DOI:10.3724/zdxbyxb-2022-0603

·细胞因子·

生长因子在眼的发育及眼部疾病调控中的作用

王晓杰,惠　琦,金　子,饶凤琴,靳　磊,余丙洁,BANDA Joshua,李校堃
温州医科大学药学院,浙江 温州 325035

[摘　要] 生长因子是一类由多种细胞分泌的活性物质,作为信使调控细胞的迁移、增殖和分化。多种生长因子参与眼组织的发育及眼部疾病的生理、病理过程。血管内皮生长因子、碱性成纤维细胞生长因子等介导糖尿病性视网膜病、脉络膜新生血管、白内障、糖尿病性黄斑水肿以及其他视网膜疾病的发生和发展。神经生长因子、睫状神经营养因子、胶质细胞源性神经营养因子、色素上皮衍生因子、粒细胞集落刺激因子等对视神经损伤有较好的修复作用。生长因子还与近视的发病密切相关,成纤维细胞生长因子、转化生长因子-β、胰岛素样生长因子影响巩膜厚度变化并调控近视的发生与发展。本文综述了生长因子参与眼的发育和眼部病理生理过程的研究进展,旨在揭示生长因子与眼部疾病的关联,为生长因子在眼科领域的应用提供思路。

[关键词] 生长因子;眼的发育;眼部疾病;眼科学;综述
[中图分类号] R77　　[文献标志码] A

Roles of growth factors in eye development and ophthalmic diseases

WANG Xiaojie, HUI Qi, JIN Zi, RAO Fengqin, JIN Lei, YU Bingjie, BANDA Joshua, LI Xiaokun (*School of Pharmaceutical Sciences, Wenzhou Medical University, Wenzhou 325035, Zhejiang Province, China*)
Corresponding author: LI Xiaokun, E-mail: xiaokunli@163.net, https://orcid.org/0000-0002-6556-6262

[**Abstract**] Growth factors are active substances secreted by a variety of cells, which act as messengers to regulate cell migration, proliferation and differentiation. Many growth factors are involved in the eye development or the pathophysiological processes of eye diseases. Growth factors such as vascular endothelial growth factor and basic fibroblast growth factor mediate the occurrence and development of diabetic retinopathy, choroidal neovascularization, cataract, diabetic macular edema, and other retinal diseases. On the

收稿日期:2022-03-01　　**接受日期**:2022-07-30
基金项目:浙江省“尖兵”“领雁”研发攻关计划(2022C03110)
第一作者:王晓杰,教授,博士生导师,主要从事生长因子创新药物及其作用机制研究;E-mail:18858811123@126.com;https://orcid.org/0000-0001-7748-1541
通信作者:李校堃,教授,博士生导师,主要从事生长因子创新药物及其临床转化研究;E-mail:xiaokunli@163.net;https://orcid.org/0000-0002-6556-6262

other hand, growth factors like nerve growth factor, ciliary neurotrophic factor, glial cell line-derived neurotrophic factor, pigment epithelial-derived factor and granulocyte colony-stimulating factor are known to promote optic nerve injury repair. Growth factors are also related to the pathogenesis of myopia. Fibroblast growth factor, transforming growth factor-β, and insulin-like growth factor regulate scleral thickness and influence the occurrence and development of myopia. This article reviews growth factors involved in ocular development and ocular pathophysiology, discusses the relationship between growth factors and ocular diseases, to provide reference for the application of growth factors in ophthalmology.

[**Key words**] Growth factor; Eye development; Ophthalmic diseases; Ophthalmology; Review

[J Zhejiang Univ (Med Sci), 2022, 51(5): 613-625.]

[**缩略语**] 表皮生长因子(epidermal growth factor,EGF);成纤维细胞生长因子(fibroblast growth factor,FGF);血管内皮生长因子(vascular endothelial growth factor,VEGF);神经生长因子(nerve growth factor,NGF);血小板衍生生长因子(platelet derived growth factor,PDGF);胰岛素样生长因子(insulin-like growth factor,IGF);转化生长因子(transforming growth factors,TGF);肿瘤坏死因子(tumor necrosis factor,TNF);FGF受体(FGF receptor,FGFR);EGF受体(EGF receptor,EGFR);视网膜神经节细胞(retinal ganglion cell,RGC);肝细胞生长因子(hepatocyte growth factor,HGF);磷脂酰肌醇3激酶(phosphoinositide 3-kinase,PI3K);蛋白激酶B(protein kinase B,AKT);胞外信号调节激酶(extracellular signal-regulated kinase,ERK);信号转导及转录激活因子(signal transduction and activator of transcription,STAT);白介素(interleukin,IL);基质金属蛋白酶(matrix metalloproteinase,MMP);准分子激光原地角膜消除术(Laser-assisted *in situ* keratomileusis,LASIK)

眼的发育是一个复杂且高度受控的过程。脊椎动物的眼睛由多种组织组成,这些组织在胚胎时期起源于表面外胚层、神经外胚层、神经嵴和中胚层的间充质[1]。眼的发育过程中,不同类型的细胞在遗传基因和生长因子的共同调控下,实现有序分化和排列[2-4]。眼睛是发育过程中容易发生畸变的器官之一。各种遗传性眼部疾病的发病率已经达到2%;近视、斜视、散光等在我国青年中的发病率已经达到50%左右;60岁以上人群眼睛的老视、白内障发生率接近80%;糖尿病性视网膜病变已成为四大主要致盲疾病之一[5]。尽管临床上已经有针对白内障、青光眼、糖尿病视网膜病变等眼部疾病的治疗手段或治疗药物,但诸如视网膜黄斑水肿、严重的视神经损伤、遗传因素引起的干眼等眼部疾病仍然缺乏令人满意的治疗方法或治疗药物。

生长因子在细胞和分子水平上控制眼形态的发生[6-7]。了解受生长因子调节的组织相互作用有助于阐明眼正常和异常发育的生理、病理机制。最近研究报道表明,EGF表达量异常会导致多种眼前节发育缺陷[8]。FGF10在兔干眼模型中可以增加泪河高度和泪河面积,促进角膜上皮愈合,减少角膜和结膜上皮细胞的凋亡并增加黏蛋白Muc1的产生[9]。VEGF是一种血管通透性因子,可诱导新生血管形成,是参与视网膜新生血管形成的最主要因素[10-11]。生长因子在眼部疾病调控作用的研究推动了生长因子及其抗体药物的研发,EGF滴眼液、碱性FGF滴眼液、NGF滴眼液已应用于临床角膜损伤治疗[12-15]。以VEGF为靶点的抗血管形成药物已经成为年龄相关性黄斑变性的临床一线用药[16]。

发育过程及正常眼组织中生长因子及其受体

表达异常将导致眼部疾病的发生，了解生长因子在眼的发育和眼部疾病调控中的作用对于眼部疾病的诊断及眼科药物的开发具有重要意义。本文综述了生长因子在眼的发育和眼部疾病调控中的研究进展，旨在为生长因子应用于眼科疾病的诊断和治疗提供依据。

1 生长因子与眼的发育

生长因子在胚胎发育过程中起到营养物质的作用，作为信使可调控细胞的迁移、增殖和分化。目前，已知包括FGF、EGF、NGF、PDGF、IGF、TGF、中胚层生长因子、TNF、血小板活化因子、睫状神经营养因子以及血管生成和抗血管生成的各种生长因子等参与眼发育的调控。以下介绍几种在眼的发育及维持眼正常功能中起重要作用的生长因子。

1.1 FGF

FGF在胚胎发育、血管生成、伤口愈合及多种组织和细胞的增殖与分化中起到关键作用[17-19]。FGF与眼部各组织的发育及分化密切相关，包括角膜[20]、视网膜[21]、晶状体[22]等。在眼发育早期，FGF1和FGF2介导视泡的神经上皮分裂为神经视网膜和视网膜色素上皮结构域[21]，并对视杯祖细胞的增殖、神经视网膜细胞分化的增强和视网膜色素上皮细胞分化的抑制起到至关重要的作用[23]。小鼠中枢神经视网膜的*FGFR1*和*FGFR2*被有条件敲除后，视杯在FGF信号缺陷区域异位形成视网膜色素上皮样结构[24]。FGF信号也与睫状缘的发育有关，发育中周围视网膜的FGF信号缺失会破坏睫状体边缘的发育并导致无虹膜[25]，如FGF9的结构性缺失会影响睫状体边缘区的发育[26]。在晶状体发育过程中，FGF1和FGF2在晶状体上皮细胞的增殖、移行和分化过程中起重要的作用[27-28]。其中，FGF2是晶状体胚胎发育的必需因子，能与Wnt信号转导通路协助促进晶状体的胚胎发育[29]。FGF2能促使G0和G1期晶状体上皮细胞进入分裂前感受态[30]，在低、中浓度时可促进大鼠原代晶状体上皮细胞增殖和迁移，在高浓度时促进纤维分化[31]，并可在骨形成蛋白的协同下进一步刺激晶状体次级纤维细胞分化[32]。此外，FGF10是人类泪腺和小鼠哈德氏腺发育所必需的[33]。FGF10从眼周间质分泌，并与其在表面外胚层上的受体FGFR2Ⅲb结合，以诱导泪腺萌芽；FGF10-FGFR2Ⅲb信号异常将导致泪腺发育异常[34]。因此，深入研究FGF对重要眼组织发育的调控，有利于为眼部疾病的防治提供新的思路和靶点。

1.2 EGF

EGF是最早发现的生长因子，通过与细胞表面的EGFR结合，激发受体酪氨酸激酶的活性，从而启动信号转导的级联反应，维持上皮细胞的正常新陈代谢。EGF在人体各种组织和体液中均可检测到，在眼部也广泛表达[35]。作为一种上皮细胞促生长因子，EGF作用的位点多为上皮细胞层[36]。成年小鼠角膜缘处的EGFR表达量高于角膜中央，提示EGFR高表达能使角膜缘干细胞保持未分化状态[37]。EGF通过影响视网膜和巩膜间的信号通路参与近视巩膜重塑[38]。郑瑾等[39]用一定浓度的EGF体外培养大鼠巩膜成纤维细胞，发现EGF对巩膜成纤维细胞的增殖有一定的促进作用。以上研究提示EGF是维持眼正常功能的重要生长因子之一。

1.3 NGF

NGF具有维持感觉神经元的存活、促进神经纤维的生长、增加感觉神经肽基因表达的作用，是较早发现的神经营养因子家族成员之一[40]。正常人的眼表上皮细胞可合成并分泌NGF，且NGF在角膜、结膜、泪囊、泪腺等中均有表达，参与调控眼表功能反应[41]。NGF对眼表具有多向调节作用，如调节免疫反应、调节角膜结膜上皮细胞增殖和杯状细胞黏蛋白的分化[42]。NGF在视觉系统的发育过程中高表达，影响神经元的增生、存活以及选择性的凋亡[43]。在形觉剥夺性近视豚鼠模型中，随着形觉剥夺时间的延长，视网膜中NGF蛋白及mRNA表达减少，推测NGF参与介导视网膜细胞的生长发育和视网膜细胞内的信息调控，促进功能性视网膜发育期的分化[44]。因此，以NGF为靶点，治疗视网膜色素变性等所致视神经萎缩、缺血性视神经病变、神经营养性角膜炎等视觉系统疾病已受到业界的关注。

1.4 PDGF

PDGF是由两条多肽链通过二硫键连接而成的同源或异源二聚体，包括PDGF-AA、PDGF-BB、PDGF-AB、PDGF-CC以及PDGF-DD[45]。PDGF与眼的发育过程密切相关。PDGF-AA在小鼠的晶状体或视网膜神经节细胞中特异性表达并促进星形

胶质细胞增殖[46]。PDGF-BB保守基序基因缺失的转基因小鼠不仅表现出周细胞丢失和异常的脉管系统[47],而且还会出现光感受器变性[48]。PDGF-BB过度表达可导致小鼠视网膜异常,如在Anestin增强剂下过表达PDGF-BB的转基因小鼠显示出视网膜缺陷,包括无组织的核层、光感受器变性和血管系统改变[49]。在髓鞘碱性蛋白特异性PDGF-BB表达转基因小鼠中也观察到视网膜折叠和视网膜毛细血管的解体[50]。因此PDGF-BB在视网膜发育中起重要作用。PDGF-CC在视网膜维护中同样具有重要性。功能获得和功能丧失试验均表明PDGF-CC通过PDGF受体-α和PDGF受体-β保护RGC[51]。PDGF-CC可改善光感受器变性但不诱导小鼠视网膜血管生成[52]。PDGF-DD可促进各种眼细胞如视网膜血管周细胞、脉络膜成纤维细胞和视网膜衍生的血管内皮细胞的增殖、存活和迁移[53]。总之,PDGF参与调控多种眼组织的发育过程,在眼发育过程中扮演重要作用。

1.5 VEGF

VEGF是血管内皮细胞特异性的肝素结合生长因子,是一种血管生成有丝分裂原,在眼部主要分布于视网膜周细胞、血管内皮细胞和色素上皮细胞等。VEGF通过结合内皮细胞上存在的酪氨酸激酶受体发挥其特有的分子作用,能促进血管内皮细胞分裂、增殖、迁移以及促进细胞外基质变性、增加血管通透性[54]。VEGF在人类中主要存在五个亚型,分别为VEGFA、VEGFB、VEGFC、VEGFD和胎盘生长因子,其中VEGFA在正常眼脉管系统和新生血管组织中表达最丰富[55],胎盘生长因子在视网膜浅表血管系统的动脉内皮细胞和生长的毛细血管芽中表达最明显[56]。研究显示,VEGF和胎盘生长因子与视网膜的发育息息相关且在血管形成方面有着协同作用,其中VEGF促使内皮细胞增殖并形成管状结构,而胎盘生长因子主要调节血管的生长和成熟[57-58]

1.6 HGF

HGF是一种可调节多种细胞生长、运动和形态发生的多功能因子,可作用于肝细胞、上皮细胞、造血细胞、血管内皮细胞等多种细胞[59]。在眼部,HGF可由成纤维细胞、血管平滑肌细胞、角膜上皮细胞、晶状体上皮细胞、虹膜及视网膜色素上皮细胞、小梁细胞等产生[60]。HGF受体激活PI3K-AKT及ERK激酶信号[61],促进细胞分裂、调控细胞周期作用及修复角膜上皮;同时HGF具有抑制成纤维细胞生成和抗纤维化作用[62]。此外,HGF在角膜损伤修复、维持角膜内皮完整性、调节晶状体上皮细胞功能等方面起着重要作用[63]。研究显示,HGF的水平和角膜病的易感性相关[64]。HGF通过维持ZO-1(角膜上皮紧密连接的标志物)的正常表达和分布,保护人角膜上皮细胞间的屏障;HGF还可以抑制细胞骨架蛋白质F-actin的重构,增强其对于角膜上皮屏障的保护作用[65]。HGF还可调节小梁细胞的生长和代谢[66],增强内皮细胞中的基质金属蛋白酶活性进而影响葡萄膜巩膜外引流和眼压[67]。总之,HGF在维持眼组织稳态中发挥重要作用。

2 生长因子与眼部疾病的调控

在正常的生理条件下,各种生长因子处于动态平衡状态,如果受到干扰,会导致眼部疾病的发生。研究生长因子与眼部疾病的关系不仅能了解人类眼部疾病的发病机制,也可用于开发新的有效治疗方法。

2.1 角膜疾病

角膜所处的解剖位置特殊,容易受到创伤和感染等各种外界因素的刺激。各种生长因子在角膜伤口的愈合方面起到了重要作用。EGF、FGF和TGF-β能在体外刺激人和牛角膜上皮细胞、成纤维细胞及内皮细胞的趋化迁移[68]。FGF10可激活角膜上皮干细胞,使其不断增殖分化,从而促进角膜上皮损伤的愈合,并在兔角膜碱烧伤模型中得到证实[69]。FGF10还可以通过减轻角膜激光烧伤后的各种炎症反应加速角膜上皮细胞的增殖和迁移,促进角膜基质纤维增生,加快激光烧伤后受损角膜的修复等[70]。EGF对角膜的主要作用包括加速角膜上皮细胞增殖、促进角膜基质层胶原合成及促进内皮细胞的增殖;EGF还具有逆转糖皮质激素抑制上皮细胞增殖和延缓创口修复的作用[71]。在一项比较研究中,EGF和FGF2均可促进角膜上皮细胞的增殖,FGF2作用更强,而长期使用EGF在促进角膜愈合过程中可减少基质新血管生成[72]。TGF-β的主要作用是加快炎症反应及刺激细胞外基质合成和不断沉积,进而加速角膜基底膜和基质的重构和修复,促进角膜伤口愈合,但后期的过度表达可导致细胞外基质合成及降解失衡,从而造成组织纤维化[73]。以上研究结果提示,

生长因子参与角膜相关疾病的发生和发展,为角膜疾病的治疗提供了重要的研究方向。

角膜新生血管是多种眼表疾病如感染性角膜疾病、眼化学伤、热烧伤、非感染性角膜疾病角膜变性的显著特征之一,不但严重影响视力,也是角膜移植排斥反应发生的高危因素。角膜新生血管的形成与多种生长因子的调控密切相关,生长因子之间的平衡是保持角膜透明的重要条件[74]。生理状态下,血管生成抑制因子与血管生成促进因子的表达处于动态平衡,因此角膜中不会有新生血管形成[75]。但创伤、低氧、感染或免疫复合物的沉积会打破生长因子之间的平衡,从而引发角膜新生血管[76]。

2.2 视网膜疾病

视网膜疾病在临床上主要分为五种:视网膜血管性疾病、视网膜炎症疾病、视网膜脱离、视网膜变性和视网膜肿瘤,以糖尿病视网膜病变和视网膜静脉阻塞为代表的血管性病变最为常见。

VEGF是一种血管通透性因子,可诱导新生血管形成,是参与视网膜新生血管形成的最主要因素[10-11]。VEGF通过蛋白激酶C介导的闭锁蛋白磷酸化破坏血-视网膜屏障,蛋白激酶C通过内吞过程诱导紧密连接的解体从而导致血管渗漏,引起黄斑水肿[77]。VEGF可上调细胞内黏附分子-1,通过促进白细胞黏附和淤滞,导致毛细血管阻塞及无灌注区形成,引起组织缺血、缺氧;而缺氧又是VEGF的强效刺激因素,可使VEGF数倍上调,形成前馈循环,从而导致视网膜血管病变不断加重[78]。高糖状态下,氧化应激、缺氧和炎症反应等均能诱导VEGF表达增加,VEGF与血管内皮细胞上的VEGF受体结合可引起内皮细胞增殖、迁移,进一步诱导视网膜新生血管形成[79]。

IGF-1是VEGF的上游因子,IGF-1可以促进VEGF的表达,特别是血-视网膜屏障破坏后,IGF-1可能会加速糖尿病视网膜病变的进展;玻璃体腔注射抗IGF-1可能可以替代抗VEGF成为一种新的疗法[80]。

FGF2也是一种很强的促血管生成因子。Dong等[81]发现,FGF2可通过FGFR信号激活STAT3,以剂量依赖的方式促进激光诱导小鼠视网膜新生血管的形成。FGF2能促使内皮细胞在缺血缺氧环境下增多,也能促进体外培养的内皮细胞[82]和视网膜色素上皮细胞[83]的增殖,引起毛细血管狭窄和闭塞,加速糖尿病视网膜病变的病理损害。FGF2还可促使层粘连蛋白、纤维连接蛋白及Ⅳ型胶原生成增加,并使糖尿病视网膜病变患者玻璃体中内皮细胞分泌纤溶酶原激活物增加[84],从而快速分解细胞基质和基底膜等大分子物质,并促使可形成毛细血管的细胞迅速穿过上述结构进行迁移和增殖,形成新生血管。

以上研究表明,多种生长因子介导了视网膜血管性疾病,是该类疾病治疗的重要靶点。

2.3 白内障和后发性白内障

白内障是指因老化、遗传、局部营养障碍、免疫与代谢异常、外伤、中毒、辐射等引起晶状体代谢紊乱,导致晶状体蛋白质变性而发生混浊。晶状体上皮细胞过度凋亡及晶状体蛋白损伤与房水内众多细胞因子含量的改变有关[85]。糖尿病性白内障患者术前房水中FGF2和IGF-1含量的增加可能与高糖状态晶状体上皮细胞受损、凋亡及血-房水屏障破坏有关,其水平差异反映了不同生长因子在不同发病阶段的作用[86]。糖尿病白内障患者房水中生长因子VEGF、TGF-β、血管内皮细胞黏附分子浓度变化与糖网增殖期变化具有一致性,且因子间存在相关性[87]。因此,白内障患者房水生长因子的浓度反映了不同生长因子在不同发病阶段的作用,可作为治疗和预后的参考指标。

后发性白内障指白内障摘除术后,或外伤性白内障部分皮质吸收后残留晶状体上皮细胞增殖、分化并移行导致的晶状体后囊膜混浊。EGF是促进白内障术后晶状体上皮细胞生长的重要因子。陶津华等[88]发现,EGF对人晶状体上皮细胞具有促进迁移的作用。Huang等[89]研究发现,EGFR的干扰小RNA能够阻断EGF-EGFR信号通路,使人晶状体上皮细胞生长周期阻滞于G1期,有效预防晶状体后囊膜混浊的发生。TGF-β1和TGF-β2均可由晶状体上皮细胞表达,活化的TGF-β水平在白内障术后显著升高;TGF-β可诱导晶状体上皮细胞发生上皮间质转换,并转分化为肌成纤维细胞,其形态学和生物学均与晶状体后囊膜混浊的形成类似[90]。白内障术后剩余的晶状体上皮细胞保留在前囊上,诱导HGF释放,激活其受体c-Met并诱导ERK和JNK/SAPK以及PI3K活化[91],从而诱导细胞周期蛋白D1的表达,刺激晶状体上皮细胞增殖并造成晶状体后囊膜混浊。因此,EGF、TGF-β和HGF都是治疗晶状体后囊膜混浊的

重要靶点。

2.4 视神经损伤

创伤、缺血、高眼压、药物中毒、代谢障碍等多种因素均可以造成视神经的不可逆损伤。神经营养因子能够促进神经元的存活和诱导轴突的生长,对中枢和外周神经系统的组织细胞均具有广泛的生物学活性[92]。神经营养因子的剥夺是视神经损伤后RGC凋亡的主要原因之一,给予外源性的神经营养因子能够促进视神经损伤后RGC的再生和发挥神经保护作用[93]。

最典型的神经营养因子是NGF。NGF具有维持感觉神经元存活、促进神经纤维生长、增加感觉神经肽基因表达的作用,是最早发现的神经营养素家族成员之一[94-95]。NGF能降低兔高眼压后视网膜髓鞘碱性蛋白的含量,提高RGC的存活数,对RGC损伤后的修复有明显的促进作用[96]。实验证实,NGF可以促进脱髓鞘性视神经炎小鼠RGC的存活[97],提高由青光眼、糖尿病视网膜病变引起的鼠RGC的存活率[98],以及促进视神经挫伤后大鼠RGC的存活和轴突生长[99]。然而,有研究表明,NGF能通过调节VEGF促进淋巴管形成,可能作为致病因素在角膜伤口修复过程中对正常神经及淋巴血管重塑起负性调节作用[100]。

除了NGF以外,睫状神经营养因子、胶质细胞源性神经营养因子、色素上皮衍生因子、粒细胞集落刺激因子等神经营养因子也对视神经损伤有较好的修复作用。睫状神经营养因子可以通过PI3K/PIP3/AKT通路,激活mTOR及其下游信号促进视神经轴突生长[101]。胶质细胞源性神经营养因子能够提高视神经损伤后RGC的存活率,通过调节增强有效跨膜转运实现神经保护[102];联合嗅神经鞘细胞移植能促进成年大鼠视神经损伤后功能恢复[103]。色素上皮衍生因子能够在视神经离断后减少神经节细胞凋亡,增加再生轴突数[104]。皮下注射粒细胞集落刺激因子能够产生剂量依赖性的视神经保护作用,且至少能在一定程度上独立于干细胞发挥治疗作用[105]。

此外,其他种类的生长因子如FGF1[106-107]、FGF2[108-109]和IGF[110-111]等也具有保护视神经的作用。

2.5 干 眼

干眼症是指泪液的量或质的异常引起泪膜不稳定和眼表损害的多种病理状态的总称。虽然诱导干眼症的因素很多,但不同类型干眼症的发病机制较为相似。眼表的炎症反应是目前干眼症发病学说中被认同度较高的观点之一[112]。干眼会导致眼表面高渗,从而引发炎症介质的释放,上调MMP-3、MMP-9、TNF-α、IL-1β等表达[113-114]。

EGF主要参与泪液的产生,为泪液中有效的蛋白成分。EGF是泪液神经调节通路的重要因素之一,若阻断EGFR系统可能导致干眼发生[115]。杨春等[116]检测干眼症患者的泪液发现EGF含量明显下降,而泪液分泌不足会导致EGF含量进一步下降,加重疾病进程,因此EGF可以作为干眼检测的可靠指标。

此外,TGF-β1可通过下游信号分子磷酸化Smad2/3与Smad4复合物限制结膜内杯状细胞增殖[117],可能与干眼形成有关。NGF异常表达直接参与了干眼局部炎症反应[118]。干燥综合征患者眼部慢性炎症反应与NGF-β/TrkA异常表达有关,其损伤机制主要为影响EGFR/MEK/ERK信号转导系统激活[119]。还有研究发现,IGF-1能有效加速LASIK术后角膜表面超微结构及神经再生的修复,并可缓解干眼症状[120]。

以上研究表明,深入了解不同生长因子在干眼调控中的作用及其分子机制,有利于针对不同类型干眼开展对因治疗。

2.6 近 视

近视是患病率最高的眼科疾病之一,生长因子与眼球发育和近视发病密切相关,FGF、EGF、TGF、IGF等具有影响巩膜厚度变化和调控近视发生发展等功能[121]。

FGF-2还能通过促进多巴胺的合成来抑制形觉剥夺性近视轴的拉长,从而拮抗形觉剥夺性近视的发生和发展[122-123];也可与TGF共同影响MMP的表达来调控细胞外基质,进而参与近视的发展[124]。同时,也有研究认为,*FGF10*基因rs399501位点与超高度近视相关[125]。

EGF参与了近视巩膜重塑。Barathi等[126]发现阿托品抗近视效应可能是由于EGFR激活ERK-MAPK信号通路,调节巩膜成纤维细胞的增殖和分化,进而影响巩膜重塑。

TGF-β与近视密切相关,能影响高度近视眼巩膜扩张中细胞的增殖、分化和迁移[43]。在形觉剥夺性近视动物模型中,TGF-β含量降低,促进MMP降解细胞外基质中胶原和蛋白多糖,使得巩膜变

薄,最终导致高度近视的发生[127-128];同时TGF-β也可通过增强巩膜收缩来诱发近视[129]。最新研究显示,在视网膜色素上皮细胞中,TGF-β2、TGF-β3等近视相关因子水平可能因转录因子HOXA9介导升高而促进近视的发展[130]。

*IGF-1*基因与高度近视显著相关[131],其能通过引起巩膜组织MMP和金属蛋白酶组织抑制物表达失衡,提高MMP活性,减少巩膜成纤维细胞生长与细胞外基质的合成,导致巩膜重塑变薄、眼轴延长而出现高度近视[26]。

3 结 语

尽管国内外学者对生长因子参与眼部疾病的发生过程形成了一定认识,但生长因子及其受体如何诱发或治疗眼部疾病的机制仍有许多未解之谜。眼发育过程中各组织相互作用,整个过程可能需要几个生长因子的协同作用。如在晶状体的发育过程中,FGF、IGF-1、PDGF、EGF、TGF-α和HGF等因子在上皮细胞增殖过程中均有促进作用。目前认为FGF是促使G0和G1期上皮细胞进入分裂前感受态的启动因子,而IGF-1则推动感受态细胞通过限制点进入S期,完成染色体DNA和相关蛋白质的合成,两者在上皮细胞增殖过程中起协同作用[30]。Chen等[132]研究发现,EGF和HGF受体通过蛋白激酶C活化和ERK磷酸化两条途径诱导视网膜色素上皮细胞迁移,并且这两种生长因子不仅可以被相应自身配体激活,而且可以被异源配体交叉激活,从而增强信号转导和细胞迁移。因此,进一步揭示生长因子与眼部疾病发生发展的分子机制,将极大推动以生长因子及其受体为靶点的眼部疾病治疗药物的开发,提高眼部难治性疾病的诊疗水平。

利益冲突 所有作者均声明不存在利益冲突

参考文献

[1] DIACOU R, NANDIGRAMI P, FISER A, et al. Cell fate decisions, transcription factors and signaling during early retinal development[J]. **Prog Retin Eye Res**, 2022: 101093.

[2] PROVIS J. Development of the primate retinal vasculature[J]. **Prog Retin Eye Res**, 2001, 20(6): 799-821.

[3] ZAGOZEWSKI J L, ZHANG Q, EISENSTAT D D. Genetic regulation of vertebrate eye development[J]. **Clin Genet**, 2014, 86(5): 453-460.

[4] STUARD W L, TITONE R, ROBERTSON D M. The IGF/insulin-IGFBP axis in corneal development, wound healing, and disease[J]. **Front Endocrinol**, 2020, 11: 24.

[5] BURTON M J, RAMKE J, MARQUES A P, et al. The Lancet Global Health Commission on global eye health: vision beyond 2020[J/OL]. **Lancet Glob Health**, 2021, 9(4): e489-e551.

[6] LOVICU F J, MCAVOY J W. Growth factor regulation of lens development[J]. **Dev Biol**, 2005, 280(1): 1-14.

[7] TRIPATHI B J, TRIPATHI R C, LIVINGSTON A M, et al. The role of growth factors in the embryogenesis and differentiation of the eye[J]. **Am J Anat**, 1991, 192(4): 442-471.

[8] YUGAWA T, HANDA K, NARISAWA-SAITO M, et al. Regulation of Notch1 gene expression by p53 in epithelial cells[J]. **Mol Cell Biol**, 2007, 27(10): 3732-3742.

[9] ZHENG W, MA M, DU E, et al. Therapeutic efficacy of fibroblast growth factor 10 in a rabbit model of dry eye[J]. **Mol Med Rep**, 2015, 12(5): 7344-7350.

[10] CARMELIET P. Mechanisms of angiogenesis and arteriogenesis[J]. **Nat Med**, 2000, 6(4): 389-395.

[11] MURAKAMI T, FREY T, LIN C, et al. Protein kinase Cβ phosphorylates occludin regulating tight junction trafficking in vascular endothelial growth factor-induced permeability *in vivo*[J]. **Diabetes**, 2012, 61(6): 1573-1583.

[12] 王瑞华, 贺 燚, 郝燕燕. 外伤性角膜上皮缺损的治疗——碱性成纤维细胞生长因子滴眼液的临床应用[J]. **眼外伤职业眼病杂志**, 2002, 24(3): 276-277.
WANG Ruihua, HE Yi, HAO Yanyan. Treatment of traumatic corneal epithelium defect[J]. **Chinese Journal of Ocular Trauma and Occupational Eye Disease**, 2002, 24(3): 276-277. (in Chinese)

[13] 梁 平, 梁 慷, 谢莉娜, 等. 贝复舒(重组bFGF)滴眼液治疗干眼症的临床研究[J]. **临床眼科杂志**, 2001, 9(6): 464-466.
LIANG Ping, LIANG Kang, XIE Lina, et al. A clinic study on effect of bFGF eye drops treated the patients with dry eye[J]. **Journal of Clinical Ophthalmology**, 2001, 9(6): 464-466. (in Chinese)

[14] 魏利军. 2017年美国、欧洲和日本批准的新药总结与点评(Ⅱ)[J]. **药学进展**, 2018, 42(2): 148-157.
WEI Lijun. Summary and review of new drugs approved by FDA, EMA and PMDA in 2017(Ⅱ)[J]. **Progress in Pharmaceutical Sciences**, 2018, 42(2): 148-157. (in Chinese)

[15] 袁鹏华. 重组人表皮生长因子衍生物滴眼剂在治疗干眼中的应用价值[J]. **中西医结合心血管病电**

子杂志, 2017, 5(22): 186.
YUAN Penghua. Application value of recombinant human epidermal growth factor derivative eye drops in the treatment of dry eye[J]. **Cardiovascular Disease Electronic Journal of Integrated Traditional Chinese and Western Medicine**, 2017, 5(22): 186. (in Chinese)
[16] CAMPA C. New anti-VEGF drugs in ophthalmology [J]. **Curr Drug Targets**, 2020, 21(12): 1194-1200.
[17] ITOH N, OHTA H. Fgf10: a paracrine-signaling molecule in development, disease, and regenerative medicine[J]. **Curr Mol Med**, 2014, 14(4): 504-509.
[18] FU Z, GONG Y, LIEGL R, et al. FGF21 administration suppresses retinal and choroidal neovascularization in mice[J]. **Cell Rep**, 2017, 18(7): 1606-1613.
[19] CAI J Q, ZHOU Q, WANG Z, et al. Comparative analysis of KGF-2 and bFGF in prevention of excessive wound healing and scar formation in a corneal alkali burn model[J]. **Cornea**, 2019, 38(11): 1430-1437.
[20] MCAVOY J W, CHAMBERLAIN C G. Growth factors in the eye[J]. **Prog Growth Factor Res**, 1990, 2(1): 29-43.
[21] CHIKAMA T, LIU C Y, MEIJ J T A, et al. Excess FGF-7 in corneal epithelium causes corneal intraepithelial neoplasia in young mice and epithelium hyperplasia in adult mice[J]. **Am J Pathol**, 2008, 172(3): 638-649.
[22] PITTACK C, GRUNWALD G B, REH T A. Fibroblast growth factors are necessary for neural retina but not pigmented epithelium differentiation in chick embryos[J]. **Development**, 1997, 124(4): 805-816.
[23] YANG C, YANG Y, BRENNAN L, et al. Efficient generation of lens progenitor cells and lentoid bodies from human embryonic stem cells in chemically defined conditions[J]. **FASEB J**, 2010, 24(9): 3274-3283.
[24] ATKINSON-LEADBEATER K, HEHR C L, MCFARLANE S. FGFR signaling is required as the early eye field forms to promote later patterning and morphogenesis of the eye[J]. **Dev Dyn**, 2014, 243(5): 663-675.
[25] CAI Z, TAO C, LI H, et al. Deficient FGF signaling causes optic nerve dysgenesis and ocular coloboma [J]. **Development**, 2013, 140(13): 2711-2723.
[26] BALASUBRAMANIAN R, TAO C, POLANCO K, et al. Deficient FGF signaling in the developing peripheral retina disrupts ciliary margin development and causes aniridia[J]. **bioRxiv**, 2018. DOI: 10.1101/443416.
[27] ZHAO S, HUNG F C, COLVIN J S, et al. Patterning the optic neuroepithelium by FGF signaling and Ras activation[J]. **Development**, 2001, 128(24): 5051-5060.
[28] 哈玲芳, 盛迅伦, 庄文娟, 等. 碱性成纤维细胞生长因子对人晶状体上皮细胞增殖及移行作用的影响[J]. **中华眼视光学与视觉科学杂志**, 2010, 12(2): 134-137.
HA Lingfang, SHENG Xunlun, ZHUANG Wenjuan, et al. Effect of basic fibroblast growth factor on proliferation and migration in cultured human lens epithelial cells[J]. **Chinese Journal of Optometry Ophthalmology and Visual Science**, 2010, 12(2): 134-137. (in Chinese)
[29] HAYASHI T, MIZUNO N, KONDOH H. Determinative roles of FGF and Wnt signals in iris-derived lens regeneration in newt eye[J]. **Dev Growth Differ**, 2008, 50(4): 279-287.
[30] ZHAO H, YANG T, MADAKASHIRA B P, et al. Fibroblast growth factor receptor signaling is essential for lens fiber cell differentiation[J]. **Dev Biol**, 2008, 318(2): 276-288.
[31] LOVICU F J, MCAVOY J W, DE IONGH R U. Understanding the role of growth factors in embryonic development: insights from the lens[J]. **Phil Trans R Soc B**, 2011, 366(1568): 1204-1218.
[32] 刘奕志, 董 夏. 干细胞与晶状体再生[J/CD]. **中华细胞与干细胞杂志(电子版)**, 2014, 4(1): 60-66.
LIU Yizhi, DONG Xia. Stem cell and lens regeneration[J/CD]. **Chinese Journal of Cell and Stem Cell (Electronic Edition)**, 2014, 4(1): 60-66. (in Chinese)
[33] ENTESARIAN M, MATSSON H, KLAR J, et al. Mutations in the gene encoding fibroblast growth factor 10 are associated with aplasia of lacrimal and salivary glands[J]. **Nat Genet**, 2005, 37(2): 125-128.
[34] PAN Y, CARBE C, POWERS A, et al. Bud specific N-sulfation of heparan sulfate regulates Shp2-dependent FGF signaling during lacrimal gland induction[J]. **Development**, 2008, 135(2): 301-310.
[35] DONG F, CALL M, XIA Y, et al. Role of EGF receptor signaling on morphogenesis of eyelid and meibomian glands[J]. **Exp Eye Res**, 2017, 163: 58-63.
[36] FREEMAN M. Reiterative use of the EGF receptor triggers differentiation of all cell types in the Drosophila eye[J]. **Cell**, 1996, 87(4): 651-660.
[37] ZIESKE J D, WASSON M. Regional variation in distribution of EGF receptor in developing and adult corneal epithelium[J]. **J Cell Sci**, 1993, 106(1): 145-152.
[38] 陈艳艳, 尹忠贵. 近视发生发展影响因素的研究进展[J]. **中国斜视与小儿眼科杂志**, 2013, 21(3): 45-48.
CHEN Yanyan, YIN Zhonggui. Recent advances on influence factors of the occurrence and the develop-

ment of myopia[J]. **Chinese Journal of Strabismus & Pediatric Ophthalmology**, 2013, 21(3): 45-48. (in Chinese)

[39] 郑 瑾, 佘振珏, 周国民. EGF与bFGF对体外大鼠巩膜成纤维细胞增殖的影响[J]. **复旦学报(医学版)**, 2006, 33(3): 301-304.
ZHENG Jin, SHE Zhenjue, ZHOU Guomin. Effect of EGF and bFGF on scleral fibroblasts proliferation *in vitro*[J]. **Fudan University Journal of Medical Sciences**, 2006, 33(3): 301-304. (in Chinese)

[40] TIRASSA P, ROSSO P, IANNITELLI A. Ocular nerve growth factor (NGF) and NGF eye drop application as paradigms to investigate NGF neuroprotective and reparative actions[J]. **Neurotrophic Factors**, 2018, 1729: 19-38.

[41] MICERA A, LAMBIASE A, ALOE L, et al. Nerve growth factor involvement in the visual system: implications in allergic and neurodegenerative diseases[J]. **Cytokine Growth Factor Rev**, 2004, 15(6): 411-417.

[42] LAMBIASE A, MICERA A, SACCHETTI M, et al. Alterations of tear neuromediators in dry eye disease[J]. **Arch Ophthalmol**, 2011, 129(8): 981-986.

[43] 訾迎新. 生长因子在高度近视中的作用研究进展[J]. **中华实验眼科杂志**, 2020, 38(6): 539-542.
ZI Yingxin. The role of growth factors in high myopia[J]. **Chinese Journal of Experimental Ophthalmology**, 2020, 38(6): 539-542. (in Chinese)

[44] DAVIS J B. ELISA for monitoring nerve growth factor[J]. **Methods Mol Biol**, 2017, 1606: 141-147.

[45] REIGSTAD L J, VARHAUG J E, LILLEHAUG J R. Structural and functional specificities of PDGF-C and PDGF-D, the novel members of the platelet-derived growth factors family[J]. **FEBS J**, 2005, 272(22): 5723-5741.

[46] RENEKER L W, OVERBEEK P A. Lens-specific expression of PDGF-A in transgenic mice results in retinal astrocytic hamartomas[J]. **Invest Ophthalmol Vis Sci**, 1996, 37(12): 2455-2466.

[47] LINDBLOM P, GERHARDT H, LIEBNER S, et al. Endothelial PDGF-B retention is required for proper investment of pericytes in the microvessel wall[J]. **Genes Dev**, 2003, 17(15): 1835-1840.

[48] GENOVÉ G, MOLLICK T, JOHANSSON K. Photoreceptor degeneration, structural remodeling and glial activation: a morphological study on a genetic mouse model for pericyte deficiency[J]. **Neuroscience**, 2014, 279: 269-284.

[49] EDQVIST P H D, NIKLASSON M, VIDAL-SANZ M, et al. Platelet-derived growth factor over-expression in retinal progenitors results in abnormal retinal vessel formation[J/OL]. **PLoS One**, 2012, 7(8): e42488.

[50] FORSBERG-NILSSON K, ERLANDSSON A, ZHANG X Q, et al. Oligodendrocyte precursor hypercellularity and abnormal retina development in mice overexpressing PDGF-B in myelinating tracts[J]. **Glia**, 2003, 41(3): 276-289.

[51] TANG Z, ARJUNAN P, LEE C, et al. Survival effect of PDGF-CC rescues neurons from apoptosis in both brain and retina by regulating GSK3β phosphorylation[J]. **J Exp Med**, 2010, 207(4): 867-880.

[52] WANG Y, ABU-ASAB M S, YU C R, et al. Platelet-derived growth factor (PDGF)-C inhibits neuroretinal apoptosis in a murine model of focal retinal degeneration[J]. **Lab Invest**, 2014, 94(6): 674-682.

[53] KUMAR A, HOU X, LEE C, et al. Platelet-derived growth factor-DD targeting arrests pathological angiogenesis by modulating glycogen synthase kinase-3β phosphorylation[J]. **J Biol Chem**, 2010, 285(20): 15500-15510.

[54] 赵 晶, 戴 虹. 中国抗血管内皮生长因子药物眼科临床应用现状及存在问题[J]. **临床药物治疗杂志**, 2020, 18(12): 1-5.
ZHAO Jing, DAI Hong. Status and challenges of anti-vascular endothelial growth factor usage in ophthalmic diseases in China[J]. **Clinical Medication Journal**, 2020, 18(12): 1-5. (in Chinese)

[55] MELINCOVICI C S, BOSCA A B, SUSMAN S, et al. Vascular endothelial growth factor (VEGF)-key factor in normal and pathological angiogenesis[J]. **Rom J Morphol Embryol**, 2018, 59(2): 455-467.

[56] FEENEY S A, SIMPSON D A C, GARDINER T A, et al. Role of vascular endothelial growth factor and placental growth factors during retinal vascular development and hyaloid regression[J]. **Invest Ophthalmol Vis Sci**, 2003, 44(2): 839-847.

[57] APTE R S, CHEN D S, FERRARA N. VEGF in signaling and disease: beyond discovery and development[J]. **Cell**, 2019, 176(6): 1248-1264.

[58] GOURVAS V, DALPA E, KONSTANTINIDOU A, et al. Angiogenic factors in placentas from pregnancies complicated by fetal growth restriction (review)[J]. **Mol Med Rep**, 2012, 6(1): 23.

[59] FAJARDO-PUERTA A B, MATO PRADO M, FRAMPTON A E, et al. Gene of the month: *HGF*[J]. **J Clin Pathol**, 2016, 69(7): 575-579.

[60] WILSON S E, WALKER J W, CHWANG E L, et al. Hepatocyte growth factor, keratinocyte growth factor, their receptors, fibroblast growth factor receptor-2, and the cells of the cornea[J]. **Invest Ophthalmol Vis Sci**, 1993, 34(8): 2544-2561.

[61] TIAN F, DONG L, ZHOU Y, et al. Rapamycin-induced apoptosis in HGF-stimulated lens epithelial cells by AKT/mTOR, ERK and JAK2/STAT3 pathways[J]. **Int J Mol Sci**, 2014, 15(8): 13833-

13848.

[62] MIYAGI H, THOMASY S M, RUSSELL P, et al. The role of hepatocyte growth factor in corneal wound healing[J]. **Exp Eye Res**, 2018, 166: 49-55.

[63] ARAKI-SASAKI K. Human hepatocyte growth factor (HGF) in the aqueous humor[J]. **Jpn J Ophthalmol**, 1997, 41(6): 409-413.

[64] YOU J, WEN L, ROUFAS A, et al. Expression of HGF and c-Met proteins in human keratoconus corneas[J]. **J Ophthalmol**, 2015, 2015: 852986.

[65] KIMURA K, TERANISHI S, KAWAMOTO K, et al. Protection of human corneal epithelial cells from hypoxia-induced disruption of barrier function by hepatocyte growth factor[J]. **Exp Eye Res**, 2010, 90(2): 337-343.

[66] WORDINGER R J, CLARK A F, AGARWAL R, et al. Cultured human trabecular meshwork cells express functional growth factor receptors[J]. **Invest Ophthalmol Vis Sci**, 1998, 39(9): 1575-1589.

[67] GATON D D, SAGARA T, LINDSEY J D, et al. Matrix metalloproteinase-1 localization in the normal human uveoscleral outflow pathway[J]. **Invest Ophthalmol Vis Sci**, 1999, 40(2): 363-369.

[68] GRANT M B, KHAW P T, SCHULTZ G S, et al. Effects of epidermal growth factor, fibroblast growth factor, and transforming growth factor-beta on corneal cell chemotaxis[J]. **Invest Ophthalmol Vis Sci**, 1992, 33(12): 3292-3301.

[69] 王晓杰, 周 鑫, 田海山, 等. 重组人角质细胞生长因子-2对兔碱烧伤模型角膜上皮损伤的治疗作用[J]. **吉林大学学报 (医学版)**, 2010, 36(4): 625-628.
WANG Xiaojie, ZHOU Xin, TIAN Haishan, et al. Therapeutic effects of kertinocyte growth factor-2 on corneal epithelial wound healing in rabbit model of alkali burn[J]. **Journal of Jilin University (Medicine Edition)**, 2010, 36(4): 625-628. (in Chinese)

[70] 高荣莲, 马 萍, 陈 鹏, 等. 角质细胞生长因子-2对角膜激光烧伤的治疗作用及机制研究[J]. **中国激光医学杂志**, 2010, 19(4): 205-209, 267-269.
GAO Ronglian, MA Ping, CHEN Peng, et al. Therapeutic effect and its mechanism of keratinocyte growth factor-2 on rabbit cornea after laser burn[J]. **Chinese Journal of Laser Medicine & Surgery**, 2010, 19(4): 205-209, 267-269. (in Chinese)

[71] 刘祖国. **眼表疾病学**[M]. 北京: 人民卫生出版社, 2003: 670.
LIU Zuguo. **Ocular surface diseases**[M]. Beijing: People's Medical Publishing House, 2003: 670. (in Chinese)

[72] YAN L, WU W, WANG Z, et al. Comparative study of the effects of recombinant human epidermal growth factor and basic fibroblast growth factor on corneal epithelial wound healing and neovascularization *in vivo* and *in vitro*[J]. **Ophthalmic Res**, 2013, 49(3): 150-160.

[73] YOSHIMURA A, WAKABAYASHI Y, MORI T. Cellular and molecular basis for the regulation of inflammation by TGF-β[J]. **J Biochem**, 2010, 147(6): 781-792.

[74] KLENKLER B, SHEARDOWN H. Growth factors in the anterior segment: role in tissue maintenance, wound healing and ocular pathology[J]. **Exp Eye Res**, 2004, 79(5): 677-688.

[75] AZAR D T. Corneal angiogenic privilege: angiogenic and antiangiogenic factors in corneal avascularity, vasculogenesis, and wound healing (an American Ophthalmological Society thesis) [J]. **Trans Am Ophthalmol Soc**, 2006, 104: 264-302.

[76] RISAU W, FLAMME I. Vasculogenesis[J]. **Annu Rev Cell Dev Biol**, 1995, 11(1): 73-91.

[77] WITMER A. Vascular endothelial growth factors and angiogenesis in eye disease[J]. **Prog Retin Eye Res**, 2003, 22(1): 1-29.

[78] SCHMIDT-ERFURTH U, GARCIA-ARUMI J, BANDELLO F, et al. Guidelines for the management of diabetic macular edema by the European Society of Retina Specialists (EURETINA)[J]. **Ophthalmologica**, 2017, 237(4): 185-222.

[79] IZUTA H, MATSUNAGA N, SHIMAZAWA M, et al. Proliferative diabetic retinopathy and relations among antioxidant activity, oxidative stress, and VEGF in the vitreous body[J]. **Mol Vis**, 2010, 16: 130-136.

[80] 张 浩, 尚利晓, 魏 菁. 胰岛素样生长因子1与糖尿病视网膜病变关系的研究进展[J]. **中国眼耳鼻喉科杂志**, 2021, 21(2): 131-134, 138.
ZHANG Hao, SHANG Lixiao, WEI Jing. Research progress on the relationship between insulin-like growth factor-1 and diabetic retinopathy[J]. **Chinese Journal of Ophthalmology and Otorhinolaryngology**, 2021, 21(2): 131-134, 138. (in Chinese)

[81] DONG Z, SANTEFORD A, BAN N, et al. FGF2-induced STAT3 activation regulates pathologic neovascularization[J]. **Exp Eye Res**, 2019, 187: 107775.

[82] BITO K, HASEBE T, MAEGAWA S, et al. *In vitro* basic fibroblast growth factor (bFGF) delivery using an antithrombogenic 2-methacryloyloxyethyl phosphorylcholine (MPC) polymer coated with a micropatterned diamond-like carbon (DLC) film[J]. **J Biomed Mater Res A**, 2017, 105(12): 3384-3391.

[83] OR C, CUI J, MATSUBARA J, et al. Pro-inflammatory and anti-angiogenic effects of bisphosphonates on human cultured retinal pigment epithelial cells[J]. **Br J Ophthalmol**, 2013, 97(8): 1074-1078.

[84] GONG C Y, YU Z Y, LU B, et al. Ethanol extract of Dendrobium chrysotoxum Lindl ameliorates diabetic

retinopathy and its mechanism[J]. **Vascular Pharmacol**, 2014, 62(3): 134-142.

[85] IYENGAR L, LOVICU F J. Aqueous humour-induced lens epithelial cell proliferation requires FGF-signalling[J]. **Growth Factors**, 2017, 35(4-5): 131-143.

[86] 褚俏梅, 李方都, 张树芬, 等. 糖尿病性白内障房水中细胞因子IGF-1、bFGF和IL-6的含量测定[J]. **眼科新进展**, 2010, 30(6): 531-533.
CHU Qiaomei, LI Fangdu, ZHANG Shufen, et al. Detection of IGF-1, bFGF and IL-6 levels in aqueous humor of diabetic cataract patients[J]. **Recent Advances in Ophthalmology**, 2010, 30(6): 531-533. (in Chinese)

[87] 甄　琪. 合并糖尿病的白内障患者房水细胞因子测定[J]. **内蒙古医学杂志**, 2020, 52(5): 521-526.
ZHEN Qi. Determination of aqueous cytokine in patients with diabetic cataract[J]. **Inner Mongolia Medical Journal**, 2020, 52(5): 521-526. (in Chinese)

[88] 陶津华, 安小玲, 孔　郡, 等. EGF 体外对人晶状体上皮细胞迁移的影响[J]. **国际眼科杂志**, 2006, 6(1): 68-71.
TAO Jinhua, AN Xiaoling, KONG Jun, et al. The effect of epidermal growth factor on human lens epithelial cells transference[J]. **International Eye Science**, 2006, 6(1): 68-71. (in Chinese)

[89] HUANG W R, FAN X X, TANG X. SiRNA targeting EGFR effectively prevents posterior capsular opacification after cataract surgery[J]. **Mol Vis**, 2011, 17: 2349-2355.

[90] ZHANG Y, HUANG W. Transforming growth factor β1 (TGF-β1)-stimulated integrin-linked kinase (ILK) regulates migration and epithelial-mesenchymal transition (EMT) of human lens epithelial cells via nuclear factor κB (NF-κB)[J]. **Med Sci Monit**, 2018, 24: 7424-7430.

[91] CHOI J, PARK S Y, JOO C K. Hepatocyte growth factor induces proliferation of lens epithelial cells through activation of ERK1/2 and JNK/SAPK[J]. **Invest Ophthalmol Vis Sci**, 2004, 45(8): 2696-2704.

[92] 宋德禄, 钟　勇. 转基因表达神经营养因子治疗视神经损伤的研究进展[J]. **中华眼科杂志**, 2008, 44(9): 858-861.
SONG Delu, ZHONG Yong. Research advancement of optic nerve injury therapy by transgenic expression neurotrophic factors[J]. **Chinese Journal of Ophthalmology**, 2008, 44(9): 858-861. (in Chinese)

[93] LV X M, LIU Y, WU F, et al. Human umbilical cord blood-derived stem cells and brain-derived neurotrophic factor protect injured optic nerve: viscoelasticity characterization[J]. **Neural Regen Res**, 2016, 11(4): 652.

[94] TIRASSA P, ROSSO P, IANNITELLI A. Ocular nerve growth factor (NGF) and NGF eye drop application as paradigms to investigate NGF neuroprotective and reparative actions[J]. **Methods Mol Biol**, 2018, 1727: 19-38.

[95] CARLETON L A, CHAKRAVARTHY R, VAN DER SLOOT A M, et al. Generation of rationally-designed nerve growth factor (NGF) variants with receptor specificity[J]. **Biochem Biophysl Res Commun**, 2018, 495(1): 700-705.

[96] 钱道卫, 刘金华, 杜秀娟, 等. 蛇毒神经生长因子对高眼压下兔视网膜髓鞘碱性蛋白的影响[J]. **眼科研究**, 2009, 27(1): 10-13.
QIAN Daowei, LIU Jinhua, DU Xiujuan, et al. The effects of venom nerve growth factor on myelin basic protein of retina in rabbits with elevated intraocular pressure[J]. **Chinese Ophthalmic Research**, 2009, 27(1): 10-13. (in Chinese)

[97] 周欢粉, 魏世辉. 神经生长因子对脱髓鞘性视神经炎小鼠视网膜神经组织保护作用的实验研究[J]. **中华眼视光学与视觉科学杂志**, 2010, 12(5): 329-334.
ZHOU Huanfen, WEI Shihui. Protective effects of nerve growth factor against retinal ganglion cell damage in demyelinated optic neuritis in mice[J]. **Chinese Journal of Optometry Ophthalmology and Visual Science**, 2010, 12(5): 329-334. (in Chinese)

[98] COLAFRANCESCO V, COASSIN M, ROSSI S, et al. Effect of eye NGF administration on two animal models of retinal ganglion cells degeneration[J]. **Ann Ist Super Sanita**, 2011, 47(3): 284-289.

[99] MESENTIER-LOURO L A, ROSSO P, CARITO V, et al. Nerve growth factor role on retinal ganglion cell survival and axon regrowth: effects of ocular administration in experimental model of optic nerve injury[J]. **Mol Neurobiol**, 2019, 56(2): 1056-1069.

[100] FINK D M, CONNOR A L, KELLEY P M, et al. Nerve growth factor regulates neurolymphatic remodeling during corneal inflammation and resolution[J/OL]. **PLoS One**, 2014, 9(11): e112737.

[101] LI H J, SUN Z L, YANG X T, et al. Exploring optic nerve axon regeneration[J]. **Curr Neuropharmacol**, 2017, 15(6): 861.

[102] KILIC U, KILIC E, DIETZ G P H, et al. The TAT protein transduction domain enhances the neuroprotective effect of glial-cell-line-derived neurotrophic factor after optic nerve transection[J]. **Neurodegener Dis**, 2004, 1(1): 44-49.

[103] LIU Y, GONG Z, LIU L, et al. Combined effect of olfactory ensheathing cell (OEC) transplantation and glial cell line-derived neurotrophic factor (GDNF) intravitreal injection on optic nerve injury in rats[J]. **Mol Vis**, 2010, 16: 2903-2910.

[104] VIGNESWARA V, BERRY M, LOGAN A, et al. Pigment epithelium-derived factor is retinal ganglion cell neuroprotective and axogenic after optic nerve crush injury[J]. **Invest Ophthalmol Vis Sci**, 2013, 54(4): 2624-2633.

[105] FRANK T, SCHLACHETZKI J C M, GÖRICKE B, et al. Both systemic and local application of granulocyte-colony stimulating factor (G-CSF) is neuroprotective after retinal ganglion cell axotomy[J]. **BMC Neurosci**, 2009, 10(1): 49.

[106] LIPTON S A, WAGNER J A, MADISON R D, et al. Acidic fibroblast growth factor enhances regeneration of processes by postnatal mammalian retinal ganglion cells in culture[J]. **Proc Natl Acad Sci U S A**, 1988, 85(7): 2388-2392.

[107] CUEVAS P, CARCELLER F, GIMÉNEZ-GALLEGO G. Acidic fibroblast growth factor prevents post-axotomy neuronal death of the newborn rat facial nerve[J]. **Neurosci Lett**, 1995, 197(3): 183-186.

[108] 周远沛, 刘苏冰, 聂晓丽, 等. bFGF对LASIK术后角膜知觉恢复和角膜神经修复的影响[J]. **眼科新进展**, 2014, 34(5): 454-458.
ZHOU Yuanpei, LIU Subing, NIE Xiaoli, et al. Effects of bFGF on corneal perception and nerve recovery after LASIK[J]. **Recent Advances in Ophthalmology**, 2014, 34(5): 454-458. (in Chinese)

[109] 李校堃, 胡爱莲, 郑远远, 等. 基因重组碱性成纤维细胞生长因子对大鼠视网膜神经节细胞的影响[J]. **中国病理生理杂志**, 2002, 18(2): 147-149.
LI Xiaokun, HU Ailian, ZHENG Yuanyuan, et al. Effects of recombinant basic fibroblast growth factor on retinal ganglion cells of rats[J]. **Chinese Journal of Pathophysiology**, 2002, 18(2): 147-149. (in Chinese)

[110] UENO H, HATTORI T, KUMAGAI Y, et al. Alterations in the corneal nerve and stem/progenitor cells in diabetes: preventive effects of insulin-like growth factor-1 treatment[J]. **Int J Endocrinol**, 2014, 2014: 312401.

[111] CHU Q, MORELAND R, YEW N S, et al. Systemic Insulin-like growth factor-1 reverses hypoalgesia and improves mobility in a mouse model of diabetic peripheral neuropathy[J]. **Mol Ther**, 2008, 16(8): 1400-1408.

[112] BRON A J, DE PAIVA C S, CHAUHAN S K, et al. TFOS DEWS Ⅱ pathophysiology report[J]. **Ocular Surf**, 2017, 15(3): 438-510.

[113] LOLLETT I V, GALOR A. Dry eye syndrome: developments and lifitegrast in perspective[J]. **Clin Ophthalmol**, 2018, 12: 125-139.

[114] ZHAO H, LI Q, YE M, et al. Tear luminex analysis in dry eye patients[J]. **Med Sci Monit**, 2018, 24: 7595-7602.

[115] 盛敏杰. 干眼的研究进展[J]. **同济大学学报(医学版)**, 2008, 29(4): 1-5.
SHENG Minjie. Research progress of dry eye[J]. **Journal of Tongji University (Medical Science)**, 2008, 29(4): 1-5. (in Chinese)

[116] 杨 春, 张延军, 孙士章. 干眼症患者泪液中EGF放射免疫分析的价值[J]. **实用医学杂志**, 2011, 27(20): 3666.
YANG Chun, ZHANG Yanjun, SUN Shizhang. The value of EGF radioimmunoassay in tears of patients with dry eye[J]. **The Journal of Practical Medicine**, 2011, 27(20): 3666. (in Chinese)

[117] MCCAULEY H A, LIU C Y, ATTIA A C, et al. TGFβ signaling inhibits goblet cell differentiation via SPDEF in conjunctival epithelium[J]. **Development**, 2014, 141(23): 4628-4639.

[118] LEE H K, LEE K S, KIM H C, et al. Nerve growth factor concentration and implications in photorefractive keratectomy vs laser *in situ* keratomileusis[J]. **Am J Ophthalmol**, 2005, 139(6): 965-971.

[119] LISI S, SISTO M, RIBATTI D, et al. Chronic inflammation enhances NGF-β/TrkA system expression via EGFR/MEK/ERK pathway activation in Sjögren's syndrome[J]. **J Mol Med**, 2014, 92(5): 523.

[120] WANG C, PENG Y, PAN S, et al. Effect of insulin-like growth factor-1 on corneal surface ultrastructure and nerve regeneration of rabbit eyes after laser *in situ* keratomileusis[J]. **Neurosci Lett**, 2014, 558: 169-174.

[121] 史德龙, 吴建峰, 李国平, 等. 生长因子在近视发病及发展中作用的研究进展[J]. **国际眼科杂志**, 2016, 16(7): 1273-1275.
SHI Delong, WU Jianfeng, LI Guoping, et al. Research progress of growth factors in the pathogenesis and developments of myopia[J]. **International Eye Science**, 2016, 16(7): 1273-1275. (in Chinese)

[122] 赵 雯, 吴建峰, 毕宏生. 碱性成纤维细胞生长因子与转化生长因子β在近视眼巩膜中作用的研究进展[J]. **中华眼视光学与视觉科学杂志**, 2013, 15(12): 765-768.
ZHAO Wen, WU Jianfeng, BI Hongsheng. Progress in research on basic fibroblast growth factor and transforming growth factor-β in the myopic sclera[J]. **Chinese Journal of Optometry Ophthalmology and Visual Science**, 2013, 15(12): 765-768.

[123] ABE M, YOKOYAMA Y, ISHIKAWA O. A possible mechanism of basic fibroblast growth factor-promoted scarless wound healing: the induction of myofibroblast apoptosis[J]. **Eur J Dermatol**, 2012, 22(1): 46-53.

[124] AN J, HSI E, ZHOU X, et al. The *FGF2* gene in a myopia animal model and human subjects[J]. **Mol Vis**, 2012, 18: 471-478.

[125] HSI E, CHEN K C, CHANG W S, et al. A functional polymorphism at the *FGF10* gene is associated with extreme myopia[J]. **Invest Ophthalmol Vis Sci**, 2013, 54(5): 3265-3271.
[126] BARATHI V A, WEON S R, BEUERMAN R W. Expression of muscarinic receptors in human and mouse sclera and their role in the regulation of scleral fibroblasts proliferation[J]. **Mol Vis**, 2009, 15: 1277-1293.
[127] MAO J F, LIU S Z, QIN W J, et al. Modulation of TGFβ2 and dopamine by PKC in retinal Müller cells of guinea pig myopic eye[J]. **Int J Ophthalmol**, 2011, 4(4): 357.
[128] MCBRIEN N A. Regulation of scleral metabolism in myopia and the role of transforming growth factor-beta[J]. **Exp Eye Res**, 2013, 114: 128-140.
[129] 张兰兰, 刘 琼, 于 健, 等. 转化生长因子-β(TGF-β)影响豚鼠巩膜成纤维细胞增殖和α-平滑肌肌动蛋白(α-SMA)表达的研究[J]. **眼科新进展**, 2016, 36(11): 1011-1015.
ZHANG Lanlan, LIU Qiong, YU Jian, et al. Effects of TGF-β on cellular proliferation and α-SMA expression in guinea pig scleral fibroblasts[J]. **Recent Advances in Ophthalmology**, 2016, 36(11): 1011-1015. (in Chinese)
[130] LIANG C L, HSU P Y, NGO C S, et al. HOXA9 is a novel myopia risk gene[J]. **BMC Ophthalmol**, 2019, 19(1): 28.
[131] ZIDAN H E, REZK N A, FOUDA S M, et al. Association of insulin-like growth factor-1 gene polymorphisms with different types of myopia in Egyptian patients[J]. **Genet Test Mol Biomarkers**, 2016, 20(6): 291-296.
[132] CHEN Y J, TSAI R K, WU W C, et al. Enhanced PKCδ and ERK signaling mediate cell migration of retinal pigment epithelial cells synergistically induced by HGF and EGF[J/OL]. **PLoS One**, 2012, 7(9): e44937.

[本文编辑 沈 敏 沈 洁]

·学术动态·

李浩洪教授团队合作成果揭示限时进食可以改善夜间过度嗜睡

白天过度嗜睡是肥胖的常见症状,初步研究表明白天嗜睡可以通过限时进食得到改善。然而相关神经机制目前仍不清楚。2022年10月16日,浙江大学脑与脑机融合前沿科学中心李浩洪教授及华中科技大学张珞颖教授合作在《国家科学评论》(*National Science Review*)在线发表题为“Time-restricted feeding is an intervention against excessive dark-phase sleepiness induced by obesogenic diet”的研究论文(DOI: 10.1093/nsr/nwac222),该研究表明限时进食是对致肥胖饮食引起的过度嗜睡的一种干预措施。

丘脑室旁核位于第三脑室下方,是大脑边缘系统的重要组成部分。丘脑室旁核不仅参与调控觉醒、摄食、奖赏及多种适应性行为,还与食物预期活动密切相关。该研究发现长期高脂饮食损害了丘脑室旁核神经元活性,其中包括降低了丘脑室旁核神经元的自身兴奋性,破坏其突触传递效能,重塑兴奋/抑制比等。值得注意的是,丘脑室旁核的失活足以使正常小鼠活跃期的清醒状态持续性降低,这类似于在高脂饮食诱导的肥胖小鼠中观察到的睡眠/觉醒改变。另外,增强丘脑室旁核神经元活性巩固了高脂饮食诱导的肥胖小鼠清醒状态的持续性。

限时进食作为一种流行的减肥方式,可以缓解肥胖小鼠的代谢异常,恢复外周组织中的时钟基因振荡,也可以改善肥胖诱导的睡眠–觉醒周期的紊乱,但其机制很大程度是未知的。该研究观察到,碎片化的觉醒可以通过限时进食消除和逆转。并验证了限时进食以进食持续时间依赖性的方式阻止了高脂饮食诱导的丘脑室旁核中突触传递的损伤。

总的来说,随机摄入高脂饮食会导致丘脑室旁核失活,引起夜间觉醒受损以及睡眠增加(小鼠的活跃相),而限时进食可以在不改变饮食结构甚至进食量的基础上预防和逆转高脂饮食引起的丘脑室旁核功能障碍和过度嗜睡。该研究在限时进食和神经活动之间建立了联系,并提出限时进食可以作为针对饮食/肥胖相关白天过度嗜睡的生活方式干预措施。

王旭博士为论文第一作者。研究受到了中国科技创新2030计划的资助。