

DOI: 10.3724/cbls.2026126

CSTR: 32203.14.cbls.2026126

文章编号: 1004-0374(2026)08-1446-17



曾艺, 研究员, 博士生导师。从事成体干细胞研究, 致力于发现组织器官中的干细胞, 对干细胞的微环境信号进行系统性解析, 并实现它们在再生医学中的转化应用。她发现了乳腺上皮、血管内皮、卵巢上皮、胰岛等多种组织的成体干细胞。近期工作利用胰岛成体干细胞在体外重构形成胰岛类器官。这一工作为胰岛再生提供了重要的理论创新, 为“胰岛体外重建”设计带来了变革, 为实现在体外大量获得糖尿病细胞治疗所需的人类胰岛细胞开创了全新的局面。获上海市自然科学奖一等奖、国家杰出青年基金、谈家桢生命科学创新奖、腾讯科学探索奖、新基石研究员。

蛋白C的生物学功能与应用研究进展

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摘 要: 蛋白C在20世纪60~70年代被发现并分离, 其最经典的功能是在受体依赖的情况下, 被活化并切割凝血因子起到抗凝血的作用。近30年来, 蛋白C被发现除了抗凝血外, 亦可以发挥包括抗炎、抗凋亡以及增强细胞屏障的细胞保护作用, 同时也可以直接参与对天然免疫以及适应性免疫细胞的调控。近年来, 蛋白C及工程化变体的研究主要集中在临床应用方面, 在脓毒症、神经炎症、糖尿病临床前动物模型上都有良好的表现, 目前在肌萎缩侧索硬化症、慢性创面等疾病上已成功进入临床试验阶段。值得注意的是, 蛋白C受体在包括造血、乳腺、血管、胰岛等多个组织中也被鉴定为成体干细胞的标志物。蛋白C在这些干细胞上通过其受体也发挥着重要的功能。本文综述了蛋白C在多种成体干细胞中的作用, 为未来联合蛋白C信号与干细胞再生医学相互结合的治疗方案提供理论支持。

关键词: 蛋白C; 蛋白C受体; 抗凝血; 细胞保护; 免疫调节; 成体干细胞

中图分类号: Q819; R341

文献标识码: A

Advances in the biological functions and clinical applications of protein C

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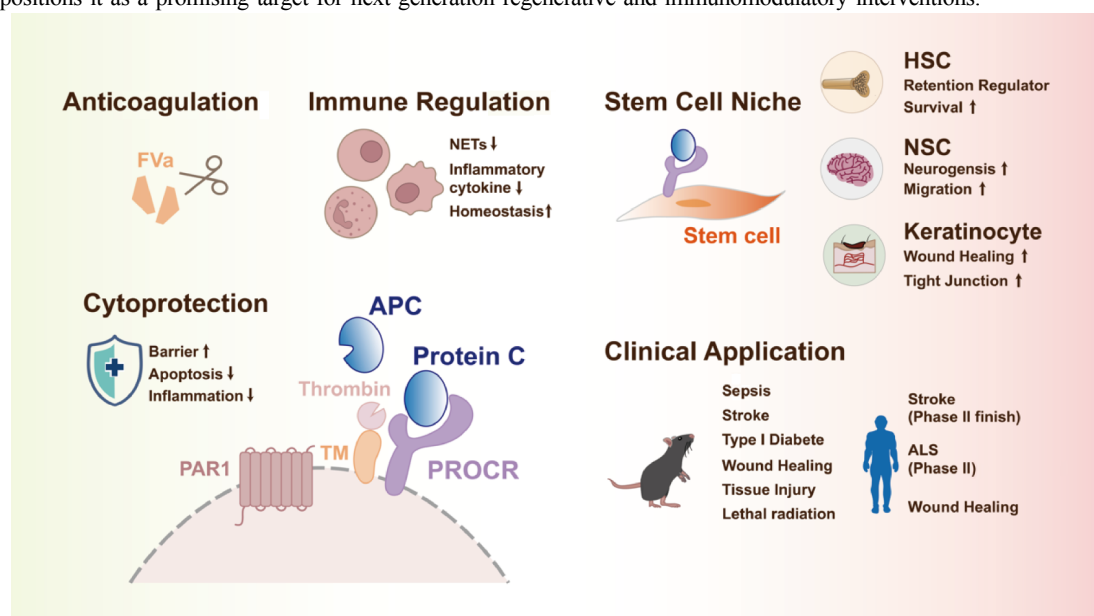
Abstract: Protein C (PC) was originally identified as a vitamin K-dependent anticoagulant zymogen, whose activated form, activated protein C (APC), down-regulates coagulation by proteolytically inactivating coagulation factors Va and VIIIa. However, research over the past five decades has revealed that the PC pathway plays far broader roles beyond anticoagulation. Through its interaction with endothelial protein C receptor (PROCR, EPCR) and protease-activated receptors (PARs), APC exerts potent cytoprotective, anti-inflammatory, anti-apoptotic, endothelial barrier-stabilizing and immunomodulatory functions in a variety of tissues. Preclinical

收稿日期: 2026-02-05; 修回日期: 2026-04-13

基金项目: 国家重点研发计划(2020YFA0509002); 国家自然科学基金卓越研究群体项目(32588301); 上海市“科技创新行动计划”细胞与基因治疗专项项目(23J21901400); 中国科学院基础研究领域青年团队计划(YSBR-014); 上海市市级科技重大专项, 中国科学院-裘槎联合实验室资助计划(CAS24801 and CAS24SC02); 新基石研究员项目(NCI202254)

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investigations have consistently shown that APC treatment confers significant therapeutic benefit across a broad spectrum of disease models, including ischemic stroke, inflammatory tissue injury, neurodegenerative disorders, diabetes, and chronic or non-healing wounds. Meanwhile, engineered APC variants with markedly reduced anticoagulant activity but preserved cytoprotective properties, such as 3K3A-APC, have demonstrated promising therapeutic potential in preclinical disease models and early-phase clinical trials. These findings highlight the PC pathway as an important molecular regulator positioned at the interface between coagulation, inflammation, immunity and tissue regeneration. The purpose of this review is to summarize current progress regarding the biological roles of PC/APC and PROCR in adult stem cells, and to discuss the implications of these findings for regenerative medicine and disease therapy. Recent work has identified PROCR as a functional marker for multiple adult stem cell types, including hematopoietic, epidermal, vascular, mammary gland and pancreatic progenitor cells. PC/APC signaling has been shown to protect stem cells from apoptosis, modulate immune cell crosstalk, regulate stem-cell quiescence and homing, and contribute to maintenance of stem cell niches. On the basis of current evidence, we propose that the PC-PROCR axis represents an emerging regulatory hub for stem cell biology and tissue protection. Future work should focus on clarifying the role of PC/APC in disease-altered stem-cell microenvironments, and optimizing PC-based targeted therapeutics with minimal bleeding risk. Integration of stem cell-based therapies and PC signaling may provide novel strategies for the treatment of inflammatory tissue injury, autoimmune diseases and degenerative diseases. Overall, the expanding understanding of the PC pathway not only revises its classical role in hemostasis, but also positions it as a promising target for next generation regenerative and immunomodulatory interventions.



Key words: protein C; PROCR; anti-coagulation; cytoprotection; immune regulation; adult stem cells

1 蛋白C的发现

20世纪60年代,蛋白C(protein C,PC)被观察到具有抗凝作用,并于1976年从牛血清中分离并鉴定为一种维生素K依赖的,带有 γ -羧基谷氨酸(γ -carboxyglutamic acid,Gla)结构的酶原^[1]。人的PC主要由肝细胞合成,并能够分泌进入血液循环^[2]。

蛋白C能够在凝血酶的切割下,去除激活肽,从而产生激活形式的蛋白C(activated protein C, APC)。这一切割过程主要发生在内皮细胞表面,由内皮细胞蛋白C受体(endothelial protein C receptor, PROCR, EPCR)和凝血酶-血栓调节蛋白复合物共同参与^[3,4]。PC被切割为APC后,具有一条轻链(21 kDa)和一条重链(41 kDa),二者通过二硫键连

接。APC的轻链包含一个能够结合其受体PROCR的Gla结构域和两个表皮生长因子样结构域,而重链则包含了一个丝氨酸蛋白酶结构域和一个激活肽段^[5]。通过人血浆样品的分析,研究人员发现血浆中PC的浓度为70 nmol/L,而其激活形式APC的浓度仅为40 pmol/L^[6]。

2 蛋白C已知生物学功能

2.1 抗凝血作用

在PROCR、凝血酶-血栓调节蛋白复合物的共同作用下,PC被切割生成APC。APC在生成后会立即从PROCR上解离,并与抗凝非酶辅因子蛋白S结合,降解促进凝血的活化因子Va(activated coagulation

factor V, FVa)和VIIIa(activated coagulation factor VIII, FVIIIa),从而起到抗凝血的作用^[7]。

PROCR在大血管和微血管中的表达存在差异,人体组织学的研究发现,PROCR在较大口径的血管(动脉及部分静脉)的内皮上表达更为丰富而连续,而在多数毛细血管中表达较低^[8,9]。PROCR能够结合循环中的PC,并将其呈递至凝血酶-血栓调节蛋白复合物,从而显著提高PC向APC的转化效率^[3,10]。PROCR的空间表达差异可能影响不同血管中APC的生成及抗凝能力。近年来的研究也发现,在临床评估中,凝血酶的空间分布差异调节了不同血管中PC的抗凝血活性^[11]。

对于PC抗凝血的经典作用,自发现以来其机制已十分明晰(图1)。近年的系列研究已将抗凝相关功能的阐释从整体生理层面细化至组织特异性调控维度,同时推动该领域研究进一步向临床风险评估与靶向疾病治疗的方向延伸。

2.2 细胞保护作用

PC被切割为APC后被报道对细胞具有保护作用,主要通过激活G蛋白偶联受体(G protein-coupled receptor, GPCR)蛋白酶激活受体1(protease-activated receptor 1, PAR1)来实现^[12]。在分子机制层面,凝血酶通过精准切割PAR1的Arg41位点完成对该受体的激活,进而招募经典G蛋白偶联信号通路,最终在血小板上介导促凝效应,同时在内皮细胞中诱导促炎反应并增强细胞通透性^[13,14]。APC则以PROCR依赖的形式水解PAR1的第46位Arg^[15-18],导致PAR1被G蛋白偶联受体激酶5磷酸化,并招募 β -arrestin-2。 β -arrestin-2作为“信号转导器”,与Dishevelled-2形成信号转导支架^[19],对细胞产生保护作用。除了APC,作为原酶的蛋白PC同样具有细胞保护功能,在PC与

其受体PROCR结合时,凝血酶切割PAR1的Arg41位点,而在下游则选择性招募 β -arrestin-2,同样与Dishevelled-2形成复合物,起到抗炎以及增强内皮细胞屏障的作用^[20,21]。近年来,在PROCR-PAR1- β -arrestin-2轴激活的内皮细胞保护作用中,stanniocalcin-1^[22]和adducin-1^[23]被证明也是必要的参与者,但是具体机制仍不明晰。

除了PAR1受体外,其同家族的PAR3也能够Arg41位点被APC进行非经典切割,该作用在体内外实验中均被证实可发挥增强内皮细胞屏障功能的保护效应^[24]。除内皮细胞之外,APC对其他细胞类型亦存在保护作用^[25]。例如,肾脏足细胞存在于肾小球的肾小囊壁层,是负责防止蛋白质渗漏入尿液的关键细胞^[26]。在糖尿病肾病模型中,APC可特异性切割肾脏足细胞表面的PAR3,在人源肾脏足细胞中形成PAR2-PAR3异源复合物,在肾脏足细胞中则形成PAR1-PAR3异源复合物,通过介导下游细胞保护信号通路,显著减少足细胞凋亡,最终改善糖尿病状态下的蛋白尿水平与肾功能损伤^[27]。另外,在神经保护层面,APC通过PAR1和PAR3阻断caspase3以及caspase8的激活,从而保护小鼠皮层神经元免受凋亡诱导剂损伤的作用^[28]。

蛋白C在细胞保护中的作用(图1),目前绝大多数报道都是基于其激活形式APC,以PAR受体依赖的机制,在内皮、神经、肾脏足细胞等多种组织细胞中发挥其功能。PC在不同组织中发挥细胞保护的具体机制,以及参与细胞保护的其他关键蛋白,仍有待进一步阐明。

2.3 免疫调节作用

除在内皮细胞中发挥经典的抗凝及细胞保护作用外,PC还可调控包括单核细胞、巨噬细胞、中性粒

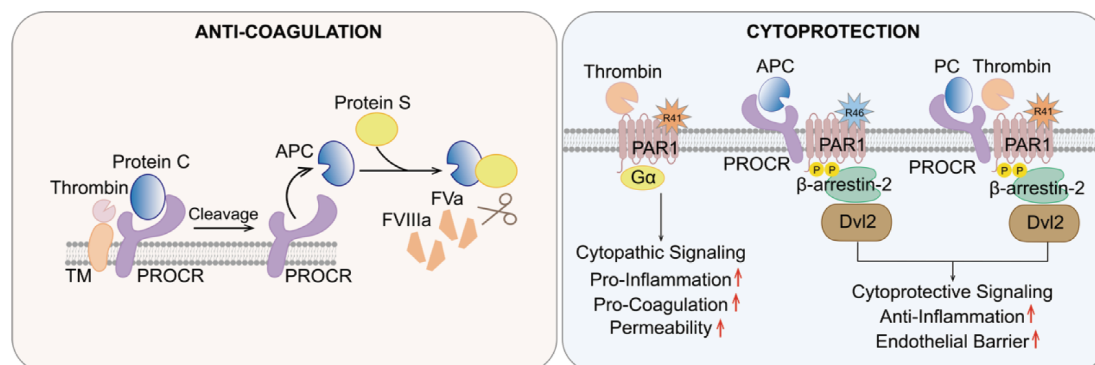


图1 蛋白C的抗凝血以及细胞保护功能

Figure 1 Anticoagulant and cytoprotective functions of protein C

细胞在内的天然免疫以及适应性免疫^[25]。

2.3.1 单核细胞及巨噬细胞

在单核细胞中,APC通过依赖PROCR和PAR1的机制,抑制肿瘤坏死因子、白介素-1 β 、白介素-6、白介素-8和巨噬细胞炎症蛋白-1 α 等炎症细胞因子和趋化因子的产生^[29,30]。对于其下游信号通路的研究,证明了APC能够抑制NF- κ B信号通路的激活,从而在单核细胞中发挥抗炎作用^[31,32]。

在巨噬细胞中,APC的抗炎作用依赖于与整合素Mac-1(CD11b/CD18)的结合,促进巨噬细胞上PAR1的激活,进而启动下游信号通路,抑制脂多糖介导的炎症发生^[33]。另外,APC可通过抑制位于NLRP3炎症小体上游的信号蛋白复合物mTORC1抑制IL-1 β 的产生^[34,35]。具体机制研究证明,PROCR、PAR1和PAR3均对APC介导的炎症小体活性抑制至关重要^[34]。

再者,APC信号通路也可以调节天然免疫细胞的表观遗传修饰。在高血糖导致的动脉粥样硬化中,斑块中的巨噬细胞会激活氧化还原调节因子p66Shc的表达并导致活性氧的产生。即使在血糖恢复到正常水平后,p66Shc介导的活性氧产生依然存在。APC可以通过PAR1信号通路诱导DNA甲基转移酶-1逆转p66Shc启动子区域葡萄糖诱导的CpG低甲基化,从而消除相关高血糖记忆^[36]。在炎症诱导的巨噬细胞中,APC被发现能够对染色质结合蛋白4B和p300/CBP相关因子进行调控,通过组蛋白乙酰化或去乙酰化进行染色质重塑,从而调控基因转录^[37]。

2.3.2 中性粒细胞

中性粒细胞在炎症的起始和放大过程中发挥重要作用,可以通过释放中性粒细胞胞外陷阱(neutrophil extracellular traps, NETs)来抵抗微生物感染^[38]。过度的NET形成则会导致血栓^[39],系统性红斑狼疮、类风湿关节炎等自身免疫性疾病,以及慢性阻塞性肺病等慢性炎症性疾病^[40]。在体外炎症诱导模型中,APC能够与中性粒细胞结合,通过结合PROCR、Mac-1和PAR3受体,抑制中性粒细胞的活化和NET的形成。在非人灵长类动物模型中,APC同样可以抑制中性粒细胞活化和髓过氧化物酶的释放^[41]。在NET形成过程中释放的细胞外组蛋白具有细胞毒性,会导致白细胞活化、内皮损伤和微血管血栓形成。APC可以直接中和中性粒细胞释放的细胞

外组蛋白,从而限制其细胞毒性^[42],这种作用能够在血浆高密度脂蛋白(high-density lipoprotein, HDL)存在时进一步增强^[43]。诸多研究都表明APC通过与多种细胞表面受体,包括PROCR、Mac1、PAR1、PAR3、VLA-3^[44]、 β 1/ β 3整合素^[45]作用来抑制中性粒细胞的活化、迁移和浸润^[46,47]。

2.3.3 T细胞

在适应性免疫层面,APC一方面直接作用于T细胞,另一方面通过重塑抗原呈递细胞影响T细胞的分化及功能。PROCR是辅助性T细胞17(IL-17-producing T cells, Th17)(常被认为是自身免疫病的驱动细胞)分化的负调节因子,APC在受体依赖的情况下可以抑制Th17的分化^[48]。APC能够重塑树突状细胞的促炎/耐受表型,削弱其促使初始CD4⁺ T细胞向Th1/Th2细胞分化的能力^[49]。

在非肥胖糖尿病小鼠模型中,APC能够减少胰腺中的免疫细胞,降低促炎细胞因子IL-1 β 和IFN- γ (interferon- γ)的分泌,并增加调节性T细胞(regulatory T cells, Treg)分化必需IL-2和TGF- β 的分泌,从而显著降低糖尿病的发生^[50]。在移植物抗宿主病(GvHD)中,APC预处理移植物能够通过Treg细胞上的PAR2/PAR3异源二聚体来抑制T细胞的活化,从而减轻GvHD^[51]。2022年,在特应性皮炎模型中,APC也被报道通过PAR2信号通路减少Th1、Th17和Treg细胞的数量^[52]。在炎症性关节炎和胶原诱导性关节炎模型中,APC均能够显著降低全身炎症细胞因子水平以及Th1和Th17细胞的数量^[53,54]。

值得一提的是,近年APC被发现参与T细胞的代谢过程。Gupta等^[55]发现,APC能够降低T细胞中谷氨酰胺和 α -酮戊二酸水平,伴随Foxp3启动子去甲基化与FOXP3表达上调,推动其获得Treg样细胞表型。

蛋白C在免疫调节中的作用贯穿天然免疫与适应性免疫过程(图2)。研究表明,蛋白C及其受体可通过PAR依赖的信号机制,在多种免疫细胞中调控炎症信号转导,从而抑制NF- κ B介导的炎症反应并降低炎症因子的释放。同时,在不同类型免疫细胞中,蛋白C还表现出多层面的调节作用,例如调控巨噬细胞炎症小体活性,限制中性粒细胞过度活化及其迁移,并减少NET形成相关的细胞毒性反应,参与T细胞分化与代谢状态的调节。通过这些综合性的调控作用,蛋白C在维持免疫反应的适度性和组织稳态方面发挥了重要作用。对蛋白C免疫调节功能

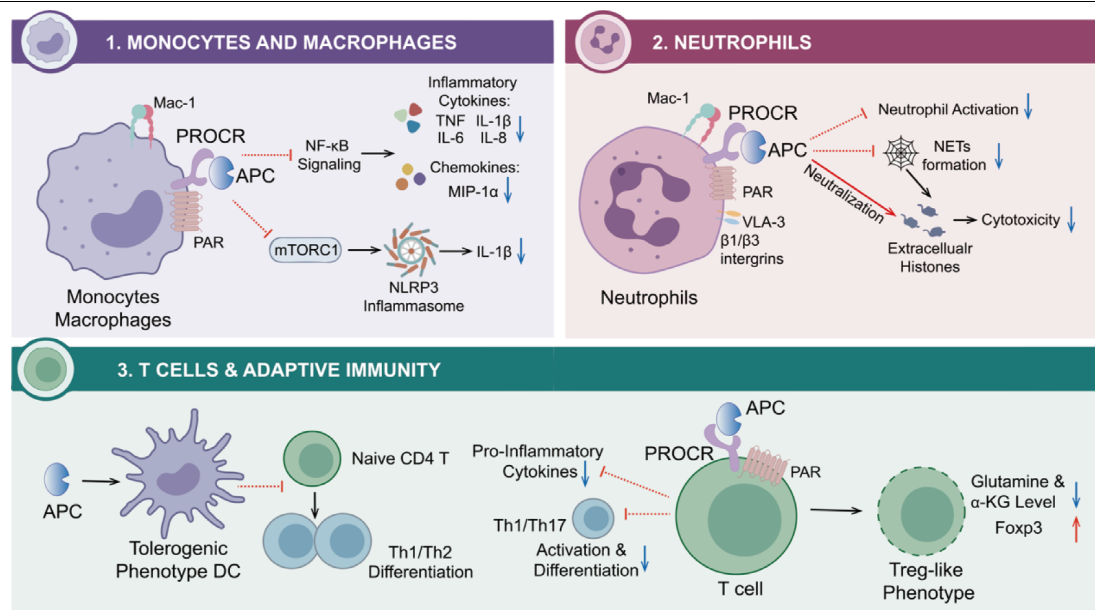


图2 蛋白C的免疫调节功能

Figure 2 Immunomodulatory function of protein C

的深入理解,为脓毒症、自身免疫性疾病以及组织炎症性损伤等疾病的治疗提供了重要理论依据。

3 蛋白C的突变体研究及工程化变体的应用

*PROC*基因突变已有诸多临床病例的报道,纯合或复合杂合突变导致了严重的蛋白C缺乏^[56]。其典型的临床表现为新生儿暴发性紫癜及弥散性血管内凝血^[57]。杂合突变同样在临床上导致青年期复发性静脉血栓栓塞等表现^[58]。例如,Arg169Trp是*PROC*基因突变经典的错义突变^[59],影响蛋白C的分泌^[60]。Lys193del影响了蛋白C与凝血因子的结合,削弱了其抗凝活性,并且具有在东亚人群中频率高的特点^[61]。近年来,随着全基因组测序技术的广泛普及,多项研究针对蛋白C缺乏症的家系样本完成了致病突变具体位点的精准鉴定^[62-66],同时结合临床层面新生儿紫癜^[67-69]、新生儿眼部病变^[70]、肺栓塞^[71]等典型表型的系统分析,为该疾病的遗传分型体系构建与精准治疗策略制定提供了关键支撑。

PC能够激活PAR受体,发挥细胞保护作用,这一点在感染^[16]、缺血性卒中^[28,72]、神经退行性疾病^[73]和自身免疫病^[74]等多个临床前模型中被证实^[75]。2001年,礼来公司的一款商品名为Xigris的重组APC,曾作为药物获得美国食品药品监督管理局(FDA)批准用于治疗重症败血症,但后来由于疗效和安慰剂相比没有显著性差异,以及可能导致的

出血风险,而在2011年撤市^[76]。此后,Griffin等发表了诸多有关于PC工程化变体的研究,目标是保留PC对于细胞的保护作用,同时避免出血相关风险。

在PC工程化变体中,3K3A-APC这一变体,是对PC与凝血因子结合相关的丝氨酸蛋白酶结构域,第191~193位的赖氨酸位点进行了突变。突变去除了该表面外位点的局部正电荷,从而大幅削弱了APC与凝血因子的结合能力,抗凝活性降低超过90%^[77]。5A-APC在3K3A-APC的基础上,增加了同样在丝氨酸蛋白酶结构域位点的229及230位精氨酸突变,抗凝活性进一步降低^[78]。E149A-APC则是将丝氨酸蛋白酶表面与抗凝功能密切相关的第149位谷氨酸进行突变。该突变增强了APC的抗凝活性,但同时削弱了APC的细胞保护作用^[79]。1997年,研究人员将位于丝氨酸蛋白酶活性中心的位点突变得到S360A-APC,发现其完全丧失了作为蛋白酶的水解活性,不能切割凝血因子,从而完全丧失了酶依赖S360A-APC抗凝活性^[80]。在细胞保护作用层面,因为其不能切割PAR1而不再具备PAR1依赖的细胞保护信号^[28]。2006年,Yang等^[81]工程化改造的APC-2Cys,是在APC丝氨酸蛋白酶域第70~80位原本与钙结合的钙离子结合区域两侧引入了工程化二硫键而形成的结构稳定突变体。次年,该团队发现APC-2Cys的抗凝活性在血浆凝血实验中几乎完全消失,但PROCR以及PAR1依赖的细胞保护信号仍然保

留^[82]。表1总结了蛋白C工程化变体突变位点及其功能变化。

基于APC及其工程化变体的细胞保护功能,开展了诸多基于动物模型的临床前研究。在血栓形成方面,人源APC和APC重组蛋白都能够减少灵长类动物的血栓形成^[84,85]。APC治疗能够促进静脉血栓模型下血栓的消融^[86]。在败血症模型中,早在1987年,PC就被发现可以保护灵长类动物免受严重致死的大肠杆菌感染^[87]。5A-APC作为没有抗凝血活性的工程化变体,也被证明在小鼠中具有抵抗内毒素血症和败血症的作用^[88,89],其机制上依赖于DC细胞^[90]、整合素CD11b^[33]、 $\beta 1$ 、 $\beta 3$ ^[45],以及细胞外组蛋白^[42]。在缺血性卒中以及神经相关疾病中,PC能够起到多方面的保护作用^[91]。PC能够直接降低大脑的内皮细胞凋亡^[92]、保护血脑屏障^[93]、抑制神经免疫反应^[94]、直接保护神经元^[28],并促进神经再生^[95]。在颅脑创伤模型中,PC同样具有多方面保护作用^[96,97]。在肌萎缩侧索硬化症(amyotrophic lateral sclerosis, ALS)中,PC能够通过保护血脑屏障延缓病程^[98,99]。

近年来,PC被发现对自身免疫脑脊髓炎^[74]、阿尔茨海默病^[73]、白质卒中^[100]以及癫痫^[101]的治疗都有益处。在糖尿病中,PC能够保护 β 细胞^[50,102],改善糖尿病肾病^[103,104]、下肢溃烂^[105]、动脉粥样硬化^[106]、心肌衰老^[107]以及帮助移植胰岛的存活^[108,109]。另外,在心脏^[110-116]、肝脏^[117]、肾脏^[118]、视网膜^[119]、肺部^[120]、胃肠损伤^[121,122]、伤口愈合^[123]模型中,PC都被报道可以减轻炎症,帮助恢复器官功能。另有研究提及,PC能够减轻致死量辐射造成的

损伤^[124],减少手术后粘连^[125],减少腹膜纤维化^[126],并促进轴突再生^[127]。在眼部,内源性及治疗型APC均可以穿越血-视网膜屏障^[128],抑制脉络膜新生血管形成^[129]以及减轻眼球内感染^[130]。

目前,已有多项围绕蛋白C(PC)及其工程化变体的研究进入临床阶段,针对静脉注射与皮下注射两种给药途径下的蛋白C药代动力学特征,学界也已形成更为系统、深入的认知^[131,132]。在卒中治疗方面,几乎无抗凝活性的APC工程化变体3K3A-APC(RHAPSODY)在I期临床试验中展现出优异的安全性及耐受性表现^[133]。临床II期公开结果显示,RHAPSODY处理组对比安慰剂组颅内出血发生率从86.5%降至67.4%($p=0.046$),总出血体积也有所下降^[134]。需要审慎的是,RHAPSODY的多篇基础研究工作及临床数据尚有争议,该药物研发目前停滞在临床II期阶段。近年来,针对RHAPSODY治疗的脑水肿影像分析^[135]和佐证APC对于脑卒中疗效的基础研究^[72]仍在持续。关于肌萎缩侧索硬化症(ALS)的临床试验II期目前也在进行中,采用静脉滴注的方式对ALS患者进行给药^[136]。慢性创面愈合领域的相关研究主要由澳大利亚Jackson教授团队主导推进,目前已有部分临床案例正在开展。针对4例长期不愈的下肢溃疡患者进行局部反复滴敷APC治疗后,所有创面均出现明显的肉芽生长与上皮化表现,其中1例在治疗8周后达到完全愈合^[105]。针对骨科术后严重骨外露的难治性创面,采用伤口负压辅助愈合治疗与APC局部给药相结合的干预方案,可有效促进肉芽组织在骨表面的覆盖生长,最终实现成功植皮并达到创面完全治愈的临床效

表1 蛋白C工程化变体突变位点及功能变化

Table 1 Mutation sites and functional changes of engineered protein C variants

工程化变体	突变位点与结构域	抗凝活性变化	细胞保护功能
WT-APC	无突变	正常抗凝活性	通过PROCR-PAR1/PAR3介导抗炎、抗凋亡及血管保护作用
3K3A-APC	K191A / K192A / K193A(位于丝氨酸蛋白酶域外位点) ^[77]	抗凝活性下降>90%,血浆凝血实验残余活性<10% ^[77,83]	保留PROCR-PAR1介导的细胞保护功能 ^[77,83]
5A-APC	K191A / K192A / K193A / R229A / R230A(均位于丝氨酸蛋白酶域外位点) ^[78]	抗凝活性进一步降低,在多种凝血实验中几乎接近最低残余水平 ^[78]	细胞保护功能基本保留 ^[78]
E149A-APC	E149A(位于丝氨酸蛋白酶域表面) ^[79]	抗凝活性增强,表现为抗凝能力强于野生型APC ^[79]	细胞保护信号显著减弱 ^[79]
S360A-APC	S360A(位于丝氨酸蛋白酶活性中心) ^[80]	完全丧失蛋白酶/酰胺水解活性,不再切割FVa / FVIIIa ^[80]	不能切割PAR1,几乎不具备APC典型的细胞保护信号 ^[28]
APC-2Cys	丝氨酸蛋白酶域70~80位Ca ²⁺ 结合环两侧引入一对半胱氨酸。形成工程二硫键,稳定Ca ²⁺ -binding loop结构 ^[81,82]	Ca ²⁺ 不再结合70~80 loop;抗凝活性在血浆凝血实验中几乎完全消失 ^[81]	仍保留内皮屏障保护、抗炎等信号作用 ^[81]

果^[137]。针对糖尿病下肢溃烂的治疗,持续20周的APC给药干预后,治疗组创面明显小于安慰剂组,同时可促进局部血管生长、减轻炎症,6例受试者中有3例达到临床治愈^[138]。针对骶骨压疮的治疗,APC同样可以促进肉芽和上皮组织的生长^[139]。

近几年来,蛋白C的临床致病机制研究与相关制剂的开发应用,已经成为该领域备受关注的热点方向。蛋白C是体内经典的抗凝因子,当前针对血友病的治疗需求,靶向PC抑制剂的多项研究正在不断开展^[140-142]。在蛋白C相关制剂的临床研究层面也有多项推进,包括重组的3K3A-APC在皮肤伤口模型^[143]、创伤性内皮病^[144]等的疗效与安全性检验,蛋白C用于治疗严重蛋白C缺失的临床表现分析^[145,146]等。

4 蛋白C及其受体在干细胞中的研究

4.1 造血干细胞

造血干细胞(hematopoietic stem cell, HSCs)能够通过产生成熟的血细胞来维持个体各种类型血细胞的平衡^[147]。其在损伤刺激以及发生感染的情况下会被激活,用来应对机体对血细胞生成增多的需求^[148]。蛋白C及其受体在造血干细胞上的研究颇为广泛(图3)。

4.1.1 PROCR在多物种多类型的造血干细胞中被鉴定为标志物

在诸多研究中,PROCR被鉴定为造血干细胞的

标志物。早在2006年,细胞表面的PROCR就被鉴定为小鼠骨髓中造血干细胞的标志物,与PROCR阴性造血干细胞相比,PROCR阳性的类群具有更高的骨髓重建效率^[149,150]。近年来,更多的研究报道PROCR也可以作为小鼠胚胎胎肝中的造血干细胞的标志物^[151]、人胚胎时期胎肝来源造血干细胞以及脐带血来源造血干细胞的标志物^[152-154]。另外,PROCR由于其膜蛋白的特性,可以用于造血干细胞的分离。通过与CD27、Flt3、CD48、CD150、CD11a等其他细胞表面标志物进行组合标记,可实现对造血干细胞的高效富集,且经该策略分选得到的细胞在后续体外克隆培养实验中,展现出更优异的干细胞干性特征^[155-157]。

4.1.2 PROCR⁺造血干细胞的空间分布

在空间位置上,PROCR阳性的造血干细胞与血栓调节蛋白高表达的内皮细胞亚群具有邻近关系^[124,151,158],可以协同对PC进行切割活化。另外,在成年小鼠骨髓中,表达血栓调节蛋白的内皮细胞在染色后呈现出了APC阳性信号,PROCR阳性长期造血干细胞(LT-HSC)恰好位于富含APC的区域附近^[158]。

4.1.3 PROCR在造血干细胞中的功能

在造血干细胞中,PC-PROCR同样具有非常重要的功能。PROCR阳性造血干细胞在移植实验中具有更加持久的自我更新能力^[159]。在小鼠胚胎胎

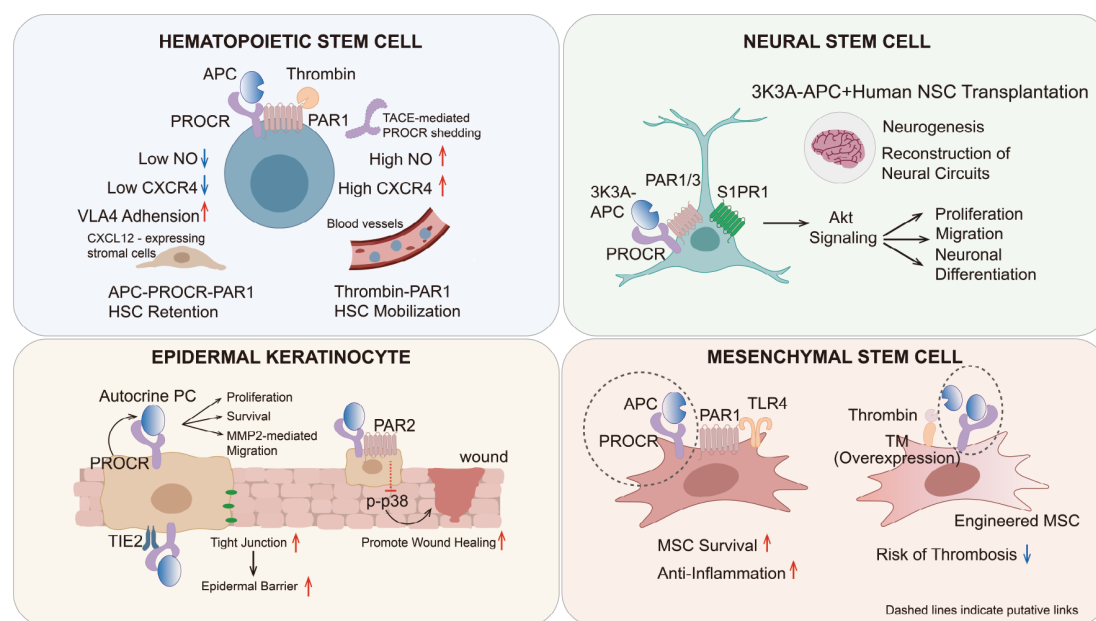


图3 PC-PROCR轴在成体干细胞上的功能

Figure 3 Functions of PC-PROCR axis in adult stem cells

肝来源造血干细胞的研究中,添加APC不会影响体外培养PROCR阳性干细胞的细胞增殖,而是剂量依赖地减少细胞凋亡,维持了造血干细胞的存活^[151]。PROCR对造血干细胞的维持功能呈现明确的配体依赖性特征;构建的PROCR配体结合位点突变型基因工程小鼠,可稳定重现造血功能衰竭伴随脾脏肿大的典型病理表型^[160]。在人脐带血来源造血干细胞研究方面,噬啉啉啉衍生物UM171能够作为激动剂促进人造血干细胞的自我更新,并上调PROCR表达^[161]。与PROCR阴性造血干细胞相比,经UM171处理后的PROCR阳性造血干细胞在免疫缺陷小鼠体内表现出更强的多系造血重建,并且具有连续移植能力^[153]。

4.1.4 APC-PROCR-PAR1信号对造血干细胞归巢和滞留的作用

造血干细胞的归巢与滞留受到多个因子精准调控。趋化因子受体CXCR4对于维持小鼠骨髓中长期造血干细胞的静止状态至关重要,在骨髓基质细胞中表达的CXCR4膜结合配体CXCL12,能够诱导CXCR4阳性长期造血干细胞的黏附与滞留^[162]。同时,细胞黏附受体整合素VLA4($\alpha\beta 1$)与纤连蛋白VCAM-1的结合是介导CXCL12-CXCR4造血干细胞滞留的重要因素^[163,164]。亦有研究表明,Cdc42的活性水平与它在造血干细胞中的极性分布调控,对于细胞黏附能力和骨髓重建潜能的维持至关重要^[165,166]。Cdc42缺陷会导致造血干细胞周期加快、归巢和滞留功能受损,从而导致大量干细胞动员^[167]。

基于前期对造血干细胞在骨髓中滞留影响因素的研究,Gur-Cohen等^[158]在2015年发现,APC-PROCR-PAR1信号通路能够通过限制一氧化氮(NO)的产生,使造血干细胞保持在低NO状态,从而导致表面CXCR4表达降低、Cdc42极化且GTP活性降低,以及VLA4介导的黏附力增强,进而促进长期造血干细胞在骨髓中的滞留^[168]。PAR1作为开关存在反向调控机制^[169]。在急性应激和临床动员的条件下,凝血酶的生成增加,继而激活PAR1信号通路^[170]。凝血酶/PAR1信号通路诱导NO生成、由TACE介导的PROCR脱落以及CXCR4和PAR1的上调,最终导致CXCL12介导的造血干细胞动员,从而克服骨髓中PROCR阳性LT-HSC的滞留,诱导它们进入血液循环^[158,169]。

4.2 神经干细胞

大脑中的神经元起源于数量相对较少的神经干

细胞和神经祖细胞^[171]。PC被认为不仅能够提供神经保护作用^[28,94,172],更能作用于神经干细胞直接促进其再生^[173]。在小鼠短暂性脑缺血模型中(大脑中动脉阻塞1小时),APC能够通过PAR1信号通路促进内源性血管新生以及神经发生。在缺血损伤3~6天后进行高剂量的APC给药,亦能够促进脑室下区神经祖细胞的增殖,并增强新形成的神经母细胞从该区域向缺血边缘的迁移^[95]。人胎儿神经干细胞中的3K3A-APC被发现能够通过PAR1/PAR3-S1PR1-Akt介导人胎儿神经干细胞的增殖迁移以及神经元分化^[174]。

基于3K3A-APC能够促进小鼠神经干细胞^[95]及人源神经干细胞^[174]的再生,一项长期脑缺血的小鼠卒中模型研究探索了人源神经干细胞移植联合3K3A-APC给药的新型治疗卒中方案。结果显示,该联合疗法能够刺激移植的人类神经干细胞产生神经元,促进神经回路的重建,并改善神经功能^[175]。

4.3 表皮角质形成细胞

角质形成细胞是表皮的主要细胞成分,负责维持表皮屏障的结构和稳态^[123]。PROCR被鉴定为表皮角质形成细胞的标志物^[176],并用于分离人皮肤表皮干细胞^[177]。

在细胞层面,PC被证明能够通过表皮角质形成细胞促进表皮愈合^[178]。除了已被广泛证实的肝脏合来源之外,现有研究已发现人表皮角质形成细胞同样具备分泌蛋白C(PC)的能力,且该局部合成的PC可作为自分泌生长因子,对人表皮角质形成细胞的增殖与凋亡过程发挥调控作用^[179]。PC可以剂量依赖地激活MMP2,刺激表皮角质形成细胞的迁移^[180]。PC也可以通过PROCR和Tie2,增强表皮层细胞间的紧密连接,从而加强表皮屏障,减少渗透^[181]。机制相关研究表明角质形成细胞中,PC通过切割PAR-2抑制磷酸化p38来促进野生型小鼠的伤口愈合^[182]。

4.4 间充质干细胞

间充质干细胞(mesenchymal stem cells, MSCs)被广泛应用于多种疾病的治疗,其能够调控损伤后的免疫反应,参与伤口愈合、组织再生等多个阶段^[183]。凝血和炎症之间存在相互作用,炎症会激活凝血系统,从而进一步加重炎症^[184]。近年来,由于间充质干细胞在临床治疗中的广泛应用及凝血系统在疾病尤其是炎症中的重要作用,有多篇

工作关注到了间充质干细胞治疗法在凝血系统中的功能^[185-187]。另外,之前的研究认为间充质干细胞也会促进凝血,具有血栓形成的风险^[188]。

PC-PROCR轴在间充质干细胞中的作用尚未得到直接、系统的验证,但现有研究提供了其可能参与抗凝和细胞保护的间接证据。研究发现,在炎症条件下,TLR4与凝血酶-PAR1信号之间的交叉调控可影响间充质干细胞的存活及治疗效果^[189]。鉴于PC也可通过PAR1介导细胞保护信号,该结果提示其可能参与了间充质干细胞对炎症环境的适应。另一方面,在工程化间充质干细胞研究中,增强细胞表面血栓调节蛋白的表达可降低间充质干细胞输注后肺栓塞和肾梗死等血栓栓塞风险^[190]。该研究明确将PC活化作为血栓调节蛋白发挥抗凝作用的理论依据,为PC-PROCR通路可能参与间充质干细胞治疗的血液相容性调控提供了重要提示^[190]。然而,目前尚缺乏PC-PROCR轴直接参与间充质干细胞存活、抗炎效应及输注安全性调控的实验证据。总体而言,上述研究线索提示,PC-PROCR轴在这些过程中的潜在功能值得进一步深入研究。

4.5 其他成体干细胞

PROCR还被鉴定为其他组织干细胞的标志物,包括乳腺^[191]、血管^[192]、卵巢表面上皮^[193]、胰岛^[194]、软骨^[195]等。

此外,已有研究探讨了PROCR在这些成体干细胞中的功能。在乳腺干细胞中,PROCR可以通过配体PC依赖的方式发挥功能:PC与PROCR结合后形成包含HSP90AA1的复合物,进一步转激活IGF1R信号通路^[196]。在表达PROCR的血管内皮上,PC可在缺血性外周动脉中通过PAR1信号通路介导,调控NO稳态,进而恢复外周血流并促进血管再生^[197]。

PROCR作为蛋白C的经典受体,已在造血系统以及乳腺、血管、胰岛等多种组织中被证实可用于标记组织成体干细胞类群。更有多项研究提示,PC-PROCR作为干细胞微环境的重要调节因子,能够影响干细胞存活、增殖、迁移并维持干细胞微环境的稳态。与此同时,在干细胞相关治疗中,PC-PROCR在凝血与免疫炎症环节的调控特性,也为降低治疗相关并发症风险、优化组织修复环境提供了潜在切入点,这些均有待在临床前模型与临床相关研究中进

一步系统的验证。

5 总结与展望

PC最初作为抗凝因子被发现,随后五十余年间对PC的大量研究表明,PC-PROCR不仅参与凝血调控过程,还参与细胞保护、抗炎反应以及免疫调节的生物学过程。值得关注的是,近年来PROCR被持续报道为多种成体干细胞的重要标志物,包括造血干细胞、表皮干细胞、乳腺干细胞及胰岛干细胞等。功能上,多项研究也证明PC-PROCR不仅是调控造血干细胞归巢和骨髓滞留的重要信号,而且在维持干细胞稳态、促进组织再生和调控损伤修复过程中均具有重要作用,为PC信号与干细胞再生医学提供了明确的切入点。

在基础研究层面,关于PC-PROCR的调控机制,尤其是该信号在PROCR⁺成体干细胞上受体复合物的构成、信号偏向性以及特定细胞类型的环境差异等方面仍然缺乏系统性的阐释。同时,干细胞是否会通过PC及其下游通路介入疾病的发生发展,以及该通路能否作为干预靶点实现可控调节,仍是需要重点回答的科学问题。

在临床转化层面,近二十年来围绕PC的结构与功能,例如以3K3A-APC为代表的低抗凝活性的工程化变体的改造,旨在在尽可能保留细胞保护及免疫调节功能的同时,降低出血风险,目前已在缺血性卒中、慢性创面修复等领域进入了临床试验阶段。与之并行的多维度针对蛋白C相关制剂的安全性评价、药代动力学特征检验,以及针对特定疾病的疗效证据也在持续积累中,为后续治疗方案的优化及规范执行提供了理论依据。

基于上述PC-PROCR信号在干细胞生物学中的潜在前景及其抗炎、细胞保护等疾病干预的相关优势,未来研究可从以下方向推进:其一,依托多组学分析技术,系统刻画PROCR标记的成体干细胞在稳态和疾病情况下的动态变化;其二,面向安全性及可靠性需求,开发信号选择性更强的PC工程化变体或通路选择性激动剂,并结合药物定向递送及控释策略来实现精准给药,降低出血风险的同时充分发挥其抗炎保护效应;其三,在治疗策略层面,探索PC信号与干细胞治疗协同诊疗策略,在临床前模型及临床研究中开展严格的验证,从而推动PC-PROCR信号在干细胞再生医学领域由机制证据走向医学

转化。

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