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A review of FGF signaling in palate development

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ABSTRACT

The fibroblast growth factors (FGFs) play a critical role during palatogenesis by mediating a variety of cellular responses. Extensive epidemiological and genetic studies over several decades in humans have revealed members of the FGF family function as candidate genes for syndromic and nonsyndromic cleft lip and cleft palate. The findings that FGFs signaling work delicately in the development of palate have been confirmed in mice carrying targeted mutations. Here we try to review recent progress toward a detailed understanding of FGF signaling including FGF7, FGF8, FGF9, FGF10, FGF18 and their receptors FGFR1, FGFR2 in palate development studies and discuss how they interact with other factors on the basis of animal studies regarding cleft palate.

1. Introduction

Cleft lip and palate (CLP) are the most common craniofacial birth defects, and approximately 1 in every 700 newborns is affected worldwide [1]. After birth, affected individuals would go through a series of difficulties including feeding, speech, hearing, and dental problems. Although clefts can be surgically repaired, a lot of patients can still experience lifelong psychosocial effects from the malformation because they can be easily recognized by the facial appearance even after multiple craniofacial and dental surgeries [2]. The typical cleft spectrum covered the following types including cleft palate only, cleft lip only, and cleft lip with palate. The studies on etiology of cleft lip and palate emerged when the genetics era began. Among the untangled candidate genes, it is believed that fibroblast growth factor (FGF) signaling pathway plays crucial roles in palatogenesis [3–5]. At least 22 distinct FGFs have been identified in a variety of organisms from nematode and drosophila to mouse and human [6]. Missense and nonsense mutations in FGF genes contribute to as much as 3–5% of nonsyndromic cleft lip and cleft palate (NSCLP) [3].

FGF10, FGFR1, and FGFR2 were found to be associated with the risk of NSCLP via Genome-wide association study conducted among different populations and several genes [7,8]. Other analysis (such as SNP genotyping, DNA sequencing, high-resolution DNA microarray analysis and long-range PCR) suggested polymorphism of FGFR1, FGFR2, FGF1, FGF2, FGF10, FGF18 and FGF19 could be associated with the risk of NSCLP as well [9,10]. Some common syndromes, with mutations in the FGFs gene, including Apert syndrome (FGFR2), Muenke syndrome (FGFR3), Crouzon syndrome (FGFR2, FGFR3), Hartsfield syndrome (FGFR1), Kallmann syndrome (FGFR1, FGF8), and 2q11.2 deletion syndrome (FGF10) have been reported to present cleft palate [11–15]. Transgenic approaches have a continuous impact on our understanding of how FGF family contribute in the palatogenesis. Studies showed much evidence in favor of Fgfr1, Fgfr2, Fgf7, Fgf8, Fgf9, Fgf10 and Fgf18 mutations in the process of palatogenesis, whereas little evidence was linked to Fgf1, Fgf2, Fgf19 or Fgfr3 mutations.

Herein, we will focus on the expressions of genes in Fgf family and their receptors concerning the palatal shelves during palatogenesis and how the loss-of-function and gain-of-function mutations in the FGFs lead to cleft palate. Then, we will discuss how FGF signaling interacts with several other signaling induced by the expression of genes such as Shh, Wnt and TGF in palatogenesis. Lastly, we will provide a short description which links teratogens to the FGF signaling during the occurrence of cleft palate.

2. Overview of the role of FGFs and palatogenesis

Known mammalian secreted signaling FGFs can be grouped into subfamilies based on biochemical function, sequence similarities, and evolutionary relationships [16]. The widely accepted concept is that there are 5 subfamilies of paracrine FGFs, one subfamily of endocrine FGFs, and one subfamily of intracellular FGFRs, known as FGF1 subfamily (FGF1, FGF2), FGF4 subfamily (FGF4, FGF5, FGF6), FGF7

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subfamily (FGF3, FGF7, FGF10, FGF22), FGF8 subfamily (FGF8, FGF17, FGF18), FGF9 subfamily (FGF9, FGF16, FGF20), and FGF15/19 subfamily (Endocrine FGFs, FGF15/19, FGF21, FGF23) [17]. Transmembrane FGF-receptor tyrosine kinases (FGFR1-4) can be bonded and activated by the secreted signaling FGFs [3,17]. FGFR protein contains an extracellular domain that consists of three immunoglobin (Ig)- like structures and the ligand- binding domain is likely to lie between Ig loops II and III [18]. According to the differences in the third Ig loop (IIIb and IIIc), FGFR1, FGFR2, FGFR3 can be divided into two isoforms respectively [19]. All the major FGFR variants can be activated by at least five FGF ligands, resulting in a significant redundancy, which was detected in FGF-FGFR interactions in vitro [17]. It has been suggested that FGFs are not the physiological ligands of FGFRs, and there are other regulators exist for the specificity of the FGF-FGFR interaction in vivo [17]. The activated FGFRs transduce the signals through four intracellular pathways including phosphatidylinositol 3-kinase/Akt (PI3K/Akt), Janus kinase/signal transducer and activator of transcription (Jak/Stat), phosphoinositide phospholipase C (PLCγ) and Erk pathways [20].

Much of our understanding of palatogenesis and its genetic control has been derived from mouse models, for the striking similarity between palate development in humans and mice [21]. Palatogenesis is a dynamic process that can basically be divided into three stages. In mice, the first stage begins when the palatal primordia stick out from the lateral edges of the oral side of the maxillary process, which composed of mesenchyme and epithelium at embryonic day 11.5 (E11.5) [21,22]. The palatal mesenchyme largely comes from the cranial neural crest (CNC), and the epithelial cells of palatal shelves are derived from pharyngeal ectoderm [23]. The initial secondary palate subsequently turns downward, vertically grows along the two sides of the tongue (Fig. 1). Afterward, the palatal shelves elevate above the dorsum of the tongue from the vertical direction to a horizontal position, which is the second stage occurs rapidly sometime at E14.5. During the final stage of the palatogenesis (E14.5–15.5), the bilateral palatal shelves grow toward each other until the medial edge epithelium from each shelf contacts to form the midline epithelial seam (MES), then the palatal shelves fuse as part of which the medial edge epithelium is dissolved [24]. The process of palatal fusion is complete by E16. The anterior two-thirds of the palate ossifies to form the hard palate once the fusion completes, while the posterior third develops into the soft palate without ossification [25].

Any error occurring during palatogenesis can cause cleft palate, which has been demonstrated in numerous studies in mouse models. However, mouse models have some shortcoming. Mouse models display a smaller frontonasal prominence, making it more likely to demonstrate a cleft palate, while gene mutations that cause cleft palate only in mice may cause cleft lip with or without cleft palate in humans [26].

3. The role of FGF signaling (Table 1)

3.1. *Fgfr1 and Fgfr2*

Fgfr1 could be detected throughout the entire palatal mesenchyme from E13.5 to E14.5 before palatal shelves elevation, and then the expression was down-regulated until palatal shelves fusion reached period E15 when it showed up-regulated [27]. There was little Fgfr1 expression in the palatal epithelium [28] (Fig. 2A). In mice, the loss-of-function mutations of Fgfr1 with the Wnt1-Cre driver in neural crest cells could lead to cleft palate [23]. Cell proliferation was decreased at E12.5–E13.5 and was increased at E14.5 in the palatal mesenchyme and epithelium [23]. When conditionally knocking out Fgfr1 with the epithelium-specific K14-Cre driver, severe enamel defects were detected but the cleft palate has not been reported [29].

Although Fgfr2 mostly located in the medial aspect of the palate, it was detected in the entire palatal epithelium and posterior palatal mesenchyme before palatal shelves elevation [27,28]. After palatal shelf shifted to the horizontal orientation, Fgfr2 started expressing in the nasal aspect of the palatal mesenchyme [27] (Fig. 2B). In $Fgfr2b^{-/-}$ mice exhibiting cleft palate, cell proliferation was decreased in the palatal epithelium and mesenchyme [30]. Similarly, $Fgfr2^{C342Y/C342Y}$ embryos displayed a cleft through the completion of palate development and cell proliferation was significantly decreased throughout palatal mesenchyme at E14.5 [31]. This gain-of-function mutation of Fgfr2 in mice also caused down-regulation on glycosaminoglycans (GAG) levels in the palatal mesenchyme near the time of palatal shelves elevation, which was consistent with the phenotype which had a delayed palatal shelves elevation [31]. Moreover, K14-Cre; $Fgfr2^{fl/fl}$ mice also showed cleft palate and a disturbance of cell proliferation in the epithelial cells [32]. However, when conditionally knocking out Fgfr2 with the mesenchyme-specific Dermo1-Cre driver, no cleft palate was detected [33]. When Fgfr1 and Fgfr2 were double knocked out with the Dermo1-Cre driver, the growth of mandibular was disturbed and the lower jaw growth obstructed the tongue from dropping into the mouth in time, which still resulted in the failure of palatal shelves elevation [27].

During palatal shelves fusion, Fgfr1 and Fgfr2 were both seen

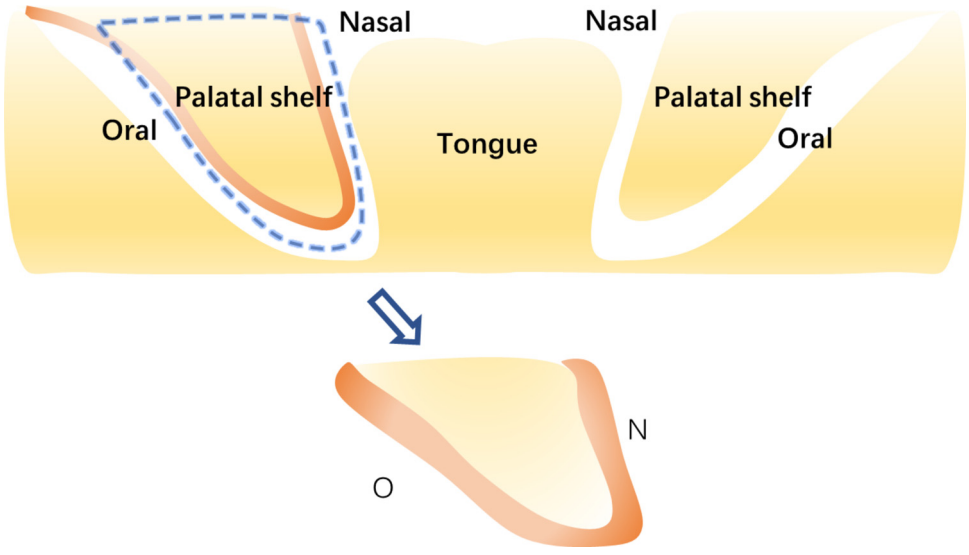

Fig. 1. Schematic diagram of embryonic palate during palatogenesis at E 13.5 (coronal view).