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RPE细胞的正常功能及其在眼科疾病中的作用

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摘　要：视网膜色素上皮 (retinal pigment epithelium, RPE) 细胞在眼的发育和视觉功能中起着重要的作用，具有分泌生长因子、抗氧化、参与视循环代谢、维持血 - 视网膜屏障和吞噬视细胞脱落的外节盘膜等重要生理功能。RPE 细胞的正常结构和功能为视网膜感光细胞的正常发育及功能发挥所必需，若 RPE 细胞出现结构或功能异常则会导致视网膜感光细胞功能受损、视网膜退化等疾病。鉴于其重要性，就 RPE 细胞的发育、正常结构和功能进行综述，为其相关眼科疾病的治疗提供一定的依据。

关键词：视网膜病变；RPE；色素细胞；眼科
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The normal functions of RPE cell and its roles in eye disease

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Abstract: The retinal pigment epithelium (RPE) cells play important roles in eye development and visual functions. RPE cells have the functions of secreting growth factor, antioxidant, involving in metabolism of visual cycle, maintaining the blood-retinal barrier, phagocytosis of detached photoreceptor outer segments and other physiological functions. RPE normality is essential for photoreceptor development and normal functions, and defects in RPE cell structure or functions will cause photoreceptor dysfunction and retinal degeneration. Recent studies have revealed new insights into important roles of RPE cells in related eye diseases. In this viewpoint, we provide an overview of some of the current understanding of RPE normal structure and functions and their roles in the development of related eye diseases.

Key words: retinal degeneration; RPE; pigment cell; eye disease

视网膜色素上皮 (retinal pigment epithelium, RPE) 由胚胎视泡发育而来，位于视网膜神经上皮层和脉络膜之间[1]，具有多种复杂的生理生化功能，与眼的正常发育及部分眼科疾病的发生密切相关。RPE 细胞在眼内发挥作用时需要具备如下功能：屏障功能、吞噬功能、参与视循环代谢、抗氧化功能和分泌生长因子等[2]。

RPE 细胞在眼的正常发育、视网膜正常结构的维持和功能发挥中起着重要的作用，并且在多种眼科疾病中扮演重要的角色，因此，学者们对其结构和功能开展了大量的工作，也得到了不少创新性的发现。在此，将从以下八个方面对 RPE 的结构和功能进行论述。

1　RPE细胞的正常发育及其调控

在脊椎动物中，RPE 细胞由视泡发育分化而来。胚胎发育过程中，早期视泡细胞具有双向发育潜能，可发育为视网膜神经上皮层或 RPE 层[3]。这种双向潜能性与早期两个潜在区域所存在的基因调控有关。转录因子 MITF (microphthalmia-associated transcription factor) 被证实参与了 RPE 细胞的正常发育

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分化过程，早期视泡都表达 MITF，而在视杯阶段，视网膜神经上皮层不再表达 MITF，而 RPE 层则继续表达 MITF[4]。若 MITF 功能异常，可引起 RPE 转分化为视网膜神经上皮细胞 [5]，*Mitf* 基因敲除或突变小鼠由于 RPE 细胞不能正常发育，继而引起神经视网膜退行性病变和小眼畸形等 (图 1)。反之，外源性 MITF 的表达能诱导视网膜神经上皮细胞转分化成为 RPE 样细胞。

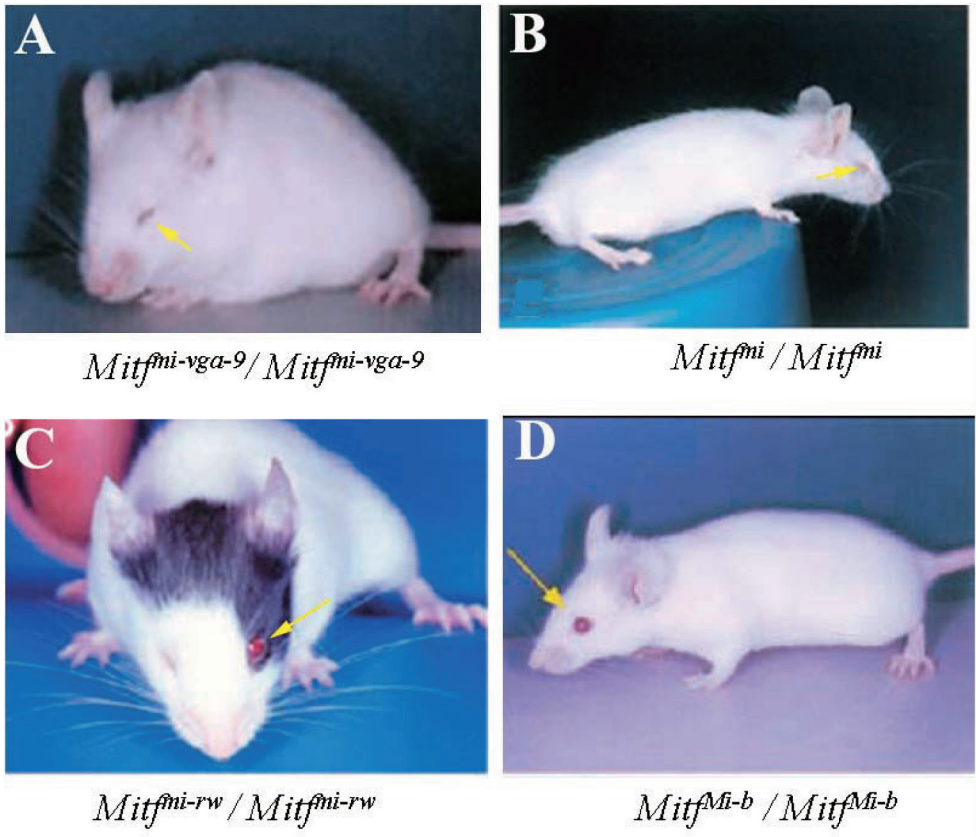
研究还证实其他转录因子或者信号通路分子同样参与了 RPE 细胞的正常发育分化的调控，如生长因子 FGF1 (fibroblast growth factor 1) 和 FGF2 可以上调转录因子 Chx10 (ceh-10 homeo domain containing homolog) 的表达，而 Chx10 则可以抑制 MITF 的表达，从而调控早期视泡细胞向神经视网膜发育分化 [8]。

通过基因敲除或基因突变小鼠研究还发现转录因子 OTX1 (orthodenticle homeobox 1) 和 OTX2 以及 Pax2 (paired box 2) 和 Pax6 也参与调控 RPE 细胞的正常发育。*Otx1*$^{-/-}$；*Otx2*$^{+/-}$ 小鼠眼中呈现不同程度的 RPE 细胞向神经视网膜细胞转分化现象 [9]。*Pax2*$^{-/-}$；*Pax6*$^{+/-}$ 小鼠 RPE 细胞则呈现 *Mitf*$^{-/-}$ 小鼠样变化，小鼠胚胎发育过程中所有视泡区域不表达 MITF，而表达神经视网膜细胞的标记分子。反之，如果利用转基因手段在视柄区域异位表达转录因子 Pax6，则可以诱导 MITF 的表达，使视柄区域分化形成 RPE 样细胞 [10]。

由此可见，RPE 细胞的正常发育是一个由转录因子、信号通路等复杂的细胞内网络途径所共同调控的发育生物学事件，RPE 细胞的正常发育与否直接影响眼的正常发育，与视网膜的正常结构和功能以及视觉功能的形成密切相关。

2　RPE细胞的正常结构

RPE 位于视网膜神经上皮层和脉络膜之间，排



A：*Mitf*$^{mi\text{-}vga9}$/*Mitf*$^{mi\text{-}vga9}$为*Mitf*基因敲除小鼠，该小鼠表现为全身白色和小眼畸形。B：*Mitf*^{mi}/*Mitf*^{mi}为*Mitf*基因功能区域发生一个3 bp碱基的缺失，该小鼠同样表现为白色和小眼畸形。C：*Mitf*$^{mi\text{-}rw}$/*Mitf*$^{mi\text{-}rw}$小鼠在*Mitf*基因启动子区域发生了一段大的缺失，该小鼠一只眼睛表现为小眼畸形，另一只眼睛大小正常，但是色素缺失。D：*Mitf*$^{Mi\text{-}b}$/*Mitf*$^{Mi\text{-}b}$小鼠MITF发生了一个G244E的点突变，该小鼠眼睛大小正常，但是色素缺失并且视网膜呈现退行性病变[6-7]。

图1　不同*Mitf*等位基因突变小鼠呈现不同程度的眼异常状态

列整齐，具有单层六边形结构[11]。RPE 细胞表面可向视锥视杆细胞层伸出微绒毛，这些微绒毛可以促进 RPE 细胞与神经视网膜层细胞之间的连接和物质转运[12]。RPE 细胞的侧膜之间是紧密的连接复合体结构，其基底膜则是一个复杂的内折状结构。RPE 细胞的这些结构为其极性的形成和屏障功能的发挥以及物质的运输起着关键性的作用[13-16]。RPE 细胞的这一生理功能异常被认为与相关眼科疾病的发生密切相关，如 RPE 细胞屏障功能异常则易导致 Best 卵黄样黄斑营养不良 (Best vitelliform macular dystrophy, BVMD)[17] 和成人卵黄样黄斑营养不良 (adult-onset vite-lliform macular dystrophy, AVMD)[18]。RPE 基底膜与 Bruch's membrane 之间的连接或功能异常被认为与年龄相关性黄斑变性 (age-related macular degeneration，AMD)[19-20] 和 Sorsby's 眼底营养不良[21] 的发生相关。

RPE 细胞的另一生理特点是其含有色素。鉴于眼结构的特殊性和正常的生理需要，神经视网膜是体内一类经常性暴露在光照下的神经组织，而与之相邻的 RPE 细胞层会为神经视网膜吸收和过滤光线。为了发挥此项功能，RPE 细胞具有吸收不同波长光线能力的色素。在 RPE 细胞中存在黑色素和脂褐素，它们可以吸收不同波长的光源，进而保护神经视网膜[22-24]。RPE 细胞中的黑色素小体与细胞的抗氧化能力相关，实验证实其参与了细胞清除氧自由基的生理过程，并具有螯合细胞内金属离子的能力[25]。如果人眼内色素水平异常，则会引起一系列的眼科疾病，如视神经异常、眼球震颤、视力减退、夜盲等等[26]。

3 RPE细胞的分泌功能

RPE 细胞的重要生理功能之一是通过分泌生长因子来影响神经视网膜细胞及其自身的生理特性，这其中包括为视网膜感光细胞提供营养、促进感光细胞的存活和维持视网膜的结构完整性等[3, 27-28]。RPE 细胞能够合成、分泌多种生长因子，有的参与 RPE 细胞自身的功能调节，有的则与某些眼科疾病的发生相关[29-30]，如研究发现，在 AMD、增殖性糖尿病视网膜病变 (proliferative diabetic retinopathy，PDR) 和青光眼的患者眼中 PEDF 的水平显著下降，VEGF 的异常高表达也被证实与 PDR 等眼科疾病的发生相关[31-39]。利用 PEDF 缺陷性小鼠研究发现，该小鼠更为容易导致视网膜血管扩张和新生血管生成[40]。

除了分泌生长因子，RPE 细胞还可以分泌其他物质，如红细胞生成素 (erythropoietin, EPO)。研究证实，EPO 及其受体 EPOR 表达于 RPE 细胞，并且具有增强细胞的抗氧化损伤、抗细胞凋亡能力，以及促进细胞生存、增殖的能力。研究提示 EPO 的表达异常可能与 PDR 及 AMD 等眼科疾病的发生密切相关[41-45]。

4 RPE细胞的抗氧化功能

由于光氧化等生理作用的存在，使得 RPE 细胞长期存在于一种高氧自由基的环境中，所以，RPE 细胞的一个重要功能就是抗氧化性，消除氧自由基。目前的研究已经发现 RPE 细胞中存在着高含量的抗氧化酶，如 SOD (superoxide dismutase) 和 Catalase[46-47]；此外还有一系列的非酶类物质，如类胡萝卜素物质、谷胱甘肽和色素等物质[23-24]。PDR 和 AMD 等眼科疾病通常被认为与 RPE 细胞的抗氧化功能下降有关[48-50]。

目前对于 RPE 细胞抗氧化能力的研究已有不少报道。2006 年，Glotin 等[51] 研究发现，ERK 信号通路参与了 RPE 细胞抗氧化能力的调控；2007 年，Alcazar 等[52] 研究证实功能基因 MMP-14 和 TIMP-2 能加强 RPE 细胞的抗氧化能力；2011 年，Lin 等[53] 研究报道 miR-23 在 RPE 细胞的氧化损伤中起调控作用；2013 年，Patel 和 Hackam[54] 研究表明，Toll-like receptor 3 (TLR3) 具有保护 RPE 细胞氧化损伤的功能。由此可见，RPE 细胞抗氧化功能同样是一个受细胞内复杂的信号网络共同调控而实现的重要的细胞生物学事件。

5 RPE细胞的吞噬功能与屏障功能

RPE 对光感受器外节脱落细胞碎片的吞噬消化对于维持视网膜正常生理结构与功能具有重要作用[55-56]。在病程较长的糖尿病患者中，发现其 RPE 吞噬功能呈现异常状态，继而伴随糖尿病性视网膜疾病的发生[57]。通过研究，目前已经证实有多种 RPE 细胞膜受体参与了 RPE 细胞的吞噬功能调节，如 IGF2R (insulin-like growth factor 2 receptor)[58]、CD36 (thrombospondin receptor)[59-60]、αVβ5 integrin[61] 以及其他的功能基因，如 MERTK(c-mer proto-oncogene tyrosine kinase)[62]、ARMS2 (age-related maculopathy susceptibility 2)[63]。如果这些基因突变或功能异常，影响 RPE 细胞的正常吞噬功能，则可引起不同程度的眼科疾病，如 MERTK 基因突变可导致视网膜营养不良和遗传性视网膜变性等眼科疾病[64-65]。

RPE 细胞在视网膜中起重要的屏障作用，是血 - 视网膜屏障的重要组成部分 [66-70]，在脉络膜和视网膜细胞之间的营养物质、水、电解质等的转运中起着非常关键的作用。RPE 细胞可从血液中吸收葡萄糖、视黄醇等营养物质并将其转运至视网膜感光细胞。同时，RPE 细胞的屏障功能还具有维持视网膜 Na^+-K^+ 平衡等生理功能。研究证实，多种细胞分子参与了对 RPE 细胞屏障功能的调控，如 GLUT1 (glucose transporter 1) 和 GLUT3 可以调控葡萄糖的转运 [71-73]，NPD1 (neuroprotectin D1) 参与了 RPE 细胞中 DHA 的运输 [74-75]。这些基因发生突变或者功能异常将可导致相关的眼科异常，如研究发现 *Glut1* 基因敲除小鼠表现为眼血管生成异常 [76]。

6　RPE细胞的视循环功能

眼因为视循环的存在而能够看得见物体，而视循环是一个复杂的细胞内代谢过程。研究已证实，RPE 细胞中的关键基因，如 RPE65[77-78]、IRBP (inter-photoreceptor retinol binding protein)[79-80]、RDH (retinol dehydrogenases)[81-82]、LRAT (lecithin:retinol acyl transferase)[83]、CRALBP (cellular retinaldehyde binding protein)[84]、RGR (RPE-retinal G protein receptor)[85] 等基因参与了视循环代谢并起重要的作用。如果视循环功能异常或视循环通路中相关基因突变可导致相关眼科疾病的发生，如 RPE65 或 LRAT 基因突变可导致 Leber 氏先天性黑蒙 (leber congenital amaurosis)[86-88]，RDH5 和 CRALBP 基因突变或功能异常可导致视网膜营养性萎缩 [89-91]。

7　RPE细胞的增殖和迁移

在正常情况下，成熟的 RPE 细胞在体内是一种单层的，处于相对静止状态的细胞。但是在某些病理状态下，如在 PVR (proliferative vitreoretinopathy, 增生性玻璃体视网膜病变)、视网膜脱离患者中，RPE 细胞可发生异常的增殖与迁移，进而导致患者的视力受损 [92]。目前 RPE 细胞异常增殖相关的眼科疾病在发达国家尤其是在视网膜手术患者人群中发病率较高，也越来越受到学者的关注。研究证实，RPE 细胞层与神经视网膜层脱离之后，RPE 细胞可进入玻璃体腔，发生上皮间质细胞转化 (epithelial-mesenchymal transitions, EMT) 之后开始异常增殖 [93-94]。不少学者对 RPE 细胞增殖调控中的分子机制进行了研究。2007 年，Li 等 [92] 在细胞生物学水平研究证实了生长因子 PDGF 可以影响 RPE 细胞的增殖。2009 年，Liu 等 [95] 利用 siRNA 技术和 *Zeb1*$^{+/-}$ 小鼠研究发现，Zeb1 可以调控转录因子 MITF 的表达进而影响 RPE 细胞的增殖调控。2009 年，Tsukiji 等 [96] 在鸡胚 RPE 细胞中研究发现如果在 RPE 细胞中过表达显性负性的 MITF 突变体则可以显著地提高 RPE 细胞的增殖率。2010 年，Schouwey 等 [97] 利用转基因小鼠证实 Notch 信号通路可以影响 RPE 细胞的增殖。关于 MITF 在 RPE 细胞中的生物学功能，本课题组也开展了相关的研究，实验结果提示，MITF 通过调控生长因子 PEDF 的表达，进而抑制 RPE 细胞的迁移 [98]。由此可见，RPE 细胞增殖与迁移的调控机制是一个由多种转录因子、信号通路和生长因子共同参与调控的复杂的过程。

8　RPE细胞与高度近视

高度近视是指近视度数在 -6D 以上，眼轴长度大于等于 26 mm 的屈光不正性眼科疾病。该类疾病的发病率呈逐年增加趋势，严重者可导致失明。基于最新的研究结果，RPE 细胞还被认为可能与高度近视的发生相关。在 RPE 细胞色素缺失的白化患者群中，高度近视的比率显著高于正常人群 [99]。

2011 年，Shi 等 [100] 通过外显子测序研究发现，ZNF644 (zinc finger protein 644 isoform 1) 基因突变与高度近视的发生存在相关性。通过后续实验，他们证实了 ZNF644 表达于 RPE 细胞中，并提示可能在 RPE 细胞中调控其他基因的表达。此外，Shi 等 [101] 还采用 GWAS (genome-wide association study) 技术研究发现，人类染色体 13q12.12 区域多态性可能与高度近视的发生相关。通过后续分析，他们明确了这段区域包含 MIPEP (mitochondrial intermediate peptidase)、C1QTNF9B-AS1 和 C1QTNF9B (C1q and tumor necrosis factor related protein 9B) 三个基因，同时，他们进一步明确了 MIPEP 和 C1QTNF9B 在 RPE 细胞中表达。这些研究结果提示了 RPE 细胞中相关基因的表达或者功能异常可能与高度近视的发生相关。但是，这一科学结论还有待于后续更多的实验数据予以支持并证明。

9　小结

目前的研究证实，RPE 是一种具有重要功能且与多种眼科疾病密切相关的色素细胞。RPE 细胞的结构或者功能异常可引起视网膜病变、视觉功能异常，严重者可致盲。但是，对 RPE 细胞的生物学

功能及其调控机制尚不完全清楚。有望通过继续深入进行相关方面的研究，全面认识RPE细胞的功能及其调控机制，为最终克服RPE细胞相关的眼科疾病起积极的推动作用。

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