering NRDP1 into ER tubules. As a result, more ERBB3 is trafficked to the cell surface, where it may engage growth factors and its co-receptors to initiate downstream signaling (Hatakeyama et al., 2016).

### 1.2. Regulation of ligand-receptor signaling complex formation

A single RTK can bind multiple different ligands, and a single ligand can bind to multiple receptors. The specificity of these interactions is primarily driven by relative ligand/receptor affinities and effective concentration of both the receptor and the ligand. While the abundance of the receptor is controlled primarily at the level of biosynthesis and internalization, the pool of available ligands can be significantly influenced by extracellular regulators. For example, HSPGs tightly bind growth factors to limit diffusion in the extracellular matrix and therefore increase their local concentration to drive paracrine signaling by FGF, EGF, MET, VEGF, and PDGF (Abramsson et al., 2007; Cecchi et al., 2012; Fager et al., 1992; Forsten and Schneider, 2005; Gengrinovitch et al., 1999; Rapraeger et al., 1991; Yayon et al., 1991). Other regulators operate intracellularly at the level of the receptor but also modulate the extent of productive ligand/receptor interactions. Recent studies have increased our understanding of such modulators and expanded our knowledge of similar types of feedback regulators beyond HSPGs. Here we discuss Anosmin 1, FLRT3, SEF, and MIG6, three FGFR and one EGFR pathway-specific protein modulators, respectively, that interact with ligand-receptor signaling complexes to mediate assembly and activation.

The *Anosmin 1* gene encodes an extracellular matrix-associated protein that is largely conserved from invertebrates to primates (de Castro et al., 2016), however, no *ANOS1* ortholog has been identified in mouse and rat (de Castro et al., 2014). Therefore, the biological functions of Anosmin 1 have primarily been probed by overexpression of human *Anosmin 1* in mouse and rat neurons, which led to effects on cell adhesion and migration and neurite outgrowth and branching (Bribian et al., 2008; Garcia-Gonzalez et al., 2016; Soussi-Yanicostas et al., 2002, 1998). In development, these processes contribute to cranial neural crest formation and several aspects of neurogenesis, as shown by *in vitro* and *in vivo* studies in *C. elegans, D. melanogaster*, chick, and zebrafish (Supplemental Table 1) (Di Schiavi and Andrenacci, 2013; Endo et al., 2012; Gianola et al., 2009; Murcia-Belmonte et al., 2016). Anosmin 1 enhances FGF2 signaling specifically through FGFR1 in a heparin sulfate (HS)-dependent manner (Bribian et al., 2006; Gonzalez-Martinez et al., 2004). Heparin-bound Anosmin 1 binds to a pre-formed FGF2/FGFR1 complex via extracellular FnIII domains to stabilize the complex, resulting in receptor activation (Fig. 1A) (Cariboni et al., 2004; Hu et al., 2009). In both *C. elegans* and *D. melanogaster*, perturbation of the FnIII domains ablated biological activity of Anosmin 1 (Andrenacci et al., 2006; Bulow and Hobert, 2004).

The three Fibronectin-like domain-containing Leucine-rich Transmembrane (*FLRT*) genes encode a highly conserved family of glycosylated proteins that mediate cell recognition and FGF signaling in vertebrates in a manner that is distinct from HSPGs and Anosmin 1. *Flrt3* was originally identified in *X. laevis* as a gene with a similar expression pattern to Fgf signaling molecules, particularly at the midbrain/hindbrain boundary (Bottcher et al., 2004). Gain- and loss-of-function of *flrt3* or *flrt2* phenocopy experiments that perturb Fgf signaling, including effects on gastrulation, microcephaly, anterior truncations, and induction of ectopic tail-like structures (Bottcher et al., 2004; Cho et al., 2013). In chick, *flrt3* is necessary but not sufficient for proper formation of the limb organizer called the apical epidermal ridge (AER) and co-localized with *fgf8* expression and Erk activity (Tomas et al., 2011). *Flrt3* knockout mice are embryonic lethal due to fusion defects and impaired definitive endoderm migration, phenotypes attributed to FLRT3's function as a cell-adhesion molecule (Egea et al., 2008; Karaulanov et al., 2006; Maretto et al., 2008; Tsuji et al., 2004). *X. laevis* biochemical analyses *in vivo* and *in vitro* revealed that FLRT proteins complex with FGFRs to promote downstream signaling of the MAPK/ERK pathway via their intracellular domain (Fig. 1B) (Bottcher et al., 2004). Although rodent FLRT3 similarly physically interacts with FGFR1 (Haines et al., 2006), deletion of *Flrt3* in mice had no effect on *Fgf8* expression or the expression of known Fgf targets, despite expression of *Flrt3* in well-known Fgf signaling centers such as the AER, the midbrain-hindbrain boundary, and the anterior visceral endoderm (Egea et al., 2008; Haines et al., 2006; Maretto et al., 2008). Taken together, these studies suggest that the degree of conservation of the FGF/FLRT3 positive feedback loop varies among species (Supplemental Table 1). Since *Flrt3* null mice die at early stages of development, it will be worthwhile to investigate whether FLRT3 modulates FGF signaling at later stages using conditional knockout mice.

Similar to *flrt3* in *X. laevis, sef* (similar expression to *fgf* gene) was originally identified in zebrafish as a gene whose expression domains overlapped with known signaling centers of Fgfs (Furthauer et al., 2002; Tsang et al., 2002). Loss- or gain -of-function of *sef* in zebrafish led to various developmental defects, including cephalic malformations, cyclopia, expansion of ventrally derived domains, and reduction of the dorsal-most mesoderm (Furthauer et al., 2002; Tsang et al., 2002). In *X. laevis*, misexpression of zebrafish *sef* in the ventral

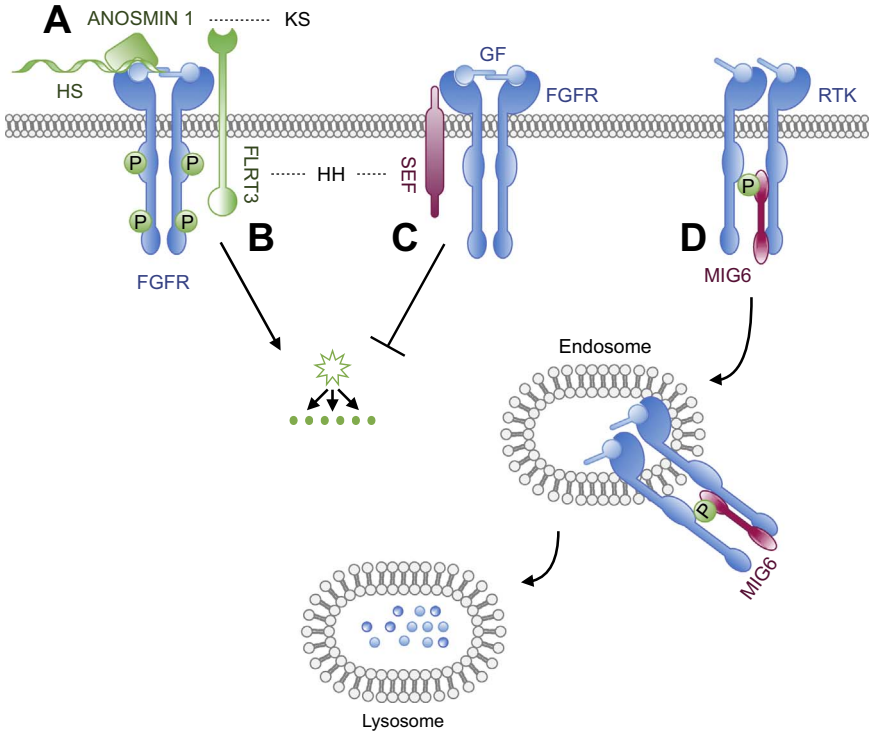


**Fig. 1. Modulation of RTK signaling by regulation of the ligand-receptor signaling complex formation.** (**A**) Heparin-bound Anosmin 1 binds to a pre-formed FGF2/FGFR1 complex, promoting its assembly and resulting receptor activation. FGFR signaling induces expression of *FLRT3* and *SEF* via transcriptional activation and translation. (**B**) FLRT3 complexes with FGFR to promote downstream signaling of the MAPK/ERK pathway via its intracellular domain. (**C**) SEF complexes with FGFR and blocks receptor phosphorylation and activation of the RAS/MAPK and PI3K/AKT signaling cascades. (**D**) EGFR signaling induces *MIG6* expression via transcriptional activation and translation. MIG6 accumulates in the cytoplasm where it binds directly with the ligand-activated ErbB kinase domain to inhibit auto-phosphorylation. This interaction can direct trafficking of the MIG-bound EGFR from the plasma membrane to late endosomes, targeting the receptor for lysosomal degradation. Dashed lines connect the human congenital disorder with the protein in the pathway encoded by the causative mutated gene. Syndromes noted in the text and/or Supplemental Table 1. HH, hypogonadotropic hypogonadism with or without anosmia; KS, Kallmann syndrome; FGFR, Fibroblast Growth Factor Receptor; GF, growth factor; HS, heparin-sulfate; P, phosphorylation; RTK, receptor tyrosine kinase.

marginal region at the 4-cell stage resulted in posterior truncations and gastrulation defects and was accompanied by suppression of Fgf target genes (Tsang et al., 2002). *SEF* transcripts have since been detected in zebrafish, chick, and mouse in numerous structures, including somites, the developing brain, limbs, and fin buds (Supplemental Table 1) (Boros et al., 2006; Furthauer et al., 2002; Harduf et al., 2005; Lin et al., 2002; Tsang et al., 2002). Surprisingly, *Sef* null mice are viable and fertile and do not show any obvious morphological phenotype during embryonic development (Abraira et al., 2007; Lin et al., 2005; Mellett et al., 2015). Lack of severe defects in the *Sef* mutant mice may be due to compensatory effects by other feedback antagonists. Indeed, *Sef* and the similarly FGF-induced *Sprouty* genes, discussed below, are expressed in overlapping regions along the anterior–posterior axis of the mouse embryo (Furthauer et al., 2002; Lin et al., 2002; Minowada et al., 1999).

The prototypic *sef* in zebrafish encodes a transmembrane receptor-like glycoprotein that blocks phosphorylation of Fgfr and subsequent activation of the Ras/Mapk and PI3K/Akt signaling cascades (Fig. 1C) (Furthauer et al., 2002; Harduf et al., 2005; Kovalenko et al., 2006, 2003; Preger et al., 2004; Tsang et al., 2002; Xiong et al., 2003; Yang et al., 2003). *In vitro* studies with mammalian SEF not only replicated the FGFR-induced antagonism seen in other species but also revealed that SEF can inhibit signaling activated by other growth factors, including EGF, PDGF, and nerve growth factor (NGF) (Kovalenko et al., 2003; Preger et al., 2004; Ren et al., 2008; Torii et al., 2004; Ziv et al., 2006). Interestingly, alternative spliced isoforms of *SEF* have been identified in humans (Preger et al., 2004; Rong et al., 2007; Ziv et al., 2006). SEF-a is similar to the prototypic SEF reported in zebrafish and mice (Furthauer et al., 2002; Lin et al., 2002; Tsang et al., 2002; Yang et al., 2003), whereas SEF-b, which lacks a signal peptide for secretion, is localized to the cytoplasm and acts at the level of, or downstream from, MEK (Fig. 2F) (Preger et al., 2004; Yang et al., 2003; Ziv et al., 2006). Although both isoforms interact with FGFR1, the outcome of this association is not identical, as the cell-surface SEF-a inhibits multiple FGF signaling pathways (Preger et al., 2004). Whether these isoforms function cooperatively or in the same developmental processes remains to be determined; though, to note, the SEF-b isoform exhibits a restricted pattern of expression in human tissues compared with SEF-a (Preger et al., 2004). Since RTKs deliver varied biological responses, it seems likely that SEF can interfere with RTK signaling at different levels to fine-tune signaling in a cell context- and isoform specific-manner.

Through an evolutionarily conserved modular domain named the ErbB binding region (EBR), the multi-adaptor protein Mitogen-Inducible Gene 6 (MIG6) mediates catalytic repression of ligand-bound ERBB receptors, namely EGFR, ERBB2, and ERBB4 (Anastasi et al., 2007; Hackel et al., 2001). Since ERBB3 signals as an obligate heterodimer with the other members of the ErbB family, MIG6 also inhibits its signaling and thus is a cellular inhibitor of the entire ErbB family. Knockout of *Mig6* in mice resulted in aberrant lung development associated with high neonatal mortality (Ferby et al., 2006; Jin et al., 2009; Zhang et al., 2005), and surviving mice developed degenerative joint diseases and spontaneous tumors in organs including the skin, gastrointestinal tract, lung, and endometrium (Supplemental Table 1) (Ferby et al., 2006; Jeong et al., 2009; Jin et al., 2009; Zhang et al., 2005). Importantly, over proliferation and impaired differentiation of epidermal keratinocytes and the resulting skin tumors could be rescued by genetic or pharmacological suppression of EGFR, indicating that unrestrained EGFR activation and sustained signaling through MAPK was a result of loss of *Mig6* (Ferby et al., 2006). Tissue-specific deletion of *Mig6* in mouse hepatocytes caused hepatomegaly and fatty liver, a phenotype similar

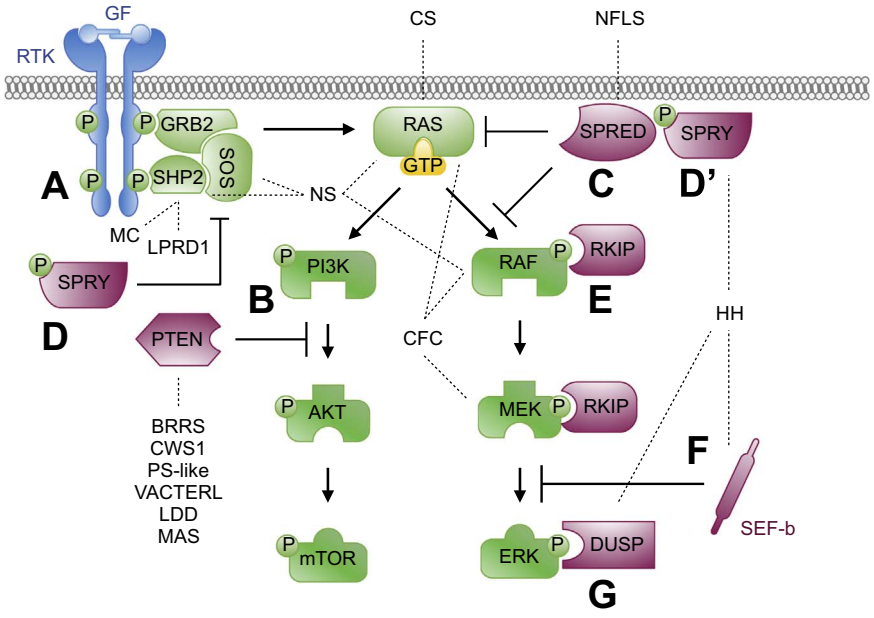


**Fig. 2. Feedback modulators of intracellular signal transduction cascades**. FGFR signaling induces expression of the SPRED family, the Sprouty family, *SEF,* and nuclear *DUSP*s via transcriptional activation and translation to attenuate RAS/MAPK signaling. (**A**) Growth factor-activated RTKs induce GRB2-mediated recruitment of SHP2 to signaling complexes. GRB2 redirects activated SHP2 to other signaling proteins that normally inhibit RTK signaling, subsequently acting as a positive regulator. (**B**) Growth factor-activated RTKs recruit and activate PI3K. The PI3K lipid signaling intermediate is dephosphorylated by PTEN, thereby attenuating PI3K/AKT signaling. (**C**) SPRED proteins increase RAF recruitment to the plasma membrane and prolongs RAS/RAF complexation, withdrawing RAF from activation by phosphorylation. (**D, D'**) Sprouty proteins translocate to the plasma membrane where they are phosphorylated. This phosphorylation induces a confirmation change that allows Sprouty proteins to bind and disrupt the GRB2/SOS complex, RAS activation, and RAF activation, thereby attenuating RAS/PI3K and RAS/MAPK signaling. (**E**) RKIP binds to both RAF1 and MEK to prevent their physical interaction and MEK phosphorylation, thereby attenuating RAS/MAPK signaling. (**F**) SEF-b suppresses activation at the level of, or downstream from, MEK. (**G**) DUSP6 dephosphorylates ERK. Dashed lines connect the human congenital disorder with the protein in the pathway encoded by the causative mutated gene. Syndromes noted in the text and/or Supplemental Table 1. BRRS, Bannayan-Ruvalcaba-Riley syndrome; CFC, cardio-facio-cutaneous syndrome; CS, Costello syndrome; CWS1, Cowden syndrome 1; HH, hypogonadotropic hypogonadism with or without anosmia; LDD, Lhermitte-Duclos disease; LPRD1, LEOPARD syndrome 1; MAS, Macrocephaly/autism syndrome; MC, Metachondromatosis; NFLS, Neurofibromatosis Legius syndrome; NS, Noonan syndrome; PS-like, Proteus-like syndrome; VACTERL, vertebral anomalies, anal atresia, congenital cardiac disease, tracheoesophageal fistula, renal anomalies, radial dysplasia, and other limb defects; GF, growth factor; P, phosphorylation; RTK, receptor tyrosine kinase.

to that observed in mice homozygous for a gain-of-function *Egfr* allele (Ku et al., 2012; Natarajan et al., 2007; Reschke et al., 2010; Scheving et al., 2014). Receptor-induced phosphorylation of the MIG6 ERB domain stabilizes the MIG6/EGFR interaction and prevents activation of EGFR by blocking an allosteric site critical for activation within the receptor dimers (Fig. 1D) (Park et al., 2015; Zhang et al., 2007, 2005). Upon docking onto EGFR, MIG6 is also capable of recruiting components of the endocytic machinery, leading to receptor degradation independent of phosphorylation and ubiquitination (Frosi et al., 2010; Segatto et al., 2011; Walsh and Lazzara, 2014; Ying et al., 2010). This two-tiered mechanism of MIG6-mediated inhibition provides for immediate repression of EGFR signaling (kinase inhibition) coupled to longer term isolation from incoming ErbB receptor ligands (endocytosis) (Anastasi et al., 2016). Whether MIG6 exerts either of these inhibitory functions on other RTKs remains to be determined. MIG6 binding to ErbB receptors is dependent on a protein interface in the kinase domain unique to the ErbB family, so involvement of MIG6 with other RTKs would involve a different mechanism or could imply that these RTKs signal in cooperation with ErbB receptors. *In vitro* analyses suggest that MET could be a potential target of MIG6, as overexpression of *MIG6* was able to inhibit the HGF/MET-induced cell migration and neurite outgrowth (Pante et al., 2005).

### *1.3. Receptor dephosphorylation*

The phosphorylation status and signaling output of RTKs is determined by a balance between the intrinsic kinase activity of the receptor and the activities of protein tyrosine phosphatases (PTPs). PTPs have evolved in a number of families that are structurally and mechanistically distinct and control a broad spectrum of RTK signaling pathways (Ostman and Bohmer, 2001; Tonks, 2006). As such, they are arguably one of the most important regulators of the extent and intensity of RTK signaling. Animal studies thus far, however, have yielded only limited insights into specific functions of individual PTPs. While knockout mouse models have been made for all classical PTP genes except *Ptpn18*, *Ptpn20, Ptpn21*, and *Ptpru* (Hendriks et al., 2013), many of these knockout models displayed only mild developmental defects, suggesting significant functional redundancy between PTPs.

*Ptpn11* is one of the few exceptions, as *Ptpn11* knockout mice died at mid-gestation with multiple defects in mesodermal patterning (Qu et al., 1997; Saxton et al., 1997). Selective deletion of *Ptpn11* in developing kidneys of mice caused reduced ureteric bud branching by downregulation of the transcription factors *Etv4* and *Etv5*, which are targets of glial-derived neurotrophic factor (GDNF)/RET signaling and of other RTKs (Willecke et al., 2011). *Ptpn11*-deficiency in cardiomyocytes resulted in early postnatal lethality and dilated cardiomyopathy associated with increased IR signaling and decreased activation of ERK1/2 and JNK2 (Princen et al., 2009). Numerous other *in vivo* studies have linked *Ptnp11* with FGF-dependent MAPK/ERK signaling and have revealed roles for *Ptnp11* in patterning and specification of the optic vesicle, lens and lacrimal gland development, chondrogenesis, intestinal progenitor cell fate, lung branching morphogenesis, and formation of the midbrain-hindbrain boundary, among others (Supplemental Table 1) (Cai et al., 2013; Dee et al., 2016; Heuberger et al., 2014; Pan et al., 2010; Tefft et al., 2005; Yang et al., 2013). *PTPN11* encodes the widely expressed non-receptor tyrosine phosphatase Src-homology 2 domain-containing phosphatase 2 (SHP2) (Dance et al., 2008), which in the absence of upstream stimulation, is kept in a low-activity state by an intramolecular interaction between the N-terminal SH2-domain and the catalytic phosphatase domain. Activation of RTKs and/or subsequent activation of scaffolding adaptor

proteins leads to recruitment of SHP2 to signaling complexes, where engagement of the SH2-domains induces a conformational change that resolves auto-inhibitory interactions. SHP2-mediated dephosphorylation of FGFRs is controlled by the adaptor protein GRB2, which recruits SHP2 to the activated receptors (Fig. 2A). GRB2 additionally redirects activated SHP2 to other signaling proteins, such as Sprouty or STAT proteins, that normally inhibit signaling through ERK1/2, AKT, or STAT5. In this manner, SHP2 can further amplify RTK signaling (Ahmed et al., 2010, 2013; Hadari et al., 1998; Hanafusa et al., 2004; Tajan et al., 2015; You et al., 1999).

### 1.4. Dephosphorylation of signaling pathway components

The intracellular events downstream of activated RTKs are responsible for transduction and amplification of ligand-induced signaling. This most commonly involves protein phosphorylation, which ultimately results in changes in gene expression and other cellular effects. The PI3K/AKT and RAS/MAPK pathways are principal signaling mechanisms for controlling cell survival, proliferation, differentiation, and migration (Fig. 2) (Mendoza et al., 2011), and as such, must be precisely spatially and temporally regulated. Phosphatase and Tensin homolog (PTEN) and Dual-Specificity Phosphatases (DUSPs) represent early and late attenuators, respectively, of RTK-induced intracellular signal transduction cascades. PTEN is the main negative regulator of the PI3K/AKT pathway, whereas DUSPs modulate activation of the RAS/MAPK pathway (Carracedo et al., 2008; Katz et al., 2011) (Fig. 2). Multiple mechanisms and modes of crosstalk have been uncovered between these two pathways, further complicating our understanding of their complex roles in development (Mendoza et al., 2011).

The first, and probably still the clearest, indication that PTEN plays an essential role in regulation of cell growth came from early studies in *D. melanogaster* (Goberdhan and Wilson, 2003). *Pten*-deficient cells proliferated at a faster rate than their heterozygous counterparts, showed an autonomous increase in cell size, and formed enlarged organs (Gao et al., 2000; Goberdhan et al., 1999; Huang et al., 1999). *In vitro* and *in vivo* studies revealed that PTEN controls cell growth and proliferation by antagonizing growth factor-induced activation of the PI3K/AKT pathway. Specifically, PTEN preferentially dephosphorylates membrane-bound $PIP_3$ into $PIP_2$. This prevents $PIP_3$-mediated recruitment of AKT to the plasma membrane and its activation (Fig. 2B) (Engelman et al., 2006; Maehama and Dixon, 1998). Numerous subsequent studies in mice and other model organisms have examined the functional role of *Pten* in various organs and tissues, yielding a diverse spectrum of phenotypes (Supplemental Table 1) (Knobbe et al., 2008). Knockout mouse models of *Pten* showed that deletion of a single allele resulted in lethal polyclonal autoimmune disorders and various forms of epithelial cancer (Di Cristofano et al., 1999, 1998). Because of the lethal nature of *Pten* loss, conditional deletion models have been used to address the roles of PTEN during development. Tissue-specific deletion of *Pten* in mouse neurons resulted in progressive macrocephaly, seizures, and ataxia, and neurons lacking *Pten* expressed high levels of phosphorylated AKT (Backman et al., 2001; Groszer et al., 2001; Kwon et al., 2001). *In vitro* and *in vivo* analyses revealed that PTEN also regulates cardiac hypertrophy and survival by blocking growth factor signaling through the PI3K/AKT pathway (Crackower et al., 2002; Schwartzbauer and Robbins, 2001). As PI3K pathway signaling is regulated in part by IR signaling and affects downstream proteins involved in metabolism such as mTOR, *Pten*-deficiency in hepatocytes led to massive hepatomegaly and steatohepatitis with triglyceride accumulation (Horie et al., 2004; Stiles et al., 2004).

DUSPs constitute a large heterogeneous subgroup of the PTP superfamily characterized by their ability to dephosphorylate tyrosine, serine, and threonine residues. Despite a fairly detailed understanding of the biochemical properties and catalytic mechanisms employed by DUSPs (Farooq and Zhou, 2004; Owens and Keyse, 2007), knowledge of their *in vivo* roles is still expanding (Supplemental Table 1). Of interest here, gene knockdown or overexpression studies in zebrafish, chick, and mouse first identified an *in vivo* role for *DUSP6* in fin/limb bud patterning as a negative feedback regulator of the FGF-RAS/MAPK signaling pathway (Fig. 2G) (Kawakami et al., 2003). FGF8 signaling induces expression of *DUSP6,* which encodes an ERK-specific DUSP, and establishes a negative feedback loop (Bermudez et al., 2010; Groom et al., 1996; Kawakami et al., 2003; Mourey et al., 1996; Muda et al., 1996). Targeted inactivation of *Dusp6* in mice led to increased levels of phosphorylated ERK, the phosphorylated ERK target *Erm*, and transcripts initiated from the *Dusp6* promoter itself (Li et al., 2007). Furthermore, *Dusp6* knockout mice displayed cardiac hypertrophy and multiple skeletal abnormalities including dwarfism, defects in the middle ear bones and otic capsule, and premature fusion of the cranial sutures (craniosynostosis); histological analysis of the long bones revealed disorganization of chondrocytes in the growth plate (Li et al., 2007; Maillet et al., 2008; Urness et al., 2008). These same skeletal phenotypes are also found in mouse models of human disorders with constitutive activating mutations in *FGFRs* (Neben and Merrill, 2015; Ornitz and Marie, 2015), highlighting the relationship between FGF signaling and DUSP6. Although many agonists in addition to FGFs activate ERK1/2 during embryonic development, including EGF, NGF, HGF, VEGF, and PDGF, few studies have examined their regulation by DUSP6 *in vivo* (Bermudez et al., 2010).

### 1.5. Non-catalytic feedback modulators of signaling pathways

Sprouty *(SPRY)* and *SPRED* genes encode highly conserved protein families with no apparent enzymatic function that inhibit different steps of the RAS/MAPK signaling pathway and fine-tune RTK signaling in a cell context- and isoform specific- manner. Some evidence suggests that Sprouty proteins indirectly regulate the PI3K/AKT pathway, however, these effects are poorly understood (Castellano and Downward, 2011; Steelman et al., 2011). As late attenuators transcriptionally induced by growth factor activation, Sprouty and SPRED proteins adapt cells to longer term external stimulation, persisting on the timescale of hours (Volinsky and Kholodenko, 2013).

The first member of the Sprouty family was found in a screen for genes involved in development of trachea and eyes in *Drosophila* (Casci et al., 1999; Hacohen et al., 1998). Like *Drosophila* Sprouty, mammalian Sprouty proteins antagonize FGF signaling in tubular morphogenesis associated with tracheal/lung development (Fig. 3A, A′) (Metzger et al., 2008; Shaw et al., 2007; Tefft et al., 1999) and angiogenesis (Taniguchi et al., 2007a, 2009). Since these initial findings, the number of pathways and biological processes regulated by Sprouty proteins continues to expand, including submandibular parasympathetic gangliogenesis (Fig. 3B, B′) (Knosp et al., 2015), ureteric branching (Fig. 3C, C′) (Basson et al., 2005, 2006; Chi et al., 2004; Gross et al., 2003; Michos et al., 2010), external genitalia development (Fig. 3D, D′) (Ching et al., 2014), endochondral bone formation (Fig. 3E, E′) (Joo et al., 2016; Minowada et al., 1999), and branchial nerve development (Fig. 3F, F″) (Simrick et al., 2011), among others (Supplemental Table 1).

As the functions of Sprouty proteins in embryonic development have been reviewed previously by others (Cabrita and Christofori, 2008; Horowitz and Simons, 2008; Warburton et al., 2008), we highlight here the specific roles of these proteins in craniofacial and tooth development as an example of the types of effects these genes can have on RTK-mediated signaling. SPRY2 and FGF8/FGFR3 signaling is required for cell fate decisions in the mouse auditory sensory epithelium, as loss of *Spry2* resulted in dramatic perturbations in organ of Corti cytoarchitecture (Fig. 3G, G′) (Shim et al., 2005). Combined deletion of *Spry1* and *Spry2* in mice caused highly disorganized palatal rugae, including broader and ectopic ruga formation, (Fig. 3H, H′) indicating that the FGF pathway is activatory in a Turing-type reaction-diffusion system for the striped pattern that establishes and maintains

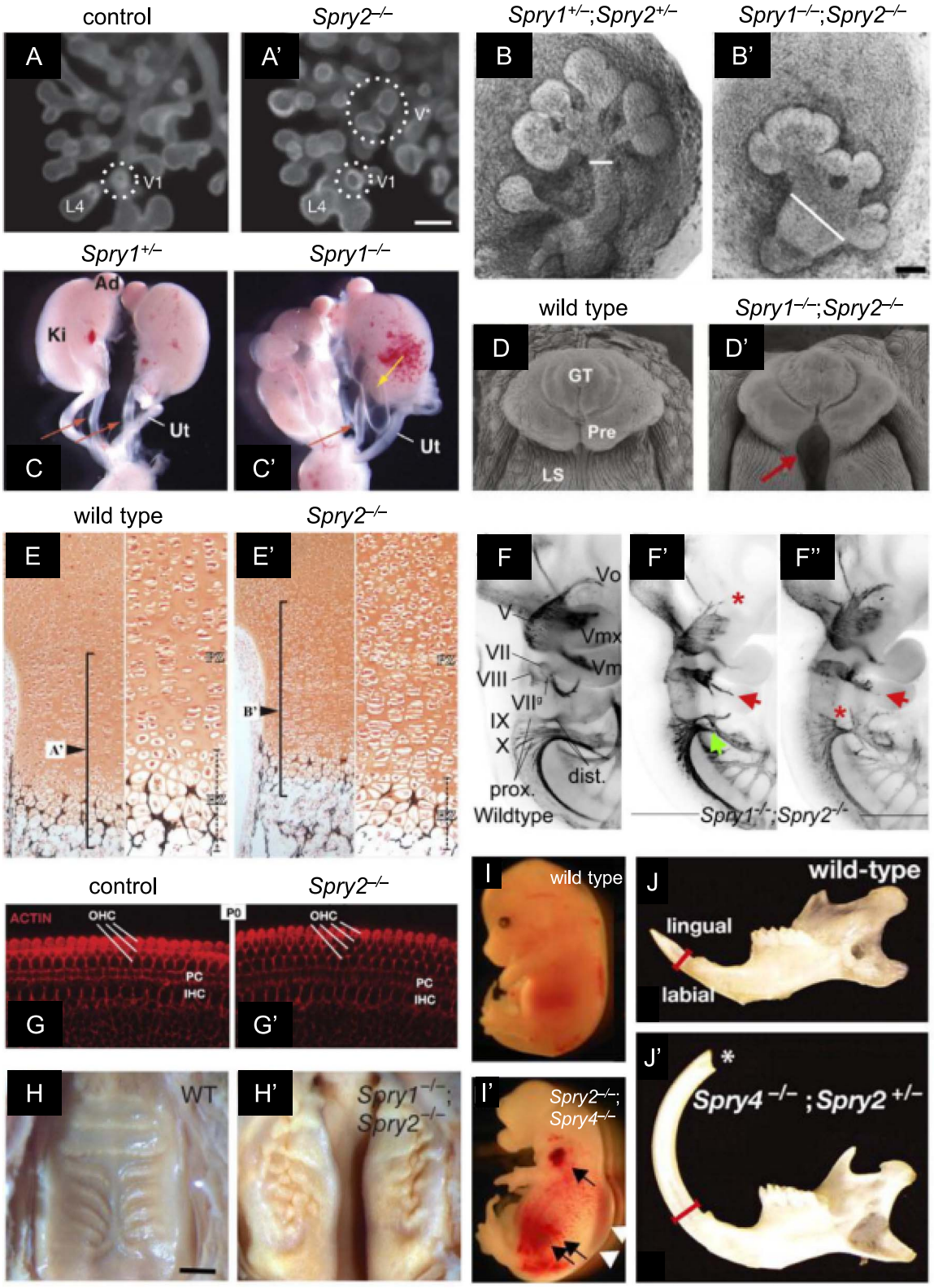


**Fig. 3. Mouse models are invaluable in decoding the developmental roles of the regulator family of Sprouty proteins**. (**A-A′**) E12.5 *Spry2*$^{-/-}$ mouse lung showing the normal ventral secondary branch (V1) and an ectopic branch (V*) that forms earlier and proximal to V1 (Metzger et al., 2008). (**B-B′**) Genetic deletion of *Spry1;Spry2* in mice disrupts submandibular gland epithelial development resulting in a wide primary duct (white lines) and abnormal branching morphogenesis at E13 (Knosp et al., 2015). (**C-C′**) Kidneys and urogenital tract abnormalities in *Spry1*$^{-/-}$ newborn pups. Normal ureters and abnormal hydroureters are indicated by red and yellow arrows, respectively. Ad, adrenal; Ki, kidney; Ut, uterus (Basson et al., 2005). (**D-D′**) Fusion of the preputial (Pre) and labioscrotal (LS) folds along the ventral surface of the genital tubercle (GT) is disrupted in E16.5 male *Spry1*$^{-/-}$;*Spry2*$^{-/-}$ mice, resulting in the absence of an internalized urethra in the proximal GT (red arrow) (Ching et al., 2014). (**E-E′**) Von Kossa/Safranin-O staining of E18.5 femur sections showed more proliferating chondrocytes in the growth plate of *Spry2*$^{-/-}$ mice than in that of wild type (Joo et al., 2016). (**F-F″**) E10.5 *Spry1*$^{-/-}$;*Spry2*$^{-/-}$ mice have trigeminal nerve defects, facial nerve defects, and glossopharyngeal and vagus cranial nerves display incomplete or irregular bridging between proximal and distal ganglia. Arrows highlight abnormal morphology, and asterisks indicate missing portions (Simrick et al., 2011). (**G-G′**) The region of the P0 *Spry2*$^{-/-}$ mouse cochlea shown has four rows of outer hair cells (OHCs) instead of

the three found in control and elsewhere in the *Spry2* null organ of Corti. PC, pillar cells; IHC, inner hair cells (Shim et al., 2005). (**H-H′**) Increased FGF signaling in *Spry1*$^{-/-}$;*Spry2*$^{-/-}$ mice resulted in disorganized and compacted rugae at P0 (Economou et al., 2012). (**I-I′**) Gross appearance of wild type and *Spry2*$^{-/-}$;*Spry4*$^{-/-}$ at E12.5. The arrow and arrowhead indicate hemorrhage and edema, respectively (Taniguchi et al., 2009). (**J-J′**) Abnormal length and thickness of adult *Spry2*$^{-/-}$;*Spry4*$^{+/-}$ incisor as well as the absence of a sharp tip (asterisk) (Klein et al., 2008). Reprinted or adapted with permission.

the palatal rugae (Economou et al., 2012). *Spry2*;*Spry4* double knockout mice are embryonic lethal by E12.5 with craniofacial and limb morphogenesis abnormalities (Fig. 3I, I′) (Taniguchi et al., 2007a, 2009). The *Spry4* loss of function phenotypes, including dwarfism and polysyndactyly, resemble mouse models of human disorders with activating mutations in *FGFRs* (Neben and Merrill, 2015; Ornitz and Marie, 2015; Taniguchi et al., 2007a), suggesting that loss of *Spry4* results in hyperactivation of FGF signaling. Mice carrying single and various combinations of Sprouty mutant alleles also possess supernumerary teeth and display abnormalities in tooth size, shape, and micro-structure (Boran et al., 2009; Charles et al., 2011; Klein et al., 2008, 2006; Lagronova-Churava et al., 2013; Lochovska et al., 2015; Marangoni et al., 2015; Percival et al., 2017). For example, *Spry2*$^{+/-}$;*Spry4*$^{-/-}$ mice develop a 'tusk'-like incisor in their lower jaws due to the presence of enamel on the lingual surface (Fig. 3J, J′)(Boran et al., 2009; Klein et al., 2008). Importantly, the lingual ameloblast phenotype can be rescued in the adult by reducing *Fgf* gene dosage (Klein et al., 2008), demonstrating the critical role of Sprouty genes in controlling the epithelial-mesenchymal FGF signaling loop.

The four mammalian orthologues of Sprouty proteins share sequence similarity to *D. melanogaster* Sprouty in the cysteine-rich C-terminus but differ significantly in the N-terminus among each other and from the fly ortholog (de Maximy et al., 1999; Leeksma et al., 2002; Mason et al., 2006). This sequence divergence could dictate differential functions, potentially by mediating protein-protein interactions. Indeed, Sprouty proteins can interact directly with multiple downstream components of the RTK pathway, including FRS2, GRB2, RAF1, B-RAF, and SHP2. In most cases, however, it remains unclear how these associations modulate signaling. The best-studied family members, SPRY1 and SPRY2, antagonize RTK signaling at multiple levels, such as binding to the GRB2/SOS complex (Fig. 2D) and inhibition of RAF1 activation by RAS (Fig. 2D′) depending on the cellular context and/or the identity of the RTK (Mason et al., 2006). The phosphorylation of SPRY1 and SPRY2 at Tyrosine 53 and Tyrosine 55, respectively, induces a conformational change that has been shown to be essential for protein binding and modulation of RAS/MAPK signaling (Alsina et al., 2012; Guy et al., 2009; Hanafusa et al., 2002; Mason et al., 2004; Sasaki et al., 2003, 2001). Sprouty proteins may mediate their actions in part by increasing active forms of such phosphatases as PTEN (Edwin et al., 2006; Patel et al., 2013). In cultured cells, SPRY2 increased overall PTEN protein levels while decreasing PTEN phosphorylation, resulting in increased PTEN activity. This was reflected in diminished activation of AKT by EGF signaling and blocked cell proliferation (Edwin et al., 2006). In the context of *in vito* EGFR signaling, SPRY2 levels are controlled through phosphorylation-dependent complex formation with C-CBL (Hall et al., 2003; Mason et al., 2004; Rubin et al., 2003). Binding of SPRY2 to C-CBL directs the proteolytic degradation of SPRY2 but also inhibits C-CBL-mediated degradation of EGFR, leading to sustained signaling activity (Egan et al., 2002; Ng et al., 2008; Rubin et al., 2003; Wong et al., 2002). This function may be limited to SPRY2, however, as SPRY4 suppression of MAPK/ERK activation by EGF stimulation did not result in interaction with C-CBL (Mason et al., 2004; Wong et al., 2001).

SPREDs (Sprouty-related PRoteins with an EVH1 Domain) are a family of membrane-associated, negative RAS/MAPK signaling modulators that possess structural and functional similarities to their relatives, the Sprouty proteins. There are four known mammalian SPRED proteins: SPRED1, SPRED2, SPRED3, and EVE-3, the last of which is a splice variant of SPRED3 (Kato et al., 2003; King et al., 2006; Wakioka et al., 2001). *Spred1* knockout mice are viable and fertile but exhibit low body weight, a shortened face, and impaired hippocampus-dependent learning capabilities (Brems et al., 2007; Denayer et al., 2008; Inoue et al., 2005; Phoenix and Temple, 2010). *Spred2* deficiency in mice suppressed aorta-gonad-mesonephros hematopoiesis and caused defects in bone morphogenesis, with the mice exhibiting a dwarfing phenotype and increase of early hematopoiesis (Bundschu et al., 2005; Nobuhisa et al., 2004). Overlapping expression patterns of different SPRED family members and their possible redundancy might preclude certain phenotypes from being observed in the single null alleles (Supplemental Table 1). Indeed, deletion of both *Spred1* and *Spred2* in mice, which have overlapping expression patterns in the heart, lung, liver, and bone, resulted in embryonic lethality with subcutaneous hemorrhage, edema, and dilated lymphatic vessels (Engelhardt et al., 2004; Kato et al., 2003; Stowe et al., 2012; Taniguchi et al., 2007b; Tuduce et al., 2010).

Like Sprouty proteins, SPRED proteins inhibit growth factor-mediated MAPK/ERK activation, albeit by different biochemical mechanisms. Overexpression of SPRED1 increases RAF recruitment to the plasma membrane and prolongs RAS/RAF interaction, thus withdrawing RAF from activation by phosphorylation (Fig. 2C) (Bundschu et al., 2005; Wakioka et al., 2001). Subsequent studies confirmed that SPRED proteins also inhibit activation of RAS by the small GTPase RAP1 without affecting receptor phosphorylation (King et al., 2006; Nonami et al., 2005; Stowe et al., 2012). Recently, it was proposed that SPRED1-plasma membrane translocation is mediated in a B-RAF- and C-RAF-dependent manner to specifically disturb K-RAS but not H-RAS membrane anchorage (Siljamaki and Abankwa, 2016). This potential mechanism may explain why it has been difficult to pinpoint whether SPRED1 acts at the level of RAS or RAF.

Originally isolated from the bovine brain (Bernier and Jolles, 1984), RAF Kinase Inhibitor Protein (RKIP; also known as PhosphatidylEthanolamine-Binding Protein, PEBP1) was renamed based on its physiologically relevant inhibition of the RAS/MEK/ERK pathway (Yeung et al., 1999, 2001). Expression of *RKIP* mRNA has since been detected in all mammalian tissues tested, with high levels in spermatids and brain oligodendrocytes, Purkinje cells, and specific cortical and hippocampal neuronal cell layers (Bernier and Jolles, 1984; Frayne et al., 1999; Theroux et al., 2007). *RKIP* deficient mice are viable but develop an olfaction deficit, a phenotype that correlates with the expression pattern of the gene in the brain (Theroux et al., 2007). Subsequent studies in model organisms have identified RKIP as critical for neurological functioning, photoreceptor degeneration, myogenesis, reproduction, and spermatogenesis (Supplemental Table 1) (Antoun et al., 2012; Gibbons et al., 2005; Murga-Zamalloa et al., 2011; Nixon et al., 2006; Subramanian et al., 2014; Yamamoto et al., 2012). RKIP inhibits RAF-1 mediated phosphorylation and activation of MEK by competitive physical association which disrupts the interaction between these kinases (Fig. 2E). Overexpression of *RKIP in vitro* reduced cell proliferation and transformation and was accompanied by alterations in MEK-, ERK-, and AP-dependent transcription (Yeung et al., 1999). Interestingly, although RKIP can interact with B-RAF, depletion of RKIP did not affect B-RAF activation, indicating that RKIP may selectively limit the dynamic range of MAPK signaling in response to growth factors (Trakul et al., 2005).

### *1.6. Early attenuation of RTK signaling via receptor ubiquitination and degradation*

Another common mechanism by which RTK signaling is down-regulated is the removal of receptors from the plasma membrane via endocytosis. This can occur either reversibly, when internalized

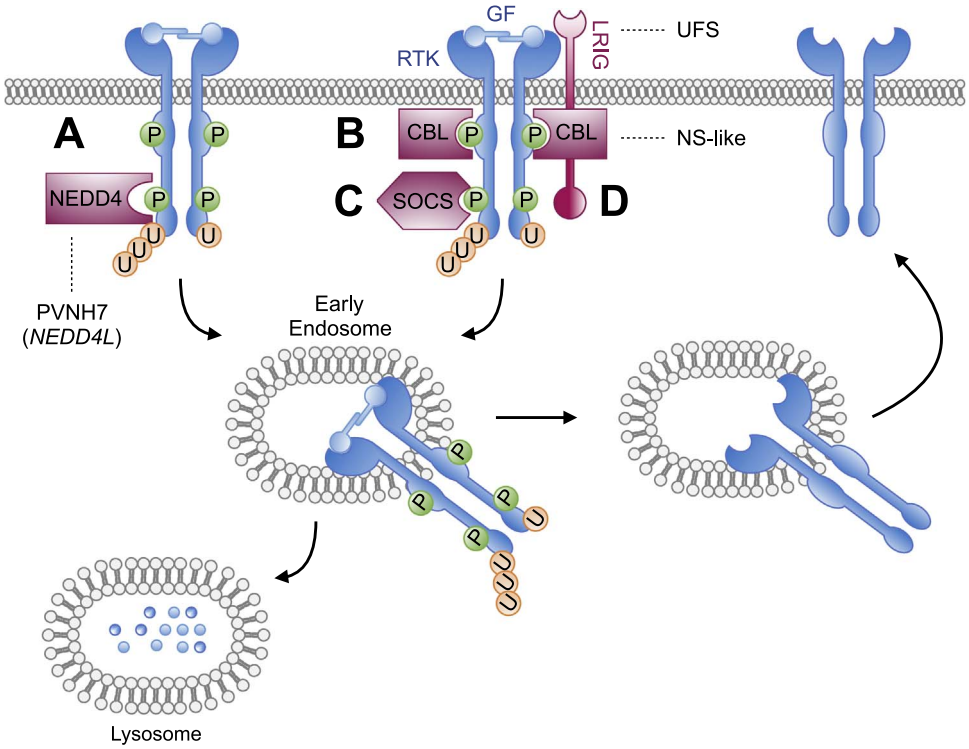


**Fig. 4. Attenuation of RTK signaling by receptor ubiquitination and degradation**. (**A**) Growth factor activation of RTKs leads to recruitment of NEDD4 to the receptor complex. (**B**) Independent and (**C**) SOCS- or (**D**) LRIG-mediated mechanisms recruit CBL to the receptor complex. NEDD4 and CBL direct the ubiquitination of RTKs, resulting in receptor endocytosis and routing to early endosomes. RTKs can then either be recycled to the plasma membrane or targeted for lysosomal degradation, thereby attenuating receptor signaling. Dashed lines connect the human congenital disorder with the protein in the pathway encoded by the causative mutated gene. Syndromes described in the text and/or Supplemental Table 1. PVNH7, Periventricular nodular heterotopia 7; NS-like, Noonan syndrome-like; UFS, Urofacial syndrome; GF, growth factor; P, phosphorylation; RTK, receptor tyrosine kinase; U, ubiquitination.

receptors are recycled back to the plasma membrane after a period of time, or irreversibly, when the downregulated receptors are sent for lysosomal degradation. RTK internalization and degradation are regulated upon growth factor-induced RTK activation through ubiquitination of the intracellular receptor domains by E3 ubiquitin ligases (Fig. 4) (Goh and Sorkin, 2013). The two main E3 ligases involved in RTK ubiquitination during development are the HECT-type ligase NEDD4 and the RING-type ligase CBL. Both NEDD4 and CBL regulate signal duration of multiple RTKs, and their disruption in development results in serious abnormalities.

NEDD4 (Neuronal precursor cell Expressed and Developmentally Downregulated) proteins are found ubiquitously in eukaryotes and have expanded to nine known family members in mammals, with two of them, NEDD4 and NEDD4L (also known as NEDD4-2) being very closely related (Supplemental Table 1) (Scheffner and Kumar, 2014). Complete loss of *Nedd4* in mice resulted in embryonic lethality at mid-gestation with pronounced heart defects, subcutaneous bleeding, and developmental delays (Fouladkou et al., 2010; Kawabe et al., 2010; Liu et al., 2009). Although NEDD4 has several additional substrates beyond RTKs, biochemical analysis suggested that the *Nedd4* loss-of-function phenotype can be at least partially attributed to abnormal RTK signaling: the growth retardation in *Nedd4* heterozygous mice is associated with reduced cell surface expression and signaling through IR and IGF-1R (Cao et al., 2008). That loss of *Nedd4* resulted in loss of IGF-1R signaling contradicts earlier *in vitro* studies which reported that NEDD4 ubiquitinates and decreases stability of IGF-1R (Vecchione et al., 2003). This suggests that NEDD4 may fine-tune RTK signaling differently in distinct cell types. In agreement with a role for NEDD4 in promoting receptor degradation, *Nedd4L*-deficient mouse embryos showed increased expression of neurotrophic RTK 1 (NRTK1, also known as TRKA), a possible contributor to the pain sensitivity phenotype in heterozygous adults (Yanpallewar et al., 2016). The binding of NEDD4L to activated NRTK1 leads to receptor ubiquitination and down-regulation and to the modulation of neuronal survival *in vitro* (Fig. 4A) (Arevalo et al., 2006; Yu et al., 2014). NEDD4 may also attenuate RTK signaling by regulating the levels of the tumor suppressor PTEN. *In vitro* studies demonstrated that NEDD4 was responsible for PTEN ubiquitination (Trotman et al., 2007; Wang et al., 2007), and subsequent studies in *X. laevis* confirmed that Nedd4-mediated ubiquitination of Pten promoted axonal and dendritic branching by allowing full activation of the PI3K/Akt pathway (Christie et al., 2010; Drinjakovic et al., 2010; Schmeisser et al., 2013). However, it does not appear that aberrant PTEN ubiquitination in mice played a role in impaired axon growth upon deletion of *Nedd4* and *Nedd4L* (Hsia et al., 2014), suggesting that NEDD4 regulation of PTEN may only occur in specific biological contexts.

The first evidence that members of the CBL (Casitas B-lineage Lymphoma proto-oncogene) family of E3 ligases (cbl in *D. melanogaster*, SLI-1 in *C. elegans,* and CBL-3, CBL-B, and C-CBL in mammals) act as negative regulators of RTKs was provided by genetic screens in *C. elegans* and *D. melanogaster* (Supplemental Table 1). These early studies demonstrated that loss-of-function point mutations in the CBL homologs *sli-1* and *cbl* resulted in aberrant signaling by the EGFR homologs LET-23 and Der, respectively (Jekely et al., 2005; Meisner et al., 1997; Pai et al., 2000; Wang et al., 2008; Yoon et al., 1995). Subsequent studies of the mammalian homologs have shown that *c-Cbl-* or *Cbl-b*-deficient mice are viable and fertile with only minor phenotypic differences, but combined deletion results in early embryonic lethality before mid-gestation (Mohapatra et al., 2013; Nakamura et al., 2001). This redundancy is consistent with *in vitro* work demonstrating that C-CBL and CBL-B work cooperatively to control the duration of EGFR signaling (Pennock and Wang, 2008). Upon ligand-induced receptor activation, phosphorylated CBL proteins complex with EGFR via a highly conserved TKB domain to facilitate

receptor ubiquitination and degradation by a catalytic RING finger domain (Fig. 4B) (de Melker et al., 2001; Haglund et al., 2003; Levkowitz et al., 1999, 1998; Longva et al., 2002). The *c-Cbl* knockout phenotype is faithfully recapitulated by a mutation in the RING finger domain that eliminates its E3 ligase activity and resulted in more severe phenotypic changes than a loss-of-function mutation in the *c-Cbl* TKB domain (Thien and Langdon, 2005; Thien et al., 2003). Thus, TKB domain-mediated interactions with RTKs does not fully explain the spectrum of C-CBL functions. Further confirmation of this hypothesis came from a study analyzing homozygous knock-in mutation of Tyrosine 737, which eliminates the binding site for PI3K in the C-terminal tail of CBL, located outside of the TKB domain (Adapala et al., 2010a, 2010b). Abrogation of the CBL/PI3K interaction resulted in perturbed RANKL-mediated signaling, leading to increased bone mass due to a cell-autonomous defect in osteoclast function, a phenotype not seen with other *Cbl* mutations (Adapala et al., 2010a, 2010b).

### 1.7. Late attenuation of RTK signaling via receptor ubiquitination and degradation

By recruitment of E3 ubiquitin ligases to the receptor complex, members of the Leucine-Rich and Immunoglobulin-like domain (LRIG) and Suppressor of Cytokine Signaling (SOCS) families accelerate receptor ubiquitination and degradation (Fig. 4C, D) (Gur et al., 2004; Laederich et al., 2004). Unlike NEDD4 and CBL ubiquitin ligases, the expression of *LRIG1* and *SOCS* genes are induced by growth factor activation of RTKs via transcriptional activation and translation (Segatto et al., 2011). The LRIG1 transmembrane protein and SOCS cytosolic adaptor proteins have been shown to interact with RTKs and attenuate receptor signaling through both ligand-dependent and independent mechanisms.

Genetic approaches *in vivo* have confirmed the essential biological functions of LRIG proteins and have provided insight into the broad range of their effects on signaling pathways (Supplemental Table 1). Deletion of *Lrig1* in mice leads to psoriasis-like epidermal hyperplasia and dramatically increased proliferation of the intestinal crypts and tracheal and bronchial epithelium (Karlsson et al., 2008; Lu et al., 2014; Luetteke et al., 1994; Suzuki et al., 2002). These phenotypes were correlated with a substantial increase in total and phosphorylated protein levels of EGFR, ERBB2, ERBB3, and MET in associated tissues (Suzuki et al., 2002), emphasizing the role of LRIG1 as a negative regulator of RTK signaling *in vivo*. Importantly, the skin and intestinal phenotypes in *Lrig1*-deficient mice could be rescued by genetic or chemical inhibition of EGFR phosphorylation, suggesting direct involvement of LRIG1 in controlling the strength of EGFR signaling (Luetteke et al., 1994). Indeed, extensive *in vitro* studies have demonstrated that LRIG1 attenuates the half-life of all four receptors of the ErbB family and of MET by amplifying C-CBL-mediated ubiquitination (Goldoni et al., 2007; Gur et al., 2004; Laederich et al., 2004; Rafidi et al., 2013; Rondahl et al., 2013; Shattuck et al., 2007; Stutz et al., 2008; Yi et al., 2011). Additional *in vitro* work suggests that limited proteolysis of the soluble ectodomain of LRIG1 may inhibit EGFR signaling by competing with ligand binding and stabilizing the receptor in the inactive monomeric state (Goldoni et al., 2007). LRIG1 was also shown to restrict RET recruitment to lipid rafts and to inhibit binding of its ligand GDNF preventing receptor activation (Ledda et al., 2008). While the functions of the other members of the LRIG family, LRIG2 and LRIG3, remain poorly understood, studies in *X. laevis* have demonstrated that *lrig3* modulates Fgf-dependent Erk phosphorylation and Wnt signaling during neural crest cell specification and induction. When co-expressed *in vitro,* Lrig3 co-immunoprecipitated with Fgfr1 via its ectodomain, and this interaction was correlated with reduced levels of Fgfr1 protein (Zhao et al., 2008), suggesting that Lrig3 may attenuate Fgf signaling by the mechanisms similar to those described for EGFR and RET.

Although the biological roles of SOCS proteins have traditionally been considered in the context of cytokine receptor signaling through the JAK/STAT pathway in immunity and hematopoiesis, emerging evidence implicates SOCS proteins in the control of RTK signaling during development (Supplemental Table 1) (Trengrove and Gray, 2013). *In vitro* and *in vivo* studies demonstrated that SOCS2 exerts a dual role in the regulation of EGF signaling: *Socs2* knockout mice displayed increased intestinal growth due to enhanced responsiveness to EGF (Michaylira et al., 2006), and cortical neurons derived from transgenic *Socs2* overexpressing mice had increased neural outgrowth, apparently also due to enhanced EGF signaling (Goldshmit et al., 2004). The gigantism phenotype of *Socs2*-deficient mice suggests an important role for SOCS2 in the regulation of growth, possibly by modulating growth hormone and IGF-1R signaling (Greenhalgh et al., 2002; Metcalf et al., 2000). These mice exhibited prolonged STAT5B activation, and loss of *Stat5b* function partially relieved the growth enhancement. In contrast to *Socs2* mutants, but similar to *Nedd4* heterozygous mice, *Socs6* knockout mice displayed a mild growth retardation thought to be due to perturbation of IGF-1R signaling (Krebs et al., 2002). Despite *in vitro* studies supporting a role for SOCS6 in neural stem differentiation and glucose metabolism (Choi et al., 2010; Gupta et al., 2011; Liu et al., 2008a, 2008b; Vlacich et al., 2010), mice deficient in *Socs6* did not display phenotypic alterations consistent with such functions (Krebs et al., 2002). However, transgenic mice overexpressing *Socs6* had altered glucose metabolism compared to wild type mice, with enhanced PI3K/AKT activation that was independent of increased IR or IGF-1R phosphorylation (Li et al., 2002). This suggests an additional mechanism by which SOCS6 regulates insulin signaling downstream of the receptor to control glucose metabolism. Similar to the engagement of LRIG1 with many RTKs, *in vitro* studies suggest that SOCS proteins regulate multiple RTKs including c-KIT, FLT3, IR, IGF-1R, and EGFR by enhancing their degradation via recruitment of E3 ubiquitin ligase complexes (Banks et al., 2005; Kario et al., 2005; Krebs et al., 2002; Nicholson et al., 2005; Trengrove and Gray, 2013). A subset of SOCS proteins – SOCS2, SOCS6, and SOCS7 – protect RTKs from SOCS-mediated degradation by interacting with the domains of other SOCS proteins responsible for the recruitment of E3 ubiquitin ligase complexes (Piessevaux et al., 2006). This suggests a role for these SOCS proteins in restoring cells to a responsive state for subsequent RTK stimulation.

### 1.8. Modulators of RTK signaling associated with human congenital disorders

Given the critical roles of RTK signaling in cell fate determination and morphogenesis, there has been great interest in understanding how RTK regulators are deregulated in human disorders. Indeed, both gain-of-function mutations, which lead to constitutive protein activation, and loss-of-function mutations, which lead to non-functional or dominant negative proteins, have been mapped to regulators of RTK signaling in human disease (Rauen, 2013; Tartaglia and Gelb, 2005). Importantly, mutations in the same gene can cause multiple conditions with wide phenotypic variability, and mutations in different genes can result in disorders with overlapping clinical features, linking these genes into overarching molecular networks. Studying the underlying pathophysiology of these disorders has uncovered novel regulators of RTKs, revealed new biological functions for those already identified, and advanced development of molecular-based therapies for treatment. We highlight here efforts that have provided information regarding human genetic disorders. Several other excellent reviews cover feedback regulators in cancer (Casaletto and McClatchey, 2012; Logue and Morrison, 2012; Regad, 2015)

The key role for *Anosmin 1* in neuronal targeting and migration was determined by the identification of missense mutations that result in inactive protein in Kallmann syndrome (KS) (Bick et al., 1992). KS is a disorder characterized by hypogonadotropic hypogonadism (HH), defined as absent or incomplete sexual maturation by the age of 18 years,

with or without anosmia. Less frequent symptoms include renal agenesis, cleft palate, mirror movements, and hearing loss (Tsai and Gill, 2006). *FGFR1* loss-of-function mutations in an autosomal dominant form of KS first suggested that Anosmin 1 was involved in FGF signaling (Dode et al., 2003). Interestingly, missense mutations in members of the FGF8 set of co-regulated genes, or synexpression group, including *DUSP6, SPRY4*, *FLRT3,* and *SEF,* have also been identified in individuals with HH with or without anosmia (Miraoui et al., 2013). The functional characterization of these mutations may offer new insight into their molecular mechanisms of action and roles of these genes in regulation of FGF signaling in gonadotropin-releasing hormone biology.

The importance of genes that encode protein components or regulators of the RAS/MAPK pathway is elegantly demonstrated by germline mutations associated with a class of developmental disorders known as the RASopathies (Goodwin et al., 2015; Goyal et al., 2017; Jindal et al., 2015, 2017; Rauen, 2013). In one of these conditions, Costello syndrome (CS), nearly all individuals have a heterozygous *de novo* germline mutation in *HRAS* that results in a constitutively active protein (Aoki et al., 2005; Estep et al., 2006), while in cardio-facio-cutaneous syndrome (CFC), patients have heterozygous activating germline mutations in *KRAS*, *BRAF*, *MEK1*, or *MEK2*, all components of the RAS/MAPK pathway (Niihori et al., 2006; Rodriguez-Viciana et al., 2006). Because of the common underlying pathway dysregulation, RASopathies exhibit numerous overlapping clinical phenotypes. Heterozygous inactivating mutations in *SPRED1* cause Neurofibromatosis Legius syndrome (NFLS), a mild form of Neurofibromatosis 1 (NF1), which is characterized by multiple cafe-au-lait skin spots, variable dysmorphic features such as hypertelorism or macrocephaly, lipomas, and mild learning disabilities or attention problems (Fig. 5A) (Brems et al., 2007, 2012). The similarities of NFLS and NF1 are explained by the shared underlying molecular mechanism: SPRED1 downregulates the RAS/MAPK pathway through neurofibromin, the *NF1* gene product (Stowe et al., 2012). Interaction between these proteins facilitates plasma membrane localization of neurofibromin, where it functions as a RAS GTPase-activating protein to negatively regulate RAS signaling (Adapala et al., 2010a; Dunzendorfer-Matt et al., 2016; Hirata et al., 2016; Martin et al., 1990; Stowe et al., 2012; Xu et al., 1990). Association of SPRED2 and SPRED3 with neurofibromin suggests that these isoforms may compensate for loss of *Spred1* and thus helps explain the milder phenotype associated with NFLS in comparison with NF1 (Stowe et al., 2012).

The manifestations of another RASopathy, LEOPARD syndrome 1 (LPRD1), are numerous: multiple lentigines, electrocardiographic conduction abnormalities, ocular hypertelorism, pulmonic stenosis, abnormal genitalia, retardation of growth, and sensorineural deafness

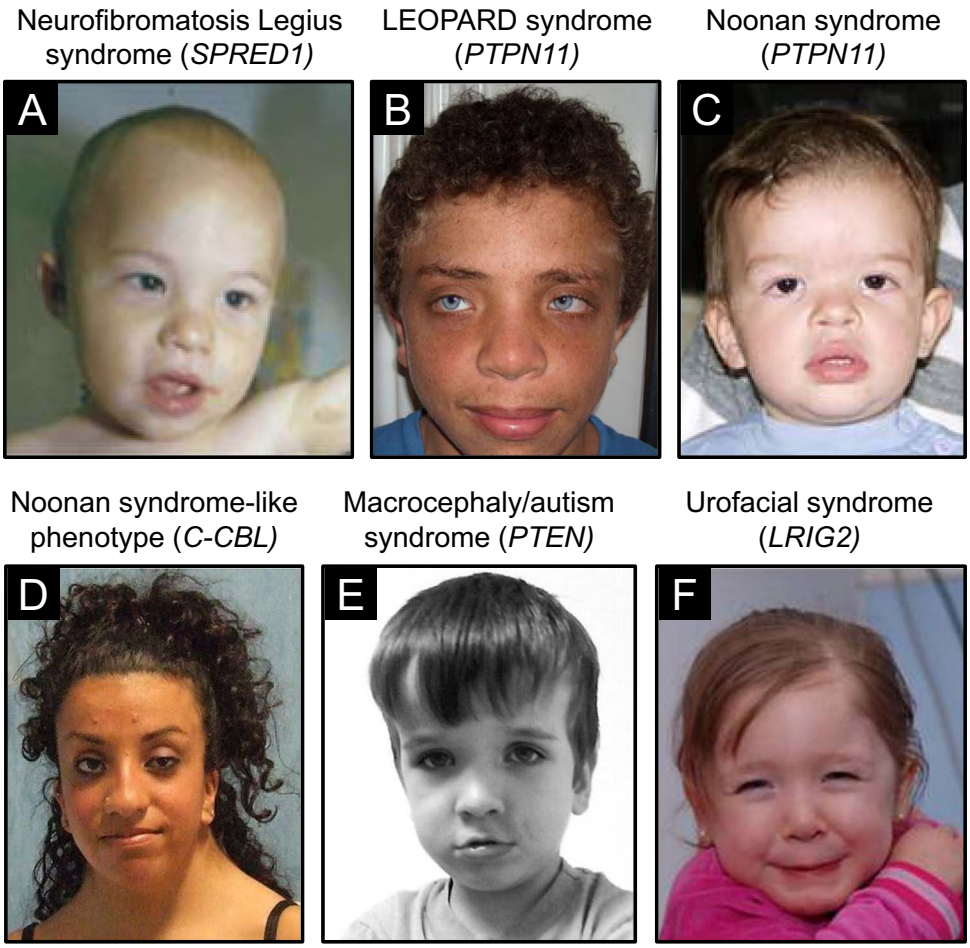


**Fig. 5. Characteristic features of craniofacial disorders associated with regulators of RTK signaling.** (**A**) Mild hypertelorism, epicanthic folds, broad nasal tip, full lips, and café-au-lait spot on the left upper arm of a child who has Neurofibromatosis Legius syndrome with a *SPRED1* mutation (Brems et al., 2007). (**B**) Dysmorphic features including hypertelorism, downslanting palpebral fissures, epicanthus, coarse facial features, and large, thick, low-set ears of an adolescent boy who has LEOPARD syndrome with a *PTPN11* mutation (Santoro et al., 2014). (**C**) Characteristic craniofacial features including hypertelorism with downslanting palpebral fissures, full or ptotic upper eyelids, and low-set, posteriorly rotated ears with a thickened helix of a young boy who has Noonan syndrome with a *PTPN11* mutation (Allanson et al., 2010). (**D**) Distinctive facial features including hypertelorism, ptosis, downslanting palpebral fissures, epicanthal folds, and low-set, posteriorly rotated ears of a woman who has Noonan syndrome-like phenotype with a *C-CBL* mutation (Martinelli et al., 2010). (**E**) Bilateral plantar creases and a flat appearing mid-face with a prominent forehead of a boy who has Macrocephaly/autism syndrome with a *PTEN* mutation (Butler et al., 2005). (**F**) Inversion of facial expression when smiling in a young girl who has Urofacial syndrome with a *LRIG2* mutation (Stuart et al., 2013). Reprinted or adapted with permission.

(Fig. 5B) (Legius et al., 2002; Mendez et al., 1985). LPRD1-associated *PTPN11* mutations lead to a catalytically defective SHP2 protein that acts in a dominant negative fashion and interferes with MAPK/ERK signaling (Digilio et al., 2002; Kontaridis et al., 2006; Tartaglia et al., 2006). In contrast, heterozygous missense mutations in *PTNP11* that result in excessive SHP2 activity are a principal cause of Noonan syndrome (NS) (Fragale et al., 2004; Tartaglia and Gelb, 2005), a relatively common disorder characterized by short stature, facial dysmorphia, and a wide spectrum of congenital heart defects (Fig. 5C) (Digilio et al., 2002; Tartaglia et al., 2001). How two mutations with opposite effects on catalytic activity result in syndromes with similar clinical symptoms is a fascinating open question. Genetic and biochemical studies in *D. melanogaster* and zebrafish successfully demonstrate that *ptpn11* mutations associated with LPRD1 and NS result in distinct but similar phenotypes, and in the case of the zebrafish, recapitulate the craniofacial and cardiac defects of human patients (Supplemental Table 1) (Bonetti et al., 2014; Jopling et al., 2007; Oishi et al., 2006, 2009; Stewart et al., 2010). Mouse models generated for the two most prevalent LPRD1 and NS *PTPN11* mutations exhibit developmental defects, including reduced length, craniofacial abnormalities, and congenital heart defects, with activation of the PI3K/AKT or RAS/ERK pathways, respectively (Araki et al., 2004; De Rocca Serra-Nedelec et al., 2012; Marin et al., 2011). Importantly, genetic deletion of *ERK1/2* prevented cardiac abnormalities in a cardiomyocyte-specific SHP2 gain-of-function mouse model of NS (Nakamura et al., 2007), and injection of the MAPK/ERK kinase inhibitor U0126 *in utero* prevented craniofacial malformations in newborn pups (Nakamura et al., 2009). Similarly, pharmacological intervention with rapamycin, an inhibitor of mTOR, reversed the hypertrophic cardiomyopathy in a mouse model of LPRD1 (Marin et al., 2011). These studies suggest that some RASopathy-associated *PTPN11* mutations can be rescued, opening a new therapeutic avenue for affected individuals. A NS-like phenotype has been associated with several additional genes including *C-CBL* (Fig. 5D) (Martinelli et al., 2010; Niemeyer et al., 2010; Perez et al., 2010). *In vitro* studies showed that the *C-CBL* mutations found in patients impaired CBL-mediated degradation of cell surface receptors in a dominant-negative fashion and caused dysregulation of intracellular signaling through RAS, explaining the overlapping phenotype in NS associated with RAS/MAPK pathway activating mutations (Martinelli et al., 2010; Schubert et al., 2006).

Germline mutations and deletions in *PTEN* that result in dysregulation of the PI3K/AKT pathway cause Bannayan-Ruvalcaba-Riley syndrome (BRRS) and Cowden syndrome 1 (CWS1) (Liaw et al., 1997; Marsh et al., 1999; Nelen et al., 1997; Zhou et al., 2003). BRRS and CWS1 are rare allelic disorders that share characteristics such as hamartomatous polyps of the gastrointestinal tract, mucocutaneous lesions, and increased risk of developing neoplasms (Blumenthal and Dennis, 2008). It has been suggested that both conditions and several other distinctive phenotypes associated with *PTEN* mutations be referred to as PTEN hamartoma tumor syndrome (Lachlan et al., 2007; Marsh et al., 1999; Nelen et al., 1997; Sarquis et al., 2006). Also included in this spectrum of disorders are *PTEN*-related Proteus syndrome (PS) and 'Proteus-like' syndrome, complex and highly variable disorders involving vascular malformations and hamartomatous overgrowth of multiple tissues associated with germline and tissue-specific somatic activating mutations in *AKT1* or *PTEN*, respectively (Cohen, 2014; Lindhurst et al., 2011; Smith et al., 2002; Turner et al., 2004; Zhou et al., 2001, 2000). These correlations demonstrate the critical involvement of PTEN in regulation of the pro-proliferative signals mediated by the PI3K/AKT pathway.

Expanding the array of clinically distinct phenotypes associated with *PTEN* mutations are VACTERL association and macrocephaly/autism syndrome (Butler et al., 2005; Reardon et al., 2001). VACTERL describes a constellation of congenital anomalies including vertebral anomalies, anal atresia, congenital cardiac disease, tracheoesophageal fistula, renal anomalies, radial dysplasia, and other limb defects (Khoury et al., 1983), whereas macrocephaly/autism syndrome is characterized by increased head circumference, abnormal facial features, and delayed psychomotor development resulting in autistic behavior or intellectual disability (Fig. 5E) (Herman et al., 2007; Tsujita et al., 2016). Whether individuals affected with macrocephaly/autism syndrome and VACTERL association develop further clinical manifestations of other PTEN-associated syndromes is unknown. Mouse models with deficient *Pten* result in macrocephaly and autistic-like behavior with abnormal activation of PI3K/AKT pathway (Supplemental Table 1) (Chen et al., 2015; Clipperton-Allen and Page, 2014; Kwon et al., 2006; Page et al., 2009). Future analyses of specific disease-causing human *PTEN* mutations will prove useful in understanding the mechanisms underlying these heterogeneous phenotypes.

The recent discovery of autosomal recessive *LRIG2* mutations in Urofacial syndrome (UFS) provides additional insight into LRIG2 function as a regulator of RTK signaling. UFS presents with urinary bladder dysfunction associated with abnormal facial expressions (Fig. 5F) (Stuart et al., 2013). Interestingly, loss of function mutations in Heparanase-2, which regulates the availability and signaling of growth factors through processing of HSPGs, were also identified as causative for UFS (Daly et al., 2010; Pang et al., 2010). In fact, deletion of *Hpse2* but not *Lrig2* in *X. laevis* and mice caused UFS-like urological phenotypes. These observations suggest that HPSE2 might functionally overlap in its mode of RTK inhibition with LRIG2 (Supplemental Table 1) (Guo et al., 2015a; Roberts et al., 2014).

## 2. Concluding remarks

From the single cell stage, RTKs guide the embryogenesis, development, and postnatal growth of nearly all animals. Our understanding of the significant contribution that RTKs play has been enabled through extensive work in model organisms and by advances in elucidating the biochemistry, cell biology, and structure of these receptors. Equally important contributions have arisen from studies of human congenital disorders and clinical analyses of RTKs in diseases. Taken together, these studies reveal that a complex network of proteins is required to guide RTKs during their lifetime in the cell, from their biosynthesis and maturation in the ER, subsequent trafficking to the cell surface, ligand-dependent activation triggering autophosphorylation and downstream signaling, and final desensitization by ubiquitination and endocytosis. Although we have come to appreciate the contributions of RTK regulators in fine-tuning the duration and extent of RTK pathway activation in development, there are still many exciting discoveries to be made about their mechanisms of action. Knowledge of RTK specificity and protein structure will help to advance development of specific therapeutics for patients in which modulation of RTK regulators could be clinically beneficial.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ydbio.2017.10.017.

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