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在线全文

·综　述·

成纤维细胞生长因子7在颅颌面发育中的作用*

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【摘要】 颅颌面发育是一系列高度有序的时间-空间上的细胞分化过程，多种细胞信号因子如成纤维细胞生长因子等在其中发挥了重要的调控作用。作为经典型成纤维细胞生长因子，成纤维细胞生长因子7（fibroblast growth factor 7，FGF7）具有广泛的调节功能。既往研究已经证实FGF7对上皮细胞有调节其增殖和迁移，保护细胞和促进修复的作用。最近研究进一步指出，FGF7广泛而强大的调控能力不仅仅局限于上皮细胞，其对骨骼系统发育也具有潜在影响。除此之外，FGF7在上颚、眼、牙齿等颅颌面器官的发育中也起着重要作用。然而，在口腔颅颌面发育中FGF7的作用还亟待进一步阐明。本文就目前已有的在口腔颅颌面发育中对FGF7的研究现状进行归纳和总结，展示FGF7在口腔颅颌面发育中的全面认知和其潜在功能。

【关键词】 成纤维细胞生长因子7　颅颌面发育　骨骼发育　综述

Role of Fibroblast Growth Factor 7 in Craniomaxillofacial Development

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【**Abstract**】 Craniomaxillofacial development involves a series of highly ordered temporal-spatial cellular differentiation processes in which a variety of cell signaling factors, such as fibroblast growth factors, play important regulatory roles. As a classic fibroblast growth factor, fibroblast growth factor 7 (FGF7) serves a wide range of regulatory functions. Previous studies have demonstrated that FGF7 regulates the proliferation and migration of epithelial cells, protects them, and promotes their repair. Furthermore, recent findings indicate that epithelial cells are not the only ones subjected to the broad and powerful regulatory capacity of FGF7. It has potential effects on skeletal system development as well. In addition, FGF7 plays an important role in the development of craniomaxillofacial organs, such as the palate, the eyes, and the teeth. Nonetheless, the role of FGF7 in oral craniomaxillofacial development needs to be further elucidated. In this paper, we summarized the published research on the role of FGF7 in oral craniomaxillofacial development to demonstrate the overall understanding of FGF7 and its potential functions in oral craniomaxillofacial development.

【**Key words**】 Fibroblast growth factor 7　Craniomaxillofacial development　Skeletal development　Review

颅颌面发育涉及一系列复杂的细胞生理过程，需要来自不同胚层及其衍生物的多个信号通道的协调整合，精确调节细胞迁移、增殖和分化[1]。大多数颅面组织起源于神经嵴细胞（cranial neural crest cells, CNCC）[2]，颅面部发育本质是许多独立结构的图案化、生长和融合，发育过程中的面部突起主要由CNCC衍生的间充质细胞构成的核心和周围环绕着的上皮细胞构成[3]。位于不同面部突起内的CNCC在遗传上保持平衡，并等待额外的信号信息以继续发育，而这些关键信号由周围和邻近组织提供[4]，包括成纤维细胞生长因子（fibroblast growth factors, FGFs）在内的多种关键信号分子参与调节[5]。

FGFs是广谱有丝分裂原，可调节多种细胞功能，包括迁移、增殖、分化和存活[6]。FGFs可分为内分泌型、胞内型和经典型FGFs三类，其中内分泌型和经典型FGFs都激活成纤维细胞生长因子受体（FGFR）发挥作用[6]。活化的FGFR磷酸化磷脂酶Cγ（PLCγ）和表皮生长因子受体底物2α（FRS2α）两种细胞内底物，并最终触发包括蛋白激酶C（PKC）、RAS-丝裂原活化蛋白激酶（MAPK）、磷酸酰肌醇3-激酶（PI3K）-蛋白激酶B（AKT）在内的多种通路[7]。而FGFRs的突变已被证明与颅颌面骨发育畸形有关[8]，如颅神经嵴细胞中*FGFR*1的突变或上皮中*FGFR*2的突变会导致面部或腭裂，颅神经嵴细胞中FGFR1和FGFR2受体的缺失会导致面中部无法联合[9]。

FGF7亚家族属于经典型FGFs，家族成员包括FGF3、FGF7、FGF10和FGF22，是唯一在间充质中表达的FGF亚家族[10]。FGF7亚家族的成员对胚胎中的器官发生和组织模式至关重要，并介导成年哺乳动物的伤口愈合和组织

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稳态。其中，FGF7又被称为角质细胞生长因子(KGF)，主要与FGFR2b结合发挥作用，是从间充质到上皮的信号分子，能够调节不同类型上皮细胞的迁移和分化，并在应激条件下保护它们免受损伤[11]。FGF7一直被认为主要作用于上皮细胞，既往研究多关注其在上皮再生、防止氧化损伤和癌症治疗方面的应用[12-13]。然而，近来研究提示FGF7可能具有更广泛的调节能力，ZHANG团队提出FGF7是肌腱分化和再生的新型调节因子[14]，LIU团队发现FGF7参与调节成骨细胞间通讯[15]。YAMAMOTO-FUKUDA团队通过耳部转染FGF7表达载体，发现FGF7的过度表达可能会增加黏膜上皮的干细胞增殖，而中耳上皮细胞来源于神经嵴和内胚层[16]。颅颌面生长发育是一个涉及多种组织和器官发生、发育的过程，FGF7对上皮和间充质细胞具有调控能力，同时FGF7能够激活对颅颌面发育十分重要的FGFR2b，这些特征提示其可能在颅颌面生长发育中具有关键作用(图1)。

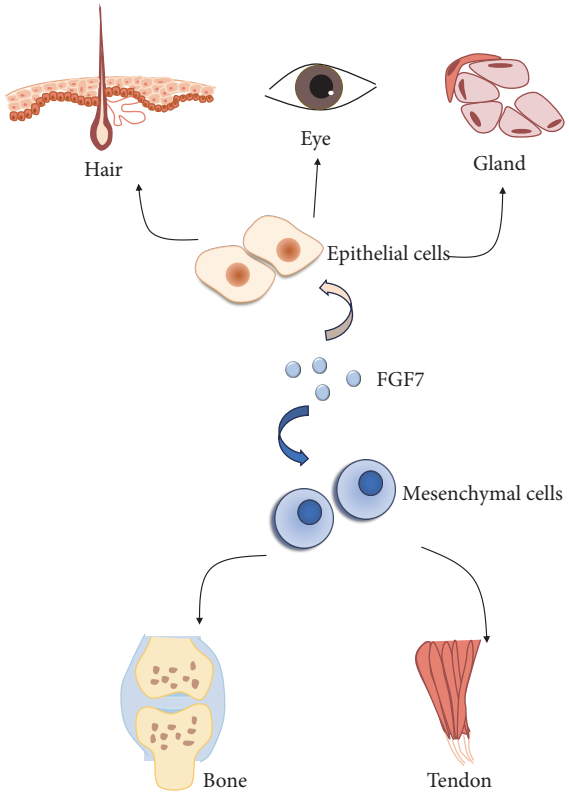

图 1 FGF7对多种细胞和组织具有广泛的调控作用

Fig 1 FGF7 is involved in the regulation of a wide range of cells and tissues

1 FGF7在骨发育过程中的作用

FGF7是骨细胞系和骨组织中表达的主要FGF成员[17]，被视为骨再生中的重要因子。以往的研究已经证明，外源性FGF7的添加可以促进小鼠胚胎干细胞的成骨分化和矿化[18-19]。在体外对大鼠骨髓基质细胞施用FGF7可以促进大鼠骨髓基质细胞矿化和迁徙，增加成骨标志基因的表达[20]。miRNA 在成骨细胞分化过程中起着关键作用[21]，其中，miR-381-3p 负向参与了骨髓间充质干细胞(BMMSCs)的成骨分化。QIU等[22]发现FGF7可被miR-381-3p直接调节，而抑制FGF7可减少MiR-381-3p下调引起的BMMSCs成骨分化的增加。

除去对细胞的分化和矿化调节外，最近的研究发现，FGF7在骨细胞之间信号传导中也有重要作用。骨骼发育和维持需要骨细胞进行信息交流，其中通过间隙连接进行直接细胞间通信是重要的通信途径[23]。其中，Cx43是骨细胞中参与间隙连接的重要蛋白[24]。LIU团队发现FGF7能够促进成骨细胞中Cx43表达，并证明FGF7通过Wnt信号通路引起β-catenin核转移，进而增加Cx43的表达[17]。既往研究提示JNK和ERK抑制剂可抑制FGF7对骨缺损修复的促进作用[20]，因此他们进一步探索MAPK通路对Cx43表达量的影响。LIU团队发现E11能够影响Cx43在原代成骨细胞中的表达，并证明了FGF7通过MAPK通路和PI3K-AKT通路增加成骨细胞中E11的表达[15]。FGF7不仅参与调节骨细胞还与磷代谢有关，而无机磷对骨发育十分重要[25]。在高磷酸血症患者中血清FGF7水平较低[26]，而在肿瘤诱导的骨软化症中，FGF7水平升高伴低磷血症[27]。同时，WHYTE团队证实FGF7能够抑制肾脏对磷的重吸收[26]。他们对非致死性小儿高磷血症的患者血液进行检测，发现患者血清FGF7较正常人低，血清FGF7的水平随着病情严重程度的增加而降低。之后他们通过大鼠实验证实了输注FGF7会降低肾脏对磷再吸收的能力。

2 FGF7在软组织发育过程中的作用

FGF7又被称为KGF，其参与调节上皮和毛发的发育已被广泛认同。在角质形成细胞分化过程中，FGF7负责维持3周后的基底细胞的增殖[28]。通过促进上皮钉突的伸长和促进整合素在各种细胞中的表达，FGF7可以促进皮肤和口腔上皮的黏附[29]。在一项人类表皮伤口中基因表达检测的研究中，FGF7被发现在表皮伤口中表达上调[30]。一项针对小鼠伤口愈合的研究指出，FGF7可能与晚期小鼠胚胎的疤痕形成相关。TAKAY团队将小鼠胚胎发育时期根据伤口愈合情况分为3个阶段，完全再生、可见疤痕残留但真皮结构再生和疤痕组织取代期，检测不同时期FGFs因子的表达情况，发现FGF7含量在完全再生期上调，而在之后的时期下降，并发现使用外源性FGF7可抑制伤口纤维化并促进表皮形成[31]，因此FGF7可能参与上

皮再生并影响伤口无疤痕愈合。FGF7还能通过TGF-β1/Smad信号通路促进成纤维细胞收缩加速伤口收缩[32]。FGF7还是刺激毛囊干细胞增殖并启动新毛发周期的重要因子。在毛发发育过程中, FGF表达上升, 而外源性FGF7也可刺激毛囊角质形成细胞的增殖[33]。

FGF7还参与其他细胞的调控。最近的研究还提出, FGF7可能参与肌腱干细胞的发育调节。ZHANG团队通过构建3D明胶微载体体外培养肌腱干细胞发现, 三维培养促进肌腱干细胞表达FGF7, 进而通过促进细胞间通讯提高了肌腱干细胞在3D微环境中的发育能力[14]。而REN团队提出, FGF7可能是针对屈肌腱愈合的新型细胞因子。体外实验发现, FGF7处理腱细胞可以增强其早期增殖能力, 并具有抗凋亡和促进迁移的作用[34]。

3　FGF7在颅颌面部器官发育过程中的作用

FGF10与FGF7结构和表达部位相似, 且都与上皮中的FGFR2b结合发挥作用。FGF10已被证明参与颅颌面部多种器官发育[35], 而FGF7与FGF10可能存在功能重叠, FGF7在发育中的舌头间充质中的表达可以补偿该部位FGF10的缺失[36]。因此, FGF7在颅颌面部发育的作用值得进一步探寻。

3.1　眼的发育

FGF7对眼的调控具有多面性。FGF7能够调节角膜缘上皮细胞增殖、迁移和分化, 促进角膜上皮和角膜新生血管形成, 促进角膜伤口愈合[37]。但另一项研究指出, FGF7可能促进青光眼发展。PENG团队发现, FGF7与已知的青光眼基因(如FBN1和TGFB2)之间存在相关性, 通过下调*FGF7*基因, 视网膜的结构和形态得到了恢复, 而沉默*FGF7*基因还能引起Muller细胞的活化, 并抑制视网膜神经节细胞的凋亡[38]。同时, 几项关注miRNA参与视网膜病变的研究指出, FGF7是miRNA调控糖尿病相关视网膜病变中内皮细胞和视网膜周细胞的增殖、迁移和侵袭的重要靶点[39]。

3.2　颌骨与腭形成

成纤维细胞生长因子信号通路对颌面部骨骼的发育至关重要, *FGFR2*的突变会导致中面部发育异常[40]。然而, FGF7尽管作为FGFR2配体之一, 已被证实参与骨组织再生, 但在人类早期颅面部骨骼形成的成骨和软骨组织中未见表达[41]。尽管一项荟萃分析显示*FGF7*基因的遗传变异与下颌骨形状差异显著相关[42], 但并无实验性研究证实FGF7参与颌骨形成。

成纤维细胞生长因子通过介导各种细胞反应在腭生成过程中起关键作用, 3% ~ 5%的唇裂和腭裂与FGF家族基因突变有关[43]。有研究表明, FGF7作用的受体FGFR2的缺失和突变会导致小鼠腭裂[44]。然而, 与同样作用于FGFR2的FGF10相比, FGF7对腭形成似乎并非正面作用。HAN等[45]体外培养腭间充质细胞发现抑制FGF7能够导致间充质细胞增殖活力上升, 并证明外源性FGF7能够抑制对腭发育十分重要的Shh表达。而FGF10的缺乏或错误表达能直接导致腭形成失败[36], 但缺乏*FGF7*基因的小鼠能够存活到成年且无腭裂[46]。

3.3　牙齿发育和疾病

FGF家族在牙齿上皮和间充质的发育过程中至关重要, 但在不同的动物模型中, FGF7的调控作用也有所不同[47]。KETTUNEN等[48]观察FGF家族mRNA在小鼠牙胚的表达情况发现, FGF7在臼齿周围骨和肌肉中表达, 在门齿靠近外釉上皮和颈袢的间充质中表达, 但其表达似乎不随牙齿发育而变化, 因此他们认为, 与重叠表达的FGF3和FGF10相比, FGF7在牙齿发育调控的作用并不突出。然而, FGF7可能具有调节人类牙齿发育的潜在作用。HUANG等[49]测量不同时期人乳牙牙胚的FGF因子表达情况发现, FGF7在帽状期主要局限于牙上皮, 在钟状期内釉上皮中的表达更为密集。同时, FGF7蛋白在钟状期分布于牙尖形成位置的成牙本质细胞和成釉细胞。最近的研究使用微型猪作为新的模型生物, GUO团队检测了FGF家族基因在微型猪第三乳磨牙帽状期、钟状早期和钟状晚期中时空表达模式。他们发现帽状期时FGF7蛋白和mRNA在牙上皮和间充质中均表达, 在钟状期早期其表达集中于间充质顶端, 晚期时仅限于成牙本质细胞层, 这可能提示FGF7参与成牙本质细胞的分化[50]。他们认为FGF3、FGF4、FGF7和FGF9牙尖形态形成中起关键作用, 而FGF3和FGF7可能在成牙本质细胞分化中起基础作用。

3.4　腺体发育

腺体发育与形成的重要步骤之一是分支形态发生, 主要由FGF家族中的FGF10和FGF7参与调节[51]。在颅颌面系统中, FGF7已被证明参与内侧鼻腺发育[52]、泪腺的分支形态发生[51]以及诱导唾液腺的发育、再生和修复[53]。SEKIGUCHI团队发现, 在体外培养唾液腺上皮组织时, 在培养基中仅添加FGF7就能实现唾液腺上皮的生长和分枝[54]。SAMUEL等[55]对比了FGF7和FGF10对体外培养大鼠腮腺细胞的作用, 他们发现FGF10可以促进细胞增殖, 而FGF7则支持腮腺细胞在三维水凝胶内的迁移和渗透, 最终形成更多分支的网络结构。FGF7参与多种唾液腺再生和修复。在下颌下腺再生中, FGF7在导管样结构和新形成的腺泡细胞中出现, 可能与其他成纤维细胞生

长因子一起参与下颌下腺修复[56]。IKAI团队体外培养唾液腺器官,发现FGF7能够通过p38-MAPK信号通路促进ΔNp63表达,进而促进受损腮腺再生[57]。FGF7还能调节干细胞分化以促进腺体修复。AKASHI团队发现,经FGF7处理的牙髓干细胞腺泡细胞标记表达增加,将FGF7处理后的牙髓干细胞移植到大鼠损伤的下颌下腺中,能够观察到其形成具有腺泡细胞标记细胞聚集体,进而有利于下颌下腺修复[58]。

4 总结

在人类颅颌面区域,通过FGFRs的FGF信号传导对面部结构的形成十分重要。FGF7是主要在间充质表达,调节上皮细胞生长、分化的生长因子,能够激活对颅颌面发育十分重要的受体FGFR2b,其参与多个颅颌面结构的形成。但FGF7常与其他成纤维细胞生长因子共同发挥生长调节作用,如FGF10与FGF7分布区域相近,并在多个部位可以代偿FGF7的缺失。这种可能存在的功能冗余对深入认识FGF家族作用有着新的启发。同时,FGF7参与颅颌面多种疾病发生,有许多临床或临床前研究开展。深入了解FGF7在颅颌面发育的作用,对未来FGF7在颅颌面疾病中的应用有着积极意义。

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