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Eph家族受体在机体生理和病理过程中作用机制的研究进展

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摘　要

促红细胞生成素肝细胞激酶(Erythropoietin-producing hepatocellular, Eph)受体家族作为目前已知最大的酪氨酸激酶受体家族，通过受体－配体结合，介导人类从胚胎发育到成人组织稳态诸多生物学功能的调节，参与机体各种免疫反应。研究发现，Eph受体在包括神经系统发育、细胞迁移、血管形成等许多生理发育过程中起重要作用，在调节免疫反应、肿瘤、炎症、损伤修复等病理过程中也发挥着重要功能。进一步深入的研究Eph家族受体的生物学功能能够更好的对临床疾病进行预防、诊断和治疗，了解调控Eph表达的转录和转录后机制在生物学上具有深远的意义。本篇综述通过从Eph受体家族参与神经发育调节、血管形成、介导免疫反应等方面探讨其在机体生理和病理中的作用机制，总结其在不同机体反应中的作用规律，对临床疾病的诊断、治疗等进一步提供新思路。

关键词

促红细胞生成素肝细胞激酶受体，免疫炎症反应，血管生成，损伤修复，神经发育

Research Progress on the Mechanism of Action of Eph Family Receptors in Physiological and Pathological Processes of the Body

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Abstract

The Erythropoietin-producing hepatocellular kinase receptor family, as the largest tyrosine kinase receptor family known to date, mediates the regulation of many biological functions from embryonic development to adult tissue homeostasis and participates in a variety of immune responses through receptor-ligand binding. It has been found that Eph receptors play important roles in many physiological developmental processes, including nervous system development, cell migration, and blood vessel formation, as well as in the regulation of immune responses, tumors, inflammation, and damage repair. Further in-depth study of the biological functions of the Eph family of receptors can lead to better prevention, diagnosis and treatment of clinical diseases, and understanding the transcriptional and post-transcriptional mechanisms that regulate the expression of Eph has far-reaching significance in biology. In this review, we explore the mechanism of Eph receptors in the physiology and pathology of the body from the aspects of their participation in neurodevelopmental regulation, angiogenesis, and mediation of immune response, and summarize the rules of their roles in different body responses, which will further provide new ideas for the diagnosis and treatment of clinical diseases.

Keywords

Erythropoietin-Producing Hepatocellular, Immune-Inflammatory Response, Angiogenesis, Damage Repair, Neurodevelopment

1. Eph 受体结构与分类

Eph 受体家族作为酪氨酸激酶受体家族中的一员，是机体生长发育和维持组织生理功能的关键介质[1]。1987 年，Hirai 等人[2]用病毒癌基因 *v-fps* 的酪氨酸激酶区序列为探针，发现在产生人促红细胞生成素肝细胞癌细胞中呈现高表达的基因片段，将其命名为 Eph，这是人类首次发现的 Eph 家族受体。其 Ephrin 配体是调节细胞间通讯的膜锚定分子，Eph 受体通过与邻近细胞表面的 Ephrin 配体蛋白相互作用触发 Eph 受体激酶依赖性信号转导发挥其生物学作用[3]。

Eph 受体是一种 I 型跨膜蛋白，其胞外结构域包括 N 端含有免疫球蛋白样基序的球状配体结合结构域(Glb)、富含半胱氨酸的结构域和两个 III 型纤维连接蛋白重复序列，是与配体结合的关键结构域，其空间构型决定了受体与配体的结合特性及亚族特异性。其胞内区包括酪氨酸激酶活性结构域、SAM 结构域以及 C 端的 PDZ 结构域结合序列[4] [5]。

Eph 受体根据其同源性及与配体结合特性的不同，可以分为 Eph A 受体和 Eph B 受体[6]。目前已知有 14 种受体在人体内表达：9 种 Eph A 受体(Eph A1~A8 和 Eph A10)和 5 种 Eph B 受体(Eph B1~B4 和 Eph B6)。Eph 受体的配体称为 Ephrin，根据胞外配体结合域内的序列差异分为 EphrinA 和 Ephri nB，包括 6 个糖基磷脂酰肌醇(GPI)连接的 Ephrin A 配体(A1~A6)和 3 个单通道跨膜连接的 Ephrin B 配体(B1~B3) [7] [8]。

2. Eph 家族受体与机体生理病理

2.1. 介导免疫炎症反应

免疫系统是机体抵抗外界病原体入侵的重要防线。正常免疫状态下，病原体入侵时，机体可以通过免疫激活，促进模式识别受体直接识别和结合病原体相关分子模式，分泌各种炎症因子，募集免疫细胞至炎症部位，进而使免疫细胞活化、迁移、粘附和增殖，迅速调动固有和适应性免疫应答来发挥强有力的免疫功能。

Eph 受体是免疫系统中的重要角色，在调节免疫细胞的发育、转运和激活过程中发挥着多重作用[9]。Eph 受体广泛表达于单核细胞、巨噬细胞、树突状细胞、T 淋巴细胞和 B 淋巴细胞等多种免疫细胞中[10] [11]。例如，Eph 可以促进 B 细胞的活化[12]，参与单核细胞转化的多个步骤，包括趋化、粘附和迁移[13] [14]。这些提示 Eph 受体具有免疫调节特性。

在炎症早期，Eph A2 受体和 Ephrin B2 在内皮细胞和上皮细胞中过表达，导致细胞表面粘附分子表达和细胞内细胞骨架重组，导致细胞排斥和内皮细胞和上皮屏障的破坏。炎症后期，白细胞和内皮细胞上 Eph A1、Eph A3、Eph B3 和 Eph B4 的表达减少，从而促进了白细胞与内皮细胞的粘附[15]。

Eph 在胸腺中广泛表达，胸腺组织和 T 淋巴细胞在胸腺微环境中的运输和成熟受 Eph/Ephrin 信号转导通路调节，Eph/Ephrin 信号传导之间的平衡对 T 淋巴细胞的发育起着非常重要的作用[16]。在胸腺器官培养中，干扰 Eph/Ephrin 与 Eph 或 Ephrin FC 融合蛋白的相互作用会影响胸腺细胞的存活和成熟，Eph A-Fc 融合蛋白阻断 Eph/Ephrin 信号转导会降低胸腺细胞 $CD4^+$、$CD8^+$的数量[11] [17] [18]。Eph A 和 Ephrin A 蛋白通过调节整合素来调节粘附，Eph A 和 Ephrin A 蛋白之间的激活平衡决定了 T 淋巴细胞与其他细胞相互作用的强度和周期，对 T 淋巴细胞的功能有着显著的影响[19]。另外，Eph B/Ephrin B 信号传导还会在 T 淋巴细胞激活过程中提供负反馈：Ephrin B1 和 Ephrin B2 在低浓度时共刺激 T 淋巴细胞，而在高浓度时共同抑制 T 淋巴细胞活化[10]。

综上所述，Eph 受体家族对免疫器官的发育、机体免疫功能的调节起着十分重要的作用。

2.2. 损伤修复

组织损伤及修复是一个有序的过程，包括诱导以下过程：急性炎症过程；细胞再生；实质和结缔组织细胞的迁移和增殖；组织重塑[20]。组织损伤后，立即出现急性炎症反应。炎症的特点是炎症细胞向感染或组织损伤部位移动。

Eph 家族成员通过信号调节对组织损伤进行适当的修复，启动炎症反应，加速伤口愈合。Eph 最初被发现在鱼类、两栖动物、啮齿动物和人类的视神经、脊髓和大脑损伤后重新表达[21]，在损伤(特别是创伤愈合)过程中发挥重要作用，是促进生理性创伤修复的重要信号分子[15] [22] [23]。在脂多糖诱导的肺损伤中，Eph A2-Ephrin A1 表达上调。Eph A2 激活的阻断会导致信号通路受阻、炎症细胞的招募和细胞因子的产生减少。Eph A2 拮抗可抑制磷酸肌醇 3-激酶-Akt 通路，Eph A2 拮抗降低 NF-κB 的表达和细胞因子的产生，从而减轻炎症反应。EPhrin A1 能够刺激 MCP-1 和 CXCL1 等促炎因子分泌，从而完成损伤修复[24]。

Nihal Kaplan 等人[25]的体外划伤创面愈合试验发现，Eph 在皮肤损伤后表达增加，促进皮肤修复。Eph A2 敲除会导致手术后真皮内胶原密度增加，造成疤痕形态的损伤和改变[26]。Ephrin B1 的敲除使皮肤损伤后粘附蛋白持续减少和上皮细胞松动丢失。

上述诸多研究足以证实 Eph 家族受体在机体组织遭受损伤后通过多种方式参与组织损伤的修复，在促进损伤修复愈合过程中发挥着重要作用。

2.3. 血管

血管生成，即从现有的血管系统中形成新的血管，是一个涉及多种分子信号组合的多步骤过程：这些因素包括刺激内皮细胞增殖、迁移，以及血管周围细胞的招募和细胞外基质重塑[11]。

Eph 受体通过 Ephrin 配体介导血管生成的关键步骤，包括近端细胞－细胞接触、细胞与细胞外基质的粘附和细胞迁移[27]。Eph 在炎症中对血管通透性的调节也具有重要的作用，例如，Eph A1、Eph A2、Eph A5、Eph A6 以及在少量 Eph A3 和 Eph A4，Ephrin A1、Ephrin A2 和 Ephrin A5 都被发现在肺血管系统中有所表达，其中 Ephrin A1 配体对 Eph A2 受体的激活对改变体内肺血管通透性起主要作用[9] [28] [29]。Eph A1 在炎症晚期的淋巴细胞和血管内皮细胞中表达降低，引起淋巴细胞和内皮细胞之间的黏附性提高，导致淋巴细胞外渗和组织迁移。

在血管发育过程中，Eph/Ephrin 信号转导通路系统通过调节内皮细胞及其支持壁细胞(包括周细胞和血管平滑肌细胞)来控制血管的生长、重塑和稳定。Eph 受体或 Ephrin 配体敲除会导致的心脏和血管缺陷[30] [31] [32] [33]。在内皮细胞中，Eph A2、Ephrin A1 与血管内皮生长因子(VEGF)相互作用来实现对血管生成和血管通透性的调控。还有 Eph B4/Ephrin B2 等其他 Eph 家族成员，也在成人心血管系统中发挥关键作用[34]。血管平滑肌细胞中表达的 Eph B6 和 Ephrin B1 可以通过收缩、舒张血管促进血压调节[35]。

2.4. 肿瘤

Eph 受体在肿瘤中异常表达，可以通过双向信号和与其他信号系统的相互作用显著影响恶性肿瘤[36] [37]。Eph 的表达可以在癌症进展过程中由于染色体扩增或丢失、致癌信号通路、启动子甲基化和 microRNAs 的转录调控而增加或减少[38] [39]。

Eph A2 和 Eph B4 是肿瘤中最广泛过表达的 Eph 受体，下调它们的表达通常会抑制致瘤性，支持其在恶性肿瘤中的作用。肿瘤细胞中 Eph 受体的高表达往往与低酪氨酸磷酸化相关，这表明 Eph 的致癌活性与 Eph 正向信号抑制恶性肿瘤有关[36]。迄今为止发现的许多癌症中 Eph 过表达影响其与 Ephrin 结合力或激酶活性[40] [41]。Eph 受体还有促进机体耐药的作用。例如，肿瘤异种移植研究表明，在乳腺癌中，Eph A2 可促进对抗他莫西芬和人表皮生长因子受体 2 (HER-2)靶向治疗的耐药性，而 Ephrin B2 可促进对胶质母细胞瘤抗 VEGF 治疗的耐药性。细胞培养研究表明 Ephrin B3 在肺癌细胞对电离辐射的耐药性中起作用[42] [43] [44]。

随着 Eph 受体家族在肿瘤中作用机制研究的不断深入，人们对于 Eph 家族受体有了更充分的认识，能够对肿瘤更及时的进行诊断，从而制定更加精准的诊疗方案。

2.5. 神经系统

神经元形成复杂的网络，电信号通过突触的特殊连接从轴突传输到树突过程。突触前末端释放的神经递质响应电信号，激活突触后离子通道受体，在突触后神经元中启动新的电信号和化学信号。神经过程的网络是嵌套在周围的胶质细胞，调节许多性质的神经元，包括他们的形成突触的能力。Eph 受体在神经系统中的活性已被广泛研究。它们通过引导轴突到适当的目标和调节突触连接的形成，在神经元连接的建立中发挥着重要作用。Eph/Ephrin 信号传导通路对神经元之间、神经元和神经胶质细胞之间的信号交流起着重要作用[45]。

Eph 受体神经系统发育过程中高度表达，调节细胞间的短距离通信、细胞群的空间组织、组织模式、轴突引导和突触连接的形成[46] [47]。Eph 受体能够神经发生和神经元迁移：调节神经管闭合、自我更新和分化、扩散、粘附，还有神经祖细胞凋亡[48] [49] [50] [51]。轴突引导：Eph-Ephrin 信号转导通路能够调节轴突生长锥，驱动生长锥内肌动蛋白动力学的区域差异，导致局部生长锥转动，从而发挥轴突引导

功能。突触形成：Eph/Ephrin 信号转导通路对于树突分枝模式和突触位置具有调节作用。在神经肌肉系统中，突触的形成涉及高度活跃的突触后树突状丝状伪足与到达的轴突在“细胞握手”中相互作用。这一过程依赖于 Eph B 受体上调丝状伪足的活性[52] [53]。Eph A7 通过 Src 激酶和 mTOR (哺乳动物雷帕霉素靶蛋白)调节因子 Tsc-1 (结节性硬化-1)来控制突触的前体——树突状轴和棘的空间结构。Eph A7 过表达导致树突分支减少，同理，Eph A7 缺失导致树突分支增加，突触功能增强[54]。

许多 Eph 受体在创伤或缺血性神经系统损伤后上调，并对轴突发育和其他修复过程产生调节作用[55]。研究表明，在啮齿动物脊髓损伤模型中，药理抑制 Eph A4-Ephrin 结合或 Eph A4 基因敲除会影响神经功能的恢复进程[55]。此外，在缺乏轴突生长抑制剂 Nogo-A 的小鼠中，上调 Eph A4 及其配体 Ephrin A3 可限制受损脊髓轴突的再生能力[56]。这些抗再生作用不仅依赖于神经元 Eph A4 与 Ephrin A3/Ephrin B3 相互作用抑制轴突生长，还依赖 Eph A4 促进反应性胶质细胞增生[57]。Hoecke 等人[58]在 Eph A4 敲除小鼠实验中发现，Eph A4 缺陷小鼠的再神经支配能力较正常小鼠强，提示 Eph A4 能够抑制运动神经轴切后的肌肉再神经支配。因此，抑制 Eph A4 等受体，可能有助于促进受损神经系统的再生和功能恢复。

2.6. 其他生物学功能

Eph 受体被发现在表皮、毛囊、皮脂腺和底层真皮中表达，其影响毛囊再生和表皮伤口。Eph A2 参与未分化角质形成细胞控制表皮的分化和动态平衡的过程。许多 Eph 受体的表达银屑病、牛皮鲜等皮肤疾病中有所改变[59] [60]。Ephrin A3 的丢失导致雄激素性脱发[61]。因此，Eph/Ephrin 信号转导系统可能是对抗衰老、脱发的一个新靶点。

Eph 受体调节骨的稳态和重塑，在体节形成、颅面发育和肢体发育中发挥作用。在成年小鼠中，Eph-Ephrin 信号转导通路通过平衡成骨的成骨细胞和骨吸收的破骨细胞控制骨稳态。研究表明，Ephrin B2 逆转信号通路抑制破骨细胞分化，选择性敲除 Ephrin B2 可在体外更有效地形成破骨细胞[62]。破骨细胞前体中编码 Ephrin B1 基因的靶向缺失会导致破骨细胞数量和骨吸收增加导致骨体积减少[63]。

Eph 受体能够控制葡萄糖稳态。当葡萄糖水平较低时，Eph A 抑制胰腺 β 细胞的胰岛素分泌，而 Ephrin A5 在葡萄糖水平升高时促进胰岛素分泌[46]。Eph A 受体在下丘脑葡萄糖感应区域起协助作用，促进激素的释放，以纠正低血糖[64]。小鼠临床研究发现，药物性抑制 Eph 激酶可以增强葡萄糖刺激的胰岛素分泌，提示其在糖尿病治疗中的潜在应用价值[65]。

3. 展望

Eph/Ephrin 信号转导通路参与相同和不同细胞生物体之间的诸多生理、病理反应。同类 Eph 或 Ephrin，绝大多数具有相似的结合亲和力，但它们在不同个体之间的作用机制和功能也有着很大的差异。目前对于 Eph/Ephrin 信号通路在疾病中作用的研究虽有所突破，但仍缺乏详细的解释。因此，进一步的研究 Eph 信号转导通路在生理、病理条件下的作用机制是必要的。这将让人们更加深入的认识 Eph 家族受体的生物学特性，为癌症、脊髓损伤和神经退行性等疾病的新疗法开辟可能性，为生物过程中的参与提供了丰富的治疗机会，在生理学、疾病发病机制和潜在治疗方面提供新的视角。

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