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抗菌肽 CRAMP 在固有免疫细胞中的分泌调控机制的研究进展

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摘要: 抗菌肽(antimicrobial peptides, AMPs)是固有免疫系统(innate immune system)中机体对抗病原微生物所产生的关键防御分子,广泛存在于植物、哺乳动物和人体内。其中 LL-37/cathelicidin-related antimicrobial peptide(CRAMP)是目前已知的唯一一种在人与小鼠中共有的抗菌肽,人源称为 LL-37,鼠源称为 CRAMP。除具有广谱的抗菌、抗病毒和抗真菌活性外,CRAMP/LL-37 还在调节宿主免疫平衡、促进伤口愈合和抵御炎症损伤等多个方面发挥着重要的作用。中性粒细胞和单核/巨噬细胞等固有免疫细胞是 CRAMP 的主要分泌来源,在识别病原体、执行吞噬功能以及分泌多种细胞因子和抗菌因子方面具有关键作用,参与机体免疫应答过程。深入研究 CRAMP 在固有免疫细胞上的分泌调控机制,对机体固有免疫具有重要贡献,也能够为理解宿主抗感染策略、开发抗菌药物和改善自体免疫疾病治疗提供新的思路。因此,结合最近的研究进展,综述 CRAMP 在固有免疫细胞中的分泌调控机制,为后续深入研究及临床应用提供参考依据。

关键词: 抗菌肽; cathelicidin 相关抗菌肽; 固有免疫细胞; 调控机制

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Research advances in the regulatory mechanisms governing cathelicidin-related antimicrobial peptide (CRAMP) secretion in innate immune cells

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Abstract: Antimicrobial peptides (AMPs) are critical defense molecules produced by the innate immune system to combat pathogenic microorganisms. These peptides are widely distributed in plants, mammals, and humans. Among them, LL-37/cathelicidin-related antimicrobial peptide (CRAMP) is the only known antimicrobial peptide shared between humans and mice, referred to as LL-37 in humans and CRAMP in mice. In addition to its broad-spectrum antibacterial, antiviral, and antifungal activities, CRAMP/LL-37 also plays a crucial role in regulating the host immune balance, promoting wound healing, and protecting against inflammatory damage. Inherent immune cells, such as neutrophils and monocytes/macrophages, are the primary sources of CRAMP secretion. These cells play a critical role in recog-

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nizing pathogens, performing phagocytosis, and secreting various cytokines and antimicrobial factors, thereby contributing to immune response of the body. In-depth research into the mechanisms regulating CRAMP secretion in innate immune cells will significantly enhance our understanding of innate immune system of the body. It will also provide valuable insights into host strategies for combating infections, the development of antimicrobial drugs, and the improvement of treatments for autoimmune diseases. Thus, this article reviews the mechanisms governing CRAMP secretion in innate immune cells, drawing on recent advancements, and aims to provide a reference for future in-depth studies and clinical applications.

Key words: antimicrobial peptides; CRAMP; natural immune cells; regulatory mechanisms

0 引言

抗菌肽依其结构可分为多种类型,其中抗菌肽和防御素为主要的类型。抗菌肽作为一类小分子、阳离子肽,广泛存在于人及其他物种中,是脊椎动物固有免疫系统的一部分,其成员 CRAMP(cathelin-related antimicrobial peptide)具有广谱抗菌活性,可有效作用于细菌、真菌及病毒,且能诱导宿主产生特异性防御反应。而固有免疫细胞分泌的 CRAMP 对于宿主调控作用机理的研究仍存在局限。本文旨在综述目前关于 CRAMP 在固有免疫细胞上的分泌调控机制的研究进展,重点围绕其结构功能、体外合成表达、免疫调控作用及应用前景展开,为其在人医和兽医学中的转化应用提供参考。

1 CRAMP 的结构与功能概述

1.1 CRAMP 的基本特点

CRAMP是由小鼠 *Camp* 基因编码、位于9号染色体上的一类阳离子抗菌肽^[1],化学结构式见图1。其前体蛋白在内质网中经信号肽引导后,经蛋白酶切割生成约34个氨基酸的成熟肽(对应人源 LL-37 的37残基长度),LL-37 和 CRAMP 被认为是同源的;它们具有相似的结构和抗菌能力(表1)。成熟 CRAMP 呈典型两性 α -螺旋结构,带正电荷,可与细菌膜磷脂负电荷区域结合,造成膜破裂并引发细胞内容物外泄^[1-2]。

1.2 CRAMP 对不同病原体的清除机制

研究发现,基于前体蛋白序列,CRAMP 的第16~33位氨基酸片段能阻断细菌胞质分裂^[3-5],其第

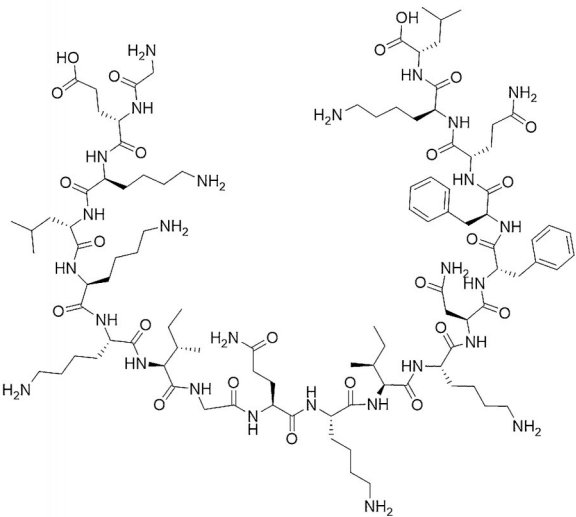


图1 CRAMP 的结构式
Figure 1 Structure of CRAMP

18~35位片段(CRAMP18-35)有显著的抗生物膜活性^[6],最后确定其发挥功能的最小氨基酸序列为第20~33位氨基酸残基,并在抗细菌、抗真菌及抗生物膜方面发挥重要作用^[7]。

1.2.1 CRAMP 的抗菌作用

CRAMP 主要通过双重途径清除细菌。一方面,其第16~33位片段可抑制细菌细胞分裂蛋白 FtsZ 组装,阻断胞质分裂^[3-5];另一方面,通过扰乱细菌细胞膜完整性,引发膜通透化^[8],同时参与巨噬细胞自噬通路,协同清除胞内细菌。实验证实,CRAMP^{-/-}小鼠巨噬细胞清除大肠杆菌(*E. coli*)能力缺陷,导致细菌滞留及细胞碎片化,而巨噬细胞受

表1 CRAMP 与 LL-37 的基本特点比较
Table 1 Comparison of features between CRAMP and LL-37

特点	CRAMP	LL-37
氨基酸序列	GLLRKGGGEKIGEKLLKIGQKIKNFFQKLVPQPEQ	LLGDFFRKSKEKIGKEFKRIVQRIKDFLRNLPRTES
净电荷	带强正电荷	带强正电荷
疏水性	略低	较高
二级结构	α -螺旋结构	α -螺旋结构

细菌刺激后产生的 CRAMP 可直接或与自噬合作发挥杀菌作用^[8]。此外, CRAMP 第 18~35 位片段 (CRAMP18-35) 具有显著抗生物膜活性, 可破坏细菌生物膜结构稳定性^[6,9]。

1.2.2 CRAMP 的抗真菌作用

抗菌肽 CRAMP 主要通过靶向真菌细胞膜核心成分发挥抗真菌效应^[1,3,9]。其特有的两性 α -螺旋结构可特异性插入真菌细胞膜脂质双层结构中, 破坏膜结构完整性, 最终导致真菌细胞内容物外泄及细胞裂亡^[2-3,7]。研究表明, 抗菌肽对念珠菌 (*Candida*)、曲霉菌 (*Aspergillus*) 等临床常见致病性真菌均表现出广谱抑制活性^[3,6]。

1.2.3 CRAMP 的抗病毒作用

CRAMP 主要通过免疫调节和直接干扰病毒生命周期, 抑制 EV71 等无包膜病毒^[10]。新生小鼠感染模型中, CRAMP 表达上调与病毒复制下降同步, 提示其在固有免疫中的关键作用^[11]; 体外研究证实, 机制包括直接干扰病毒与宿主细胞的结合过程, 以及调控宿主细胞的固有免疫反应, 如通过增强干扰素 β (IFN- β) 表达及 IRF3 磷酸化来建立抗病毒状态^[12]。这与人类同源肽 LL-37 抗流感病毒的双重机制相似^[13], 而猪源 CATH-B1 及其衍生物的相关研究^[14], 进一步印证抗菌肽家族通过双重通路发挥广谱抗病毒活性。

1.3 CRAMP 与其他典型抗菌肽的比较及其作用机制

CRAMP 与 LL-37、防御素等经典宿主防御肽 (host defense peptides, HDPs) 均为固有免疫系统的核心效应分子^[15], 共同构成宿主抵御病原体入侵、维持免疫稳态与组织完整性的第一道分子屏障。均以

带正电荷的两亲性结构为基础, 通过静电作用靶向结合细菌细胞膜表面的负电荷组分, 进而以膜穿孔、膜去稳定或干扰胞内代谢等方式实现广谱、快速的杀菌活性^[16-18]。它们不仅是天然的“抗生素”, 更是重要的免疫调节因子, 能够通过激活特定受体 (如 FPR2) 招募免疫细胞^[19]、中和内毒素 (如 LPS)^[20] 并参与组织修复过程。尽管 CRAMP 与其他抗菌肽存在诸多共性, 但在来源物种、分子空间构象、功能延伸范围及潜在应用等方面仍存在显著差异^[21-35], 如表 2 所示。

2 CRAMP 的表达与调控

2.1 固有免疫细胞 CRAMP 的产生

固有免疫细胞在免疫监视、炎症反应和组织修复中起着关键作用。这类细胞来源于骨髓中的造血干细胞 (hematopoietic stem cells, HSCs), 具有高度的可塑性, 并在迁移到其他组织后, 能够分化为中性粒细胞和单核/巨噬细胞两大类^[36-40]。

由中性粒细胞的核糖体合成的 CRAMP 前体蛋白包含: N 端信号肽 (引导内质网定位并被切除)、保守的 Cathelin 结构域 (抑制蛋白酶并稳定前体)、C 端抗菌肽区 (具直接杀菌活性)。新合成的 pro-CRAMP 经高尔基体修饰后, 与带负电的载体蛋白结合, 浓缩储存于溶酶体相关细胞器 (lysosome-related organelles, LROs) 的致密核心基质中。在病原体刺激下, 颗粒与吞噬溶酶体或细胞膜融合, 前体被丝氨酸蛋白酶 (如蛋白酶 3) 切割, 释放活性 CRAMP 抗菌肽^[41-42]。

2.2 关键路径与转录调控

Camp 基因的转录受多条信号通路的调控, 其中

表 2 CRAMP 与其他典型抗菌肽的比较
Table 2 Comparison of CRAMP with other typical antimicrobial peptides

典型抗菌肽	来源	结构类型	主要功能	应用	参考文献
CRAMP	小鼠	α -螺旋	广谱抗菌 (G^+ / G^- 菌、真菌)、抗病毒, 趋化免疫细胞调节炎症, 促进伤口修复调控巨噬细胞极化	小鼠疾病模型 (如结肠炎、皮肤感染)	[21-23]
LL-37	人类	α -螺旋	强效抗炎, 抑制促炎因子, 负向调控固有免疫, 抑制 NF- κ B、MAPK 通路, 减轻自身免疫与炎症损伤	炎症性肠病、慢性伤口、败血症辅助治疗	[24-27]
防御素	全物种	β -折叠	极高的结构稳定性, 广谱抗菌、抗病毒、抗真菌, 趋化免疫细胞调节炎症与获得性免疫肿瘤杀伤相关活性	呼吸道感染、肠道黏膜免疫、新药开发模板	[28-30]
蛙皮素	两栖	α -螺旋	广谱抗菌 (G^+ / G^- 、真菌)、抗寄生虫, 部分抗病毒膜破坏机制为主	糖尿病足溃疡 (临床药物 Pexiganan 原型)	[31-32]
乳酸链球菌素	细菌	环状/羊毛硫肽	强效抑制 G^+ 菌, 芽胞破坏细胞膜与细胞壁合成, 对 G^- 菌作用较弱	食品防腐剂 (乳制品、肉制品) 饲料添加剂、口腔抗菌制剂	[33-35]

经典 TLR(Toll 样受体)-NF- κ B 通路、锌等物质诱导的 MAPK(丝裂原活化蛋白激酶)途径,均能显著促进 *Camp* 基因的转录进程^[43-48]。在 TLR-NF- κ B 通路中,单核细胞的表面与胞内分布有多种可识别病原体相关分子模式(PAMPs)的 TLRs,当病原体或 LPS 等炎症信号刺激时,会激活单核细胞表面或胞内的 TLR2、TLR4、TLR9 等受体,进而触发下游信号传导,促使 NF- κ B 活化并发生核移位,随后与 *Camp* 基因启动子的特定区域相结合,启动该基因的转录^[43-44];而在 MAPK 途径中,ERK、p38、JNK 等亚家族构成了 MAPK 家族的核心^[45],微量元素锌可诱导 ERK 与 p38MAPK 发生磷酸化,进而激活下游转录因子,推动 *Camp* 基因的转录及 LL-37/CRAMP 的合成,在 Caco-2 等肠道上皮细胞模型中已被证实;锌刺激可显著提升细胞内 LL-37 的 mRNA 水平与蛋白分泌量,且该过程依赖于 MEK/ERK 和 p38MAPK 信号通路的活化^[46]。

2.3 钙离子与维生素 D 协同调控

病原体刺激可迅速引起单核细胞胞内 Ca^{2+} 水平的波动,进而激活胞质中的多种 Ca^{2+} 依赖性酶与蛋白(如钙调素、蛋白激酶 C 家族成员等),促进分泌泡向质膜的转运与融合,从而调节胞外因子和抗菌肽的释放^[47-48]。与此同时,TLR 信号通路在单核细胞中上调 25-羟基维生素 D₃-1 α 羟化酶(CYP27B1)表达,将血浆中惰性的 25(OH)D₃ 转化为活性 1,25(OH)₂D₃,后者与维生素 D 受体(VDR)形成 VDR-RXR 异源二聚体,结合靶基因启动子上的 VDRE 元件,增强 *Camp* 基因的转录与表达^[49-50]。此外,细胞内基础水平的钙离子可磷酸化 VDR 的特定氨基酸位点(Ser208),磷酸化的 VDR 与 VDRE 的结合亲和力显著提升,进而加速 *Camp* mRNA 的转录。研究证实,若细胞内钙离子浓度过低,维生素 D 诱导的 CRAMP 转录效率会大大下降。这种由 Ca^{2+} 信号与活性维生素 D 共同驱动的双重调控,既优化了分泌机制,也强化了单核细胞的抗菌防御能力。

2.4 代谢物调控

肠道菌群代谢产物——短链脂肪酸(丁酸盐)作为功能性代谢信号,可通过调控表观修饰或免疫细胞活化,间接影响 CRAMP 等抗菌肽的表达,尤其在肠道黏膜免疫中发挥核心作用。短链脂肪酸可通过 3 种途径调控 CRAMP 表达:其一,通过抑制组蛋白去乙酰化酶(histone deacetylase,HDAC)活性,上调 *Camp* 基因启动子区域组蛋白 H3 的乙酰化水平,进而促进基因转录激活^[51-52];其二,激活丝裂原活化蛋白(mitogen-activated protein,MAP)激酶磷酸化通

路,直接启动 *Camp* 基因的转录过程,强化 CRAMP 的合成^[31];其三,与肠道上皮细胞表面的 G 蛋白偶联受体(GPR43/GPR109A)特异性结合,触发细胞内钙信号通路激活,间接促进 CRAMP 的合成与分泌,该调控路径对肠道黏膜免疫屏障功能的稳定具有特殊意义^[52]。

2.5 CRAMP 体外合成

体外高效合成与异源表达技术是 CRAMP 从基础研究向临床及产业转化的核心支撑,目前已逐步形成化学合成与基因工程表达两大技术体系。两类技术路径各具特色、互补适配不同应用场景,且通过系列技术优化持续突破规模化、高活性制备瓶颈。

2.5.1 化学合成

固相合成法是 CRAMP 化学合成的主流技术,通过 Fmoc 或 Boc 策略在树脂上逐步偶联氨基酸残基构建肽链,可精准控制氨基酸序列^[53]。通过乙酰化、酰胺化等末端修饰手段,可显著提升 CRAMP 的体内稳定性与抗蛋白酶降解能力^[54-55]。该技术便于开展结构修饰优化(如引入非天然氨基酸、荧光标记等),适用于制备 CRAMP18-35 等活性片段^[9]。然而,化学合成存在规模化生产成本较高、长肽合成过程中易形成错误折叠等局限,限制了其在大规模产业化应用中的推广。

2.5.2 基因工程表达

为突破化学合成的规模化瓶颈,目前以大肠杆菌为宿主的原核表达系统,通过构建 pET 系列重组载体(如 pET-28b)可实现 CRAMP 的高效表达,经 GST 或 His 标签亲和层析纯化后产物具有生物活性,具备表达周期短、成本相对低廉的优势^[56]。但受限于原核生物缺乏翻译后修饰系统,重组 CRAMP 易形成包涵体,需经变性-复性处理方可恢复正确构象与活性。更关键的是,活性抗菌肽对原核宿主(如大肠杆菌)具有固有剧毒性,会直接杀伤宿主细胞、阻碍多肽高效表达,这是规模化生产的核心瓶颈^[57]。为克服包涵体与宿主毒性难题,融合表达策略已成为研究热点,通过将 CRAMP 与 SUMO、硫氧还蛋白(Trx)等可溶性标签融合表达^[58],可显著提升重组肽可溶性并降低宿主毒性风险。

尽管原核系统优化取得了一定进展,真核表达系统(如真菌)的尝试仍未突破核心瓶颈。研究尝试采用毕赤酵母等真菌表达抗菌肽类抗菌肽(如:抗菌肽-BF、抗菌肽-1),虽可实现分泌表达、规避部分原核宿主毒性问题,但存在表达量偏低、发酵周期长、成本上升等局限,且对宿主仍存在潜在毒性影响,未实现临床级活性肽的稳定、低成本规模化制备。相

关研究包括:在真菌中尝试抗菌肽表达,验证了真核系统的可行性但产量有限^[59-60]。抗菌肽的广谱杀菌特性,高浓度表达时会反噬宿主细胞,导致发酵后期细胞活力快速下降,因此宿主毒性及规模化生产瓶颈仍是抗菌肽(含抗菌肽)基因工程表达尚未根本解决的核心问题,严重制约其临床应用。

3 CRAMP参与固有免疫与适应性免疫的互作调控

CRAMP兼具直接抗菌活性与固有免疫调控功能,通过多通路、多靶点调控固有免疫应答,同时平衡炎症反应,维持固有免疫稳态^[61]。首先,CRAMP能够特异性结合并激活G蛋白偶联受体Fpr2(formyl peptide receptor 2),启动G α_i -依赖的信号传导通路,进而激活ERK1/2和p38-MAPK等下游分子,从而诱导白细胞发生定向趋化迁移(chemotaxis),增强局部抗感染能力,高效清除病原体^[62]。此外,CRAMP的同源肽LL-37在人体中通过中和细菌内毒素(LPS)及脂壁酸(lipoteichoic acid, LTA)减轻过度炎症反应,其主要机制是带阳离子电荷的LL-37与带负电荷的LPS和LTA直接结合,从而使内毒素失活抑制TNF- α 的产生^[63-69]。同时通过诱导IL-1RA、IL-10等抗炎细胞因子的表达,调控炎症进程,维持固有免疫的炎症平衡^[67-68]。在免疫细胞之间,LL-37还可增强外周血单核细胞对IL-1 β 的响应,协同产生更多趋化因子(如MCP-1),进一步促进免疫细胞向炎症部位的聚集^[69]。LL-37在呼吸道及肠道上皮中诱导CXCL8等趋化因子的分泌,调节黏膜免疫稳态及嗜酸性粒细胞的募集,对黏膜屏障的防御和修复具有重要意义^[24,70]。这说明CRAMP/LL-37介导的趋化作用与多重抗炎机制协同运作,不仅有效提高了病原体的清除速率,还可以调节炎症与修复过程,在固有免疫调控中发挥作用,维持机体免疫稳态。

近年来的研究指出,CRAMP不仅仅是固有免疫的一部分,还可增强树突状细胞的抗原呈递功能、平衡Th1/Th17与调节性T细胞(Treg)的应答,以参与适应性免疫的启动与调控,从而在感染环境中维持免疫稳态^[19,71-73]。研究发现,LL-37/CRAMP可通过与类甲酰肽受体1(FPR1)相互作用,将中性粒细胞、单核细胞和T细胞招募至微生物侵袭部位,从而有助于固有免疫和适应性免疫^[19]。此外,研究人员发现,利用LL-37/CRAMP处理PBMC细胞,可提高其存活率,并对T细胞反应产生广泛影响。在激活状态下,LL-37/CRAMP处理组的T细胞增

殖减少,同时Tregs的生成显著增加^[71]。综上所述,CRAMP/LL-37桥接了固有与适应性免疫,协同维持机体免疫稳态。

4 CRAMP调节组织微环境稳态调控炎症反应

CRAMP还可以通过肠道菌群参与对炎症的调控。结肠稳态的紊乱会导致其微生物群组成发生改变,已有充分证据表明,肠道微生物群与结肠黏膜的相互作用会引发炎症性肠病^[74]。当巨噬细胞受到细菌及其产物刺激时,会激活Toll样受体通路并增强CRAMP的产生。CRAMP可单独或与自噬机制协同作用,杀灭并清除有害细菌,上调MUC1和MUC2表达并激活MAPK激酶信号通路,直接刺激上皮细胞的黏液合成,维持肠道菌群稳态,从而调节肠道炎症^[25]。先前的研究发现,CRAMP^{-/-}小鼠对DSS诱导的结肠炎高度敏感,表现出黏膜损伤更为严重以及促炎细胞因子水平增高且肠道炎症细胞浸润增加。当用抗生素处理可减轻CRAMP^{-/-}小鼠的DSS结肠炎症状^[75]。这说明CRAMP可通过调控肠道微生物群来发挥其抗炎和屏障保护功能。此外,在TNBS诱导的小鼠结肠炎模型中,肠腔内给药CRAMP或静脉注射过表达Camp基因的慢病毒,均可缓解结肠炎症^[76],提示CRAMP可减轻与急性及慢性炎症相关的结肠炎。

鸡防御素-2(chicken cathelicidin-2, Cath-2)作为禽类固有免疫系统的关键宿主防御肽,在禽类肠道健康中的作用与CRAMP在哺乳动物中的功能具有相似性。Cath-2作为禽类固有免疫系统的重要HDPs,兼具广谱抗菌活性与多元免疫调节功能,其与空肠弯曲杆菌(*Campylobacter jejuni*)相互作用,对雏鸡肠道菌群的调控及免疫调节效应。Cath-2可缓解LTA诱导的肠道炎症反应,降低促炎细胞因子、升高抗炎细胞因子水平,发挥抗炎效应^[77]。胚内注射Cath-2的D-氨基酸类似物(D-Cath-2)可显著改变7日龄雏鸡肠道菌群组成,维持肠道微生态平衡^[78]。

5 未来研究方向与挑战

目前已有部分抗菌肽作为药物进入临床试验阶段。例如,pexiganan作为马加宁肽的类似物,曾在Ⅲ期临床试验中作为局部乳膏用于治疗糖尿病足感染性溃疡。然而,由于其疗效未优于现有治疗方案,相关研发项目被终止。同时,针对抗菌肽衍生抗菌化合物在局部治疗玫瑰痤疮中的长期安全性进行的Ⅲ期临床试验仍在进行。此外,在一项住院患者的Ⅱ期临床试验中,局部应用含人乳铁蛋白衍生肽

PXL01的水凝胶被证实安全且耐受性良好,并且在肌腱修复术后抗粘连治疗中显示出有效性^[79]。此外,关于LL-37局部治疗下肢静脉性溃疡的临床试验也正在进行中^[80]。尽管如此,目前将抗菌肽作为药物治疗疾病的失败率仍居高不下,成功上市的抗菌肽衍生药物仍然较少。其中,PAC-113(一种组蛋白类似物)作为外用治疗药物在台湾地区用于治疗念珠菌病,而达巴万星(dalbavancin)作为一种半合成脂糖肽类药物,已在美国获批用于急性皮肤感染的静脉给药治疗^[81]。

CRAMP作为一种具有较广谱的杀菌作用,因其较低的耐药性,成为新型抗菌药物开发中的一个潜在方向。然而,其体外合成复杂、生产成本较高且体外稳定性差,这些问题仍未得到有效解决。因此,研究CRAMP分泌的调控机制,尤其是固有免疫细胞如何调控其分泌,可能为以抗菌肽为核心的药物或辅助疗法的研发提供新思路。例如,通过调控特定信号通路增强CRAMP分泌,可能提高机体对多重耐药菌的防御力;在自身免疫或慢性炎症疾病(如炎症性肠病、类风湿关节炎等)中,适度提升CRAMP水平或许也可帮助缓解病理过程。先前的研究还发现,CRAMP在寄生虫感染过程中发挥作用,通过调控宿主肠道菌群和抑制性免疫,形成有利于寄生虫定植的免疫抑制微环境^[11]。这一发现提示,通过靶向CRAMP,可能成为抵抗寄生虫感染、预防相关寄生虫疾病的有效策略。随着基础研究的不断深入和技术手段的升级,CRAMP在单核细胞的分泌调控机制将会被阐释得更加透彻,并为人类的健康与疾病防治事业作出更大贡献。

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