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综 述

# 前列腺素E2受体EP4在心血管疾病中的作用

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**摘 要**：前列腺素E2 (prostaglandin E2, PGE2)是花生四烯酸的代谢产物，作为一种重要的活性脂质介质，在多种生命活动中发挥重要作用。PGE2通过4种G蛋白耦联受体发挥其功能，包括EP1、EP2、EP3和EP4。其中，EP4广泛表达于人体多种器官和组织中。大量研究显示，EP4在心血管稳态调节和重大心血管疾病发生中具有重要作用，但其具体功能和机制尚不明确。本文从炎症调控的角度，分析和总结EP4与心血管功能调节和重大心血管疾病的关系。

**关键词**：前列腺素E2；EP4；信号转导；炎症；心血管疾病
**中图分类号**：R363；R363.1

## Role of prostaglandin E2 receptor 4 in cardiovascular diseases

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**Abstract:** Prostaglandin E2 (PGE2) is a cyclooxygenase metabolite of arachidonic acid. It acts as a bioactive lipid and plays an important role in regulating many biological processes. PGE2 binds to 4 different G protein-coupled receptors including prostaglandin E2 receptor subtypes EP1, EP2, EP3 and EP4. The EP4 receptor is widely expressed in most of human organs and tissues. Increasing evidence demonstrates that EP4 is essential for cardiovascular homeostasis and participates in the pathogenesis of many cardiovascular diseases. Here we summarize the role of EP4 in the regulation of cardiovascular function and discuss potential mechanisms by which EP4 is involved in the development of cardiovascular disorders with a focus on its effect on inflammation.

**Key words:** prostaglandin E2; EP4; signal transduction; inflammation; cardiovascular disease

## 1 引言

前列腺素 E2 (prostaglandin E2, PGE2) 由花生四烯酸经环氧合酶 (cyclooxygenases, COXs) 催化而成，在体内通过四种 G 蛋白耦联受体 ( 即 EP1~4) 发挥调控机体生理和病理过程的作用 [1] ( 图 1)。研究表明，EP4 广泛分布于肺血管、肾动脉的中膜、阴茎海绵体、颈动脉粥样硬化斑块、腹主动脉动脉瘤、角膜内皮和基质细胞、肾小球、睫状体上皮以及牙龈纤维母细胞等组织和细胞内 [2]。虽然 EP4 可与多种前列腺素类似物相结合，但其与 PGE2 的亲和力最高 [3]，故 EP4 的功能与 PGE2 的生物效应密切相关，其被激活时可解除平滑肌及相关组织的收缩状态，故称为舒张型前列腺素受体 [4]。人和动物 EP4 的氨基酸序列高度同源 ( 同源性 88%) [3]，尽管人和动物之间存在种系差异，但是根据现有的大量动物研究也能分析和总结出 EP4 的生物学功能和作用机制，并对人类疾病的生理和病理过程有指导意义 [5]。本文将分别从 EP4 信号转导通路及其与心血管疾病发生的关系角度对 EP4 的研究进展作一简要综述。

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## 2 EP4的信号转导通路

### 2.1 EP4的G蛋白激活通路

PGE2有四种G蛋白耦联受体，G蛋白含有α、β、γ亚基，α亚基又包含了Gs蛋白、Gi蛋白、Gq蛋白和G12蛋白四种不同亚型[6]。每个受体相耦联的G蛋白有较大差异。其中，EP1主要与Gq蛋白耦联，升高胞内钙离子水平，EP3则主要与Gi蛋白耦联，降低cAMP水平[7, 8]；EP2和EP4两种受体尽管都主要与Gs蛋白耦联，使胞内cAMP水平升高[8]，但它们的作用并不完全一致，因为EP4与Gs蛋白耦联后激活cAMP的能力要低于EP2[9]。亦有研究表明，EP4还可耦联Gi蛋白以抑制腺苷酸环化酶(adenyl cyclase, AC)/cAMP通路[10]。Gs蛋白激活AC，升高细胞内cAMP浓度，进而激活蛋白激酶A (protein kinase A, PKA)[11]，最终激活cAMP反应元件结合蛋白(cAMP response element binding protein, CREB)，使得c-fos蛋白、生长抑素(somatostatin)、促肾上腺皮质素释放激素(corticotropin-releasing hormone, CRH)等合成增多，以发挥调控细胞增殖、分化，以及血管生成(angiogenesis)的功能[12]。若激活cAMP/Epac (exchange protein activated by cAMP)通路，可使Rap1蛋白变为有活性的Rap1 GTP蛋白，报道显示EP4可经Epac通路调控动脉导管平滑肌细胞的迁移[6]。当G蛋白自身解离时，Gβγ复合物作为信号分子也能调控包括钾离子通道、钙离子通道、磷脂酶C (phospholipase C, PLC)以及AC在内的G蛋白通路[13]。当G蛋白与EP4相解离后，G蛋白耦联受体激酶(G protein-coupled receptor kinases, GRKs)将磷酸化EP4的胞内结构域并抑制其与G蛋白结合。EP4磷酸化后将与β-arrestin相结合，β-arrestin 1/c-Src通路在结直肠癌转移中发挥重要作用[6, 14]。研究表明，激活血管平滑肌细胞的EP4可抑制细胞增殖和血管再狭窄的发生[15] (图2)。

### 2.2 EP4的PI3K激活通路

Gβγ复合物可介导EP4对磷脂酰肌醇3激酶(phosphatidylinositol 3-kinase, PI3K)的激活[6, 16]，其通路可抑制PKA活化，同时激活蛋白激酶B (protein kinase B，PKB，又称AKT)，通过CREB发挥其生物学功能[17]。有报道表明，EP4敲除可抑制PI3K/AKT通路、降低Bad磷酸化，增加巨噬细胞凋亡，并显著抑制早期动脉粥样硬化斑块的形成[18]。若经PI3K/Akt通路激活糖原合成酶激酶-3β (glycogen synthase kinase 3β, GSK-3β)/β-catenin通路则可调控细胞的增殖、分化以及凋亡[19]。同时，EP4可经由PI3K/AKT/mTOR通路调控肿瘤细胞的迁移[20]。

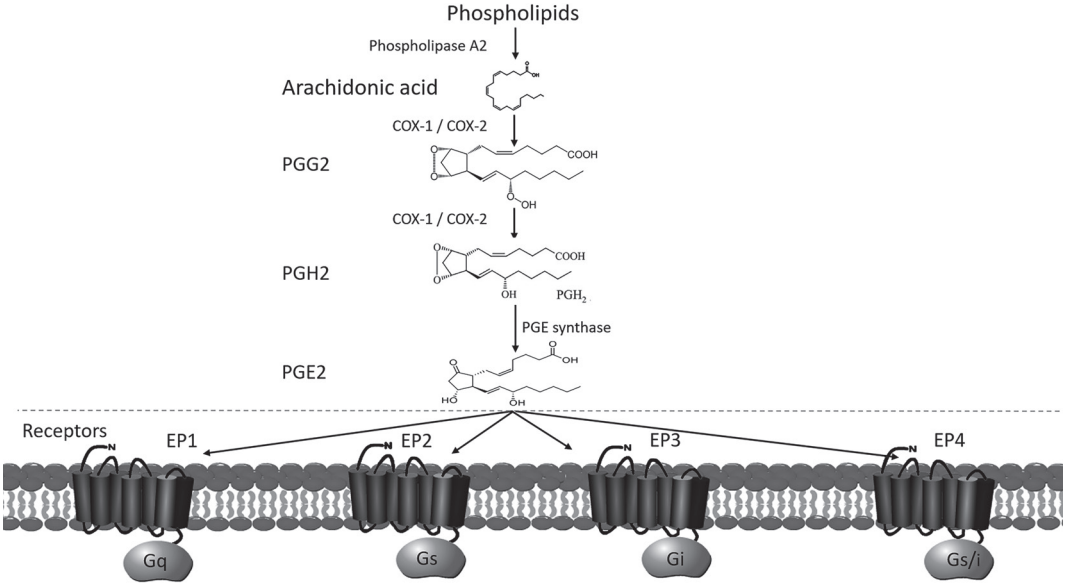


图 1. PGE2生成途径和受体

Fig. 1. PGE2 synthesis and its receptors. Phospholipids are catalyzed by phospholipase A2 to form arachidonic acid, which is catalyzed by cyclooxygenase-1 (COX-1) or cyclooxygenase-2 (COX-2) to further synthesize prostaglandin G2 (PGG2). Prostaglandin H2 (PGH2) synthesizes prostaglandin E2 (PGE2) under the catalysis of PGE synthase. PGE2 acts through four different G-protein coupled receptors (EP1–4) *in vivo*.

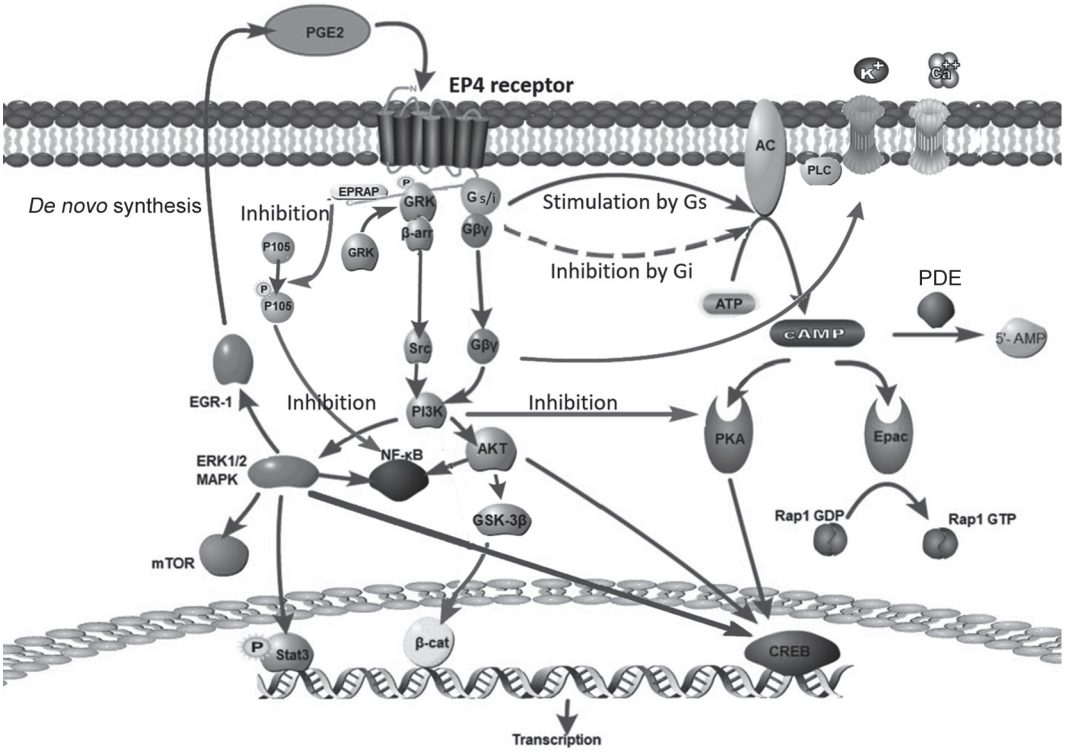


图 2. EP4的信号转导通路

Fig. 2. The signal transduction of EP4 receptor. After activation by PGE2, EP4 coupled with Gs protein or Gi protein to accelerate or inhibit activity of adenyl cyclase (AC) respectively, which causes a corresponding change in cyclic adenosine monophosphate (cAMP). The isolated Gβγ complex can regulate the activity of potassium channel, calcium channel, phospholipase C (PLC) and AC. The AC/cAMP/PKA (protein kinase A) pathway ultimately activates cAMP response element binding protein (CREB) to regulate gene transcription, while the AC/cAMP/Epac (exchange protein activated by cAMP) pathway activates Rap-1 (Ras-related protein 1), and eventually cAMP is inactivated by phosphodiesterase (PDE) degradation. EP4 can also directly activate β-catenin by the GRK (G protein-coupled receptor kinases)/β-arrestin/Src/PI3K (phosphatidylinositol 3-kinase) pathway or indirectly activate Stat3 (signal transducer and activator of transcription 3) via MAPK (mitogen-activated protein kinase)/ERK1/2 (extracellular signal-regulated kinases 1/2) to regulate gene transcription. Additionally, PGE2 can also be *de novo* synthesized by early growth response protein 1 (EGR-1). EP4 can inhibit the activation of nuclear factor κB (NF-κB) by inhibiting phosphorylation of p105 by EPRAP (prostaglandin E receptor 4-associated protein). β-arr: β-arrestin; GSK-3β: glycogen synthase kinase 3β; β-cat: β-catenin; 5'-AMP: 5'-adenosine monophosphate.

EP4 也可通过促分裂素原活化蛋白激酶 (MAPK) 通路显著促进心肌肥大，抑制 MAPK 的亚家族成员细胞外信号调节激酶 1/2 (extracellular signal-regulated kinases 1/2, ERK1/2) 的激活，通过增加早期生长反应因子 1 (early growth response protein 1, EGR-1) 的表达，明显减轻 PGE2 造成的心室肌肥大 [21–23]，并且 ERK1/2 激活 Stat3 (signal transducer and activator of transcription 3) 时，心肌细胞蛋白合成及细胞体积显著增加将加重心肌肥大程度 [24]。研究也显示 EP4 可由 MAPK 途径产生正反馈效应，增加 PGE2 合成 [25, 26]。此外，EP4 还可以通过与前列腺素 E 受体 4 相关蛋白 (prostaglandin E receptor 4-associated protein, EPRAP) 的相互作用来抑制蛋白酶体蛋白 p105 的磷酸化，进而抑制细胞中调控细胞生长和存活的转录因子 NF-κB 的活化能力 [27, 28]。

大量证据表明，EP4 在不同的组织和条件下其信号转导通路和生物学作用并不完全相同 [29]。目前，除其经典信号转导途径在具体的组织器官内的作用仍有待阐明外，EP4 与很多其它新发现的信号转导途径的关系也有待研究，这些经典和非经典通路与特定心血管疾病的关系是近年的研究热点，该领域的研究进展有力地推动了心血管疾病的预防和治疗。

### 2.3 EP4通路与炎症反应的关系

EP4 在 B 淋巴细胞、T 淋巴细胞、NK 细胞、树突状细胞、嗜酸性粒细胞、单核细胞以及巨噬细胞等免疫细胞中广泛存在，并对其功能发挥重要的

调控作用[30]。一般认为PGE2主要通过EP4来发挥抗炎作用[31]，但亦有研究指出在Th17细胞介导的疾病中EP4的激活能促进炎症反应[32]。

辅助T细胞分为Th1、Th2、Th17三种亚型[33]，其中Th1和Th17在炎症性疾病和自身免疫疾病中占主导地位[34]，它们介导多种炎症反应和组织损伤。研究显示，PGE2作用于初始T细胞(naïve T cell, Th0)上的EP4，通过cAMP/PKA通路增加白介素12 (interleukin-12, IL12)和γ干扰素(interferon γ, INFγ)合成，进而促进T细胞向Th1细胞分化[35]。众所周知，转化生长因子β (transforming growth factor-β, TGFβ)和IL6促进T细胞向Th17分化，这些细胞因子使Th17细胞表面表达IL23受体，而EP4经cAMP途径增加树突状细胞IL23的合成，继而促进Th17细胞的扩增[36–39]。完成细胞分化和扩增后，Th1细胞通过分泌INFγ、TGFβ、IL2和IL10[40]，Th17细胞通过分泌IL17A、IL17F、IL21、IL22和粒细胞-巨噬细胞集落刺激因子(granulocyte-macrophage colony-stimulating factor, GM-CSF)参与炎症反应[41](图3)。

## 3 EP4在心脏疾病中的作用

### 3.1 EP4在心脏生理调节中的作用与心肌肥大

EP4在心肌细胞[42]、成纤维细胞[43]、平滑肌细胞[44]、内皮细胞[7]等心脏相关细胞中广泛表达。既往研究显示，在新生大鼠心肌细胞中激活EP4，可通过ERK1/2通路促进蛋白合成并增大其细胞面积[45]。在心肌细胞中敲除EP4后，导致Stat3通路无法被激活，从而减小心肌肥大程度[46]。此外，EP4可由PKA和PI3K通路发挥保护心肌细胞免于缺血性损伤的作用[47]。上述研究说明EP4可经由经典信号转导通路发挥其维持正常心脏功能的作用。目前，对EP4在不同心脏疾病中的作用及调控机制还有待阐明，越来越多的研究提示EP4可通过调控炎症反应对心脏疾病的进展发挥重要调控作用。

PGE2能以剂量依赖的方式促进心室肌细胞蛋白合成，并上调细胞肥大标记基因的表达，增加钠尿肽(atrial natriuretic peptide, ANP)和脑利钠肽(brain natriuretic peptide, BNP)的水平，并促进心肌肥大的发生[23, 45, 48]。虽然激动β1肾上腺素受体可通过cAMP-PKA通路使心肌收缩蛋白磷酸化，导致心肌

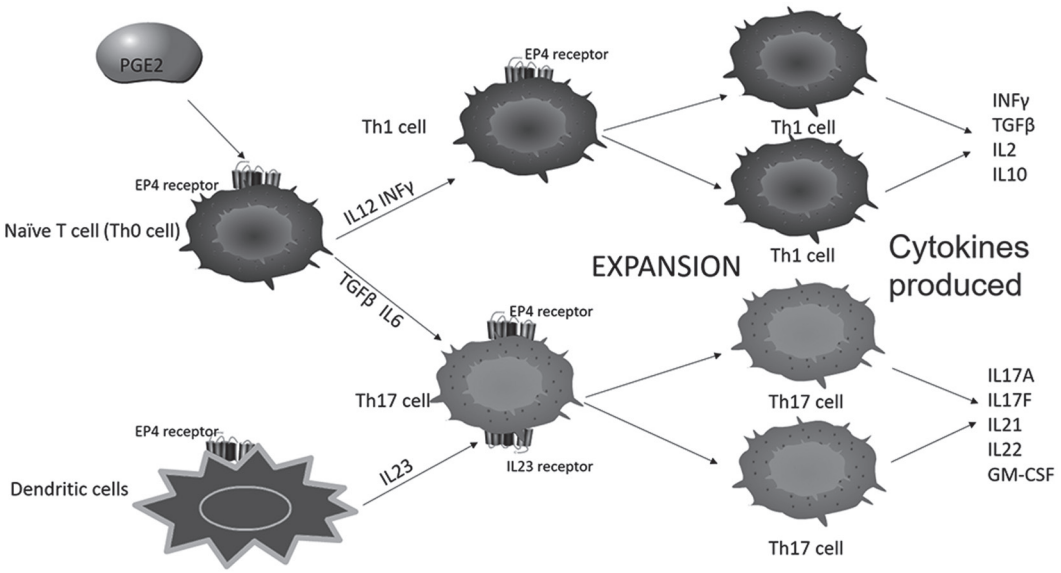


图 3. EP4与Th细胞分化、增殖的关系

Fig. 3. The relationship of EP4 receptor with Th cells' differentiation and expansion. PGE2 regulates the differentiation of naïve T cells (Th0 cells) by EP4. Th0 cells differentiate into type 1 T helper (Th1) cells under the action of interleukin 12 (IL12) and INFγ (interferon γ), and release cytokines such as INFγ, transforming growth factor β (TGFβ), interleukin 2 (IL2) and interleukin 10 (IL10) after proliferating in a large amount. Th0 cells differentiate into Th17 cells under the action of TGFβ and interleukin 6 (IL6), and the subsequent proliferation process can be facilitated by interleukin 23 (IL23) produced by dendritic cells. Type 17 T helper (Th17) cells release cytokines such as interleukin 17A (IL17A), interleukin 17F (IL17F), interleukin 21 (IL21), interleukin 22 (IL22), and granulocyte-macrophage colony-stimulating factor (GM-CSF).

细胞肥大[49]，但使用 cAMP、PKA 抑制剂、Epac 激动剂均对 PGE2 导致的心肌肥大无任何影响[21, 23, 24]，提示 EP4 的 cAMP/PKA 经典信号通路可能不是导致其促进心肌肥大的主要因素。此外，有研究显示 EP4 敲除小鼠和野生型小鼠的心肌横截面积与心脏 / 体重比在基础状态下无明显差异，行主动脉弓缩窄术 (transverse aortic constriction, TAC) 后两种小鼠的心肌肥大程度也无显著差异，但 EP4 敲除小鼠在 23~33 周龄内出现了自发性扩张性心肌病[8, 43, 50]。

上述研究表明，EP4 在心肌肥大中的作用可能不是由经典信号转导通路介导的，其它非经典途径可能参与了 EP4 对心肌肥大的调控。尽管有研究表明炎症能显著地促进心肌肥大[51]，但其与 EP4 的关系目前尚缺乏研究证明，EP4 是否通过炎症反应途径参与调控心肌肥大，这有待进一步研究。

### 3.2 EP4在心肌缺血再灌注损伤中的作用

在心肌缺血再灌注模型和心梗模型中均发现 EP4 敲除小鼠发生代偿性心肌肥大，且心肌细胞的损伤和坏死也更为显著[43, 52]。有研究显示，巨噬细胞等炎症细胞可移行至心肌缺血部位产生 TNFα、IL6、IL1β、单核细胞趋化蛋白 -1 (monocyte chemotactic protein 1, MCP1) 等致炎细胞因子，加重心肌损伤[53]。而 EP4 激动剂能显著抑制上述细胞因子的产生[54]。因此，推测 EP4 可能通过其抗炎作用减轻心肌缺血导致的损伤，EP4 在保护心肌免受损伤的过程中可能起到了至关重要的作用。

### 3.3 EP4在心脏纤维化中的作用

有研究表明，对小鼠行 TAC 手术增加心脏后负荷后，使用 EP4 激动剂能显著减轻心脏纤维化，保护心功能[55]。最新研究也证实，EP4 过表达小鼠可显著减轻心梗后心脏纤维化的发生[52]。EP4 的这种心脏保护作用可能是通过抑制 MCP1 表达，继而降低 T 细胞激活，最终减轻炎性反应来实现的[56]。此外，有证据表明肺动脉高压患者使用 EP4 激动剂，可抑制 TGF-β 表达，降低内皮 - 间质转化 (endothelial-mesenchymal transition, EndMT)，从而减轻右心室纤维化并增强心功能[57]。有研究显示，IL6、IL8 以及 TNFα 在发生 EndMT 的内皮细胞中高表达[58]，而 PGE2 可刺激新生心肌细胞 IL6 的合成[59]，并与心肌纤维化程度呈正相关[60]，提示 EP4 可能通过抑制心脏炎症反应发挥其减轻心脏纤维化的作用。

### 3.4 EP4在心力衰竭中的作用

研究表明，使用 EP4 激动剂能显著增加 TNFα 和 IL6 等细胞因子的合成[61]，而这些炎症标记物的高表达提示心衰病情严重以及预后不良[62]，它们还可刺激细胞释放大量花生四烯酸，并通过 COX-2 途径使其产物增多[63]。在大鼠心衰模型中，药物抑制 TNFα 和 IL6 的合成，可缓解心肌凋亡并保护心功能[64]。虽有研究表明使用 EP4 拮抗剂能显著抑制 T 细胞活化及炎症因子释放，缓解炎症所致的组织损伤[39]，但也有观点认为 EP4 不仅可以抑制细胞因子的释放，还能抑制巨噬细胞的活化，显著增强心肌细胞的炎症抑制效应[65]。最近的临床实验表明对急性心衰患者使用 EP4 激动剂 (ONO-4232) 可调控钙离子以促使血管和左心室舒张，降低收缩压，同时也出现诸如直立性低血压的副作用[66]。以上结果说明 EP4 激动剂对心力衰竭具有疗效，但其对心肌细胞的舒张效应是否与炎症反应有关，及其产生的并发症的处置方法，仍需进一步深入研究，以期早日应用于临床。

### 3.5 EP4在其它心脏疾病中的作用

EP4 敲除小鼠在高脂或普通饲料喂养条件下，体重和脂肪含量均低于野生型小鼠，但血甘油三酯水平明显升高[67]，从而显著增加了心肌细胞的脂毒性，导致心功能降低[68]，这可能部分解释了为什么 EP4 敲除小鼠寿命较野生型小鼠明显缩短[67]。给予自身免疫性心肌炎模型大鼠 EP4 激动剂后，MCP1 表达和 T 细胞激活被抑制，从而减轻炎症反应对心功能的负面影响[56]。此外，EP4 还能通过抑制 INF-γ 显著降低同种异体 (allograft) 移植心脏淋巴浆细胞的渗入，并促进起抗炎作用的 IL10 的分泌[69]，最终降低大鼠的移植后排斥反应，增加生存时间[70]。在小鼠心梗模型中使用 EP4 激动剂后，巨噬细胞标记物——诱导型一氧化氮合酶 (inducible nitric oxide synthase, iNOS) 显著降低[52]，结合 PGE2 对巨噬细胞释放 MCP-1 和 IL8 等细胞因子的抑制作用[71]，推测心肌梗死程度可因 EP4 的抗炎作用而有所减轻。

## 4 EP4在血管疾病中的作用

### 4.1 EP4在血管生理功能中的作用

EP4 影响血管的自然发育进程，激活 EP4 可促进出生后动脉导管的闭锁[72]。正常生理状况下，动脉导管平滑肌细胞中 EP4 表达较高[73]，其参与动脉导管关闭的作用较其它 EP 受体重要[74]。在治疗罹患大动脉转位的新生儿时，应用前列腺素可促进动脉导管保持开放，维持正常血供[75]。但目前，使

用药物影响 EP4 是否可发挥相同的作用仍有待研究。激活 EP4 还能通过 PKA 通路介导组胺 H1 受体磷酸化，促使组胺从活化的 PLC 上分离，降低细胞内钙离子浓度从而舒张血管 [11]。此外，激活 EP4 可保护肾血管，减轻血管紧张素 II (angiotensin II, AngII) 介导的氧化应激损伤和血流动力学改变 [76]。目前认为，EP4 在维持血管的生理功能上有不可或缺的作用，EP4 在血管疾病中的作用和机制正成为研究重点。

### 4.2 EP4在血管病理过程中的作用

流行病学研究显示，并发肺动脉瘤的先天性心脏病的最常见病因是动脉导管未闭 [77]，因此，高表达于肺动脉和动脉导管中的 EP4 可能是造成肺动脉瘤发生甚至破裂的关键因子。此外，EP4 在腹主动脉瘤和肺动脉瘤瘤体和撕裂部位中的表达也显著增加 [44, 78]，且在四种 EP 中对疾病进程起主要调控作用 [79]。使用 EP4 拮抗剂可使腹主动脉管径缩小，并显著降低动脉瘤发生率 [80]，EP4 拮抗剂的这种作用可能是通过抑制 Th17 细胞活化，从而使体内 IL17 合成减少实现的 [80]。这一结论也被 EP4 激动剂促进 IL17 的合成所支持 [39, 81]。进一步的研究表明，EP4 激动剂导致的细胞因子增加，可促进巨噬细胞表型转换并加重炎性程度，促进基质金属蛋白酶 (matrix metalloproteinase, MMP) 的合成，最终导致血管细胞外基质降解、动脉瘤形成 [82, 83]。此外，还有研究表明 EP4 的激活可延长巨噬细胞的生存时间，细胞的持续活化和增多的细胞因子加重炎症反应、损伤血管弹力板，导致血管壁功能性损伤，从而促使动脉瘤形成 [18, 78]。上述研究表明血管局部炎性反应可经 EP4 的激活而加重，并促进动脉瘤的形成。

尽管以上研究认为 EP4 激活促进血管局部炎症反应，但也有研究得出相反结论。譬如 Tang 等人在骨髓来源细胞特异性敲除 EP4 的小鼠中使用 AngII 诱导动脉瘤形成，却发现其动脉瘤发生率明显高于野生型小鼠 [84]。其原因可能与 EP4 敲除小鼠的腹主动脉瘤损伤处 MCP-1 显著增加和血管壁变薄有关。因 MCP-1 能募集巨噬细胞和 T 细胞以显著促进局部炎症，并在被侵袭血管壁内大量表达 MMP 和组织蛋白酶 (cathepsins)，进而导致血管基质损伤和动脉瘤形成 [85]，以上研究提示 EP4 可通过抑制炎症反应降低血管瘤的发生率。

大量研究表明，EP4 与动脉粥样硬化发生相关。当体内 PGE2 增加时，作用于巨噬细胞表面的 EP4，使其合成并释放大量抗炎细胞因子 IL10，同时减少促炎细胞因子 TNFα 的合成，从而缩小动脉粥样硬化斑块面积 [86]。有研究报道，在给予高脂饮食 5 周诱导的早期斑块形成中，EP4 对炎症反应和斑块面积无显著调控作用，但在高脂饮食诱导 10 周的成熟斑块中，特异性敲除骨髓来源细胞的 EP4 可使小鼠主动脉根部斑块高表达 T 细胞趋化因子，如 MCP-1 和 γ 干扰素诱导蛋白 10 (interferon-γ inducible protein 10, IP-10)，并显著加重粥样斑块形成 [87]。上述实验证明 EP4 能通过抑制血管局部炎症反应，从而缓解动脉粥样硬化的病程。

目前，有关 EP4 与血管病变的研究结论尚有争议，其原因可能是不同疾病进程中参与的细胞类型不同，故其作用不一致；也可能是 EP4 对疾病进展存在阈值效应，即在一定程度内激活表现为保护组织免于炎症损害，超过该阈值便导致炎症加重；亦有可能是 EP4 对炎性调控存在时间依赖性。然而不管其机制如何，现有的研究均提示，EP4 介导的局部炎症反应在血管疾病的发生和发展中发挥重要作用。

## 5 小结

大量针对 EP4 的生理、病理和信号转导通路的研究揭示了 EP4 对心血管系统稳态的调节作用。由于 EP4 在心脏和血管中既有直接作用，又有间接作用，因此有关 EP4 对心血管系统作用的研究产生了不一致、甚至截然相反的结果。目前较为一致的观点认为，EP4 可能在不同部位，通过不同的途径来发挥对组织结构的保护或破坏的作用；EP4 对于心血管疾病的调节作用可能存在阈值效应和时间依赖性。阐明 EP4 对心血管组织炎性反应的调控作用及机制，不仅有助于解决动脉瘤的临床治疗难题，也将为心肌肥大和心脏纤维化病程的干预、以及心梗和动脉粥样硬化患者预后的改善提供可能。

* * *

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