Molecular and Cellular Endocrinology 346 (2011) 37–43

Contents lists available at ScienceDirect

Molecular and Cellular Endocrinology

journal homepage: www.elsevier.com/locate/mce

Review

Role of fibroblast growth factor (FGF) signaling in the neuroendocrine control of human reproduction

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ARTICLE INFO

Article history:
Available online 1 June 2011

Keywords:
GnRH deficiency
Kallmann syndrome
FGF signaling
FGFR1
FGF8
Oligogenicity

ABSTRACT

Fibroblast growth factor (FGF) signaling is critical for a broad range of developmental processes. In 2003, Fibroblast growth factor receptor 1 (*FGFR1*) was discovered as a novel locus causing both forms of isolate GnRH Deficiency, Kallmann syndrome [KS with anosmia] and normosmic idiopathic hypogonadotropic hypogonadism [nIHH] eventually accounting for approximately 10% of gonadotropin-releasing hormone (GnRH) deficiency cases. Such cases are characterized by a broad spectrum of reproductive phenotypes from severe congenital forms of GnRH deficiency to reversal of HH. Additionally, the variable expressivity of both reproductive and non-reproductive phenotypes among patients and family members harboring the identical FGFR1 mutations has pointed to a more complex, oligogenic model for GnRH deficiency. Further, reversal of HH in patients carrying *FGFR1* mutations suggests potential gene–environment interactions in human GnRH deficiency disorders.

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1. Introduction

Puberty is a signal developmental event leading to fertility. Its timing varies greatly in the general population and is influenced by both genetic and environmental factors (Nathan and Palmert, 2005). In extreme cases of pubertal delay, sexual maturation progresses only partially or not at all, resulting in the clinical picture of idiopathic hypogonadotropic hypogonadism (IHH). This rare form of congenital gonadotropin-releasing hormone (GnRH) deficiency (incidence 1:10,000–1:40,000) results in incomplete/absent of sexual maturation and infertility and may present with anosmia (termed Kallmann syndrome [KS]) or with a normal sense of smell (nIHH). These disorders have a male to female ratio of 4:1 (Seminara et al., 1998; Hu et al., 2003) and are both clinically and genetically heterogeneous. Notably, studies on the critical roles of mutated genes causing human GnRH deficiency in the fate specification, proliferation, developmental migration, secretory function, and/or survival of GnRH neurons have formed the basis for much of our current understanding of GnRH biology (Bianco and Kaiser, 2009). In this review, we focus on the role of fibroblast growth factor (FGF) signaling pathway in human GnRH deficiency.

2. Lessons from FGFR1

In 2003, Fibroblast growth factor receptor 1 (*FGFR1*) was identified as the first gene causing the autosomal dominant form of KS by mapping overlapping deletions on chromosome 8p11–p12 in two KS patients with contiguous gene syndromes (Dode et al., 2003). Mutations in *FGFR1* have now been identified in as many as 10% of KS cases, mostly in the heterozygous state (Dode et al., 2003; Sato et al., 2004; Pitteloud et al., 2006a; Trarbach et al., 2006; Raivio et al., 2009; Sykiotis et al., 2010; Shaw et al., 2011).

FGFR1 encodes one of four FGFRs, which are cell surface receptors of the tyrosine kinase family. The extracellular immunoglobulin domains two and three (D2 and D3) determine ligand binding,

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doi:10.1016/j.mce.2011.05.042

affinity, and specificity. Alternative splicing of the carboxy-terminal half of D3 plays a pivotal role in modulating FGF binding specificity via the generation of the isoforms FGFR1-IIIb and FGFR1-IIIc. The IIIb isoform encoded by exon 8a is expressed in epithelial tissue, while IIIc isoform enocoded by exon 8b is mesenchymal tissue specific. Activation of FGFR1 requires dimerization that is mediated by the binding of two FGFs and heparan sulfate (HS) proteoglycans to the receptor leading to the autophosphorylation of the tyrosine kinase domains (TKD). These interactions then induce the downstream signaling pathways (Fig. 1) (mitogen activated protein kinase [MAPK], phosphatidylinositide 3 kinase/AKT [PI3K/AKT], and phospholipase C gamma [PLCγ] pathways) (Mohammadi et al., 2005; Miraoui and Marie, 2010).

During development, *FGFR1* has a critical role in gastrulation, organ specification, and patterning of many tissues including the brain (Itoh and Ornitz, 2011). Further, the FGF pathway has a crucial role for the development of the olfactory system, with *Fgfr1* hypomorphs showing grossly normal cortex development but lacking olfactory bulbs (OB) (Hebert et al., 2003). Transgenic mice with targeted expression of dominant-negative *Fgfr1* in the GnRH neurons exhibit delayed puberty and decreased number of GnRH neurons in the hypothalamus (Tsai et al., 2005). These mice studies revealed a role for FGFR1 in the olfactory system and GnRH ontogeny consistent with the KS patient phenotype.

While initially thought to underlie only KS (Dode et al., 2003), subsequent reports revealed that *FGFR1* mutations also underlie normosmic IHH (nIHH) (Fig. 2) suggesting a role for *FGFR1* beyond olfactory bulb formation (Sato et al., 2004; Kim et al., 2005; Pitteloud et al., 2006a; Trarbach et al., 2006; Zenaty et al., 2006; Xu et al., 2007; Raivio et al., 2009). In addition, the association of identical mutations with both KS and nIHH suggested that these two related clinical entities might be different manifestations of the same pathological process. GnRH deficient carrying *FGFR1* mutations exhibit variable reproductive phenotypes with different degrees of GnRH deficiency as evidenced by complete absent puberty with microphallus and cryptorchidism in some cases, to partial puberty, or the fertile eunuch subset, where patients are fertile but totally un-virilized (Pitteloud et al., 2006b; Trarbach et al., 2007). Further, demonstrated reversals of the GnRH deficiency later in adult life in patients carrying an *FGFR1* mutation indicating a gene-environment interaction in this disorder (Pitteloud et al., 2005; Raivio et al., 2007, 2009). Moreover, loss-of-function mutation in *FGFR1* can cause delayed puberty in family members of GnRH deficient probands (Pitteloud et al., 2005). Finally, *FGFR1* mutations underlying cases of hypothalamic amenorrhea (a form of female infertility caused by transient GnRH deficiency), a condition previously thought to be functional in nature (Caronia et al., 2011), further expands the spectrum of GnRH deficient states associated with perturbed FGF signaling.

While patients harboring *FGFR1* mutations exhibit a spectrum of reproductive phenotypes, there is an equally broad range of associated, non-reproductive phenotypes (Table 1). However, to date, *FGFR1* mutations have not been associated with unilateral renal agenesis as is seen commonly in KS patients with *KAL1* mutations, a point that could be used in targeting genetic testing. This broad array of associated phenotypes mirrors the pleiotropic roles of FGF signaling in brain, ear, craniofacial structures, kidney, and limb formation (Beenken and Mohammadi, 2009). A number of groups have reported the variable expressivity of GnRH deficiency and associated phenotypes within and across families carrying

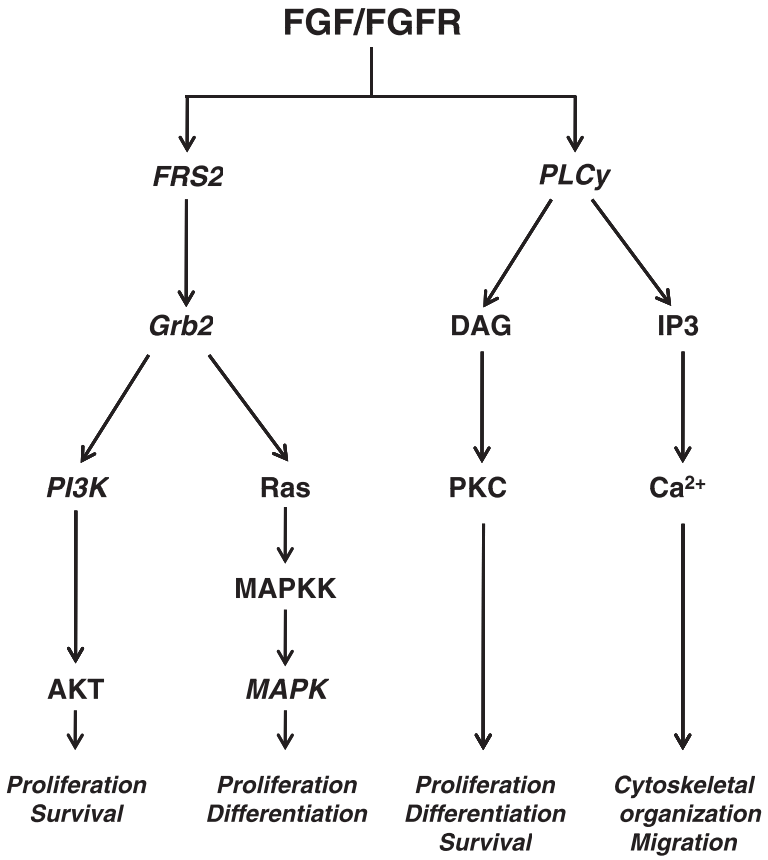

Fig. 1. Pathways downstream of FGFR signaling. FGF/FGFR binding leads to activation of several signal transduction pathways including phospholipase Cγ (PLCγ), mitogen-activated protein kinases (MAPK), and phosphatidylinositol 3-kinase (PI3K). FGF signaling cascades are implicated in the control of several cellular processes including cell proliferation, differentiation, and survival in multiple tissues and cell lines.