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综述

潘氏细胞及其分泌的抗菌肽与肠道功能稳定和疾病的关系

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摘要 潘氏细胞是一类独特的分泌型肠道上皮细胞, 其细胞质顶部含有丰富的颗粒, 这些颗粒含有抗菌肽和生长因子等重要物质并且在宿主与微生物的相互作用中发挥着重要作用。抗菌肽可以调节微生物群的组成, 防御共生菌和致病菌对黏膜的穿透, 保护肠道上皮; 而潘氏细胞分泌的多种因子则可以维持干细胞的生态位。潘氏细胞破坏或功能出现障碍会导致各种肠道炎症, 主要与肠道菌群紊乱和肠屏障破坏相关。在多种疾病中也存在潘氏细胞的异常, 异常的潘氏细胞可能与疾病的发生与进展互为因果、相互影响。该文旨在梳理潘氏细胞分泌的主要抗菌肽种类, 并对与潘氏细胞关联的几种疾病进行综述。

关键词 潘氏细胞; 抗菌肽; 溶菌酶; 防御素; 肠道感染

Paneth Cells and the Antimicrobial Peptides Secreted by Them: Link to Intestinal Stability and Diseases

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Abstract Paneth cells are a unique type of secretory intestinal epithelial cells. They possess abundant granules in their apical cytoplasm. These granules contain important substances such as antimicrobial peptides and growth factors, and play an important role in the interaction between the host and microorganisms. Antimicrobial peptides can regulate the composition of the microbiota, defend against the penetration of commensal bacteria and pathogenic bacteria into the mucosa, and protect the intestinal epithelium. The various factors secreted by Paneth cells can maintain the ecological niche of stem cells. The destroyed or dysfunction of Paneth cells can lead to various intestinal inflammations, which are primarily associated with gut microbiota dysbiosis and intestinal barrier disruption. Furthermore, abnormalities in Paneth cell function are implicated in a range of diseases, suggesting a potential causal relationship with disease onset and progression. The article aims to summarize the main types of antimicrobial peptides secreted by Paneth cells and to provide an overview of several diseases associated with Paneth cells.

Keywords Paneth cell; antimicrobial peptide; lysozyme; defensin; enteric infections

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肠上皮由单层上皮细胞组成, 其上覆盖黏液层, 是将肠道内容物与组织分隔开的重要屏障[1], 肠上皮细胞由吸收细胞(如肠细胞)和分泌细胞组成, 分泌细胞又包括肠内分泌细胞、杯状细胞和潘氏细胞(Paneth cell, PC)[2]。PC是一类特殊的分泌细胞, 因为它主要位于肠隐窝的底部, 并且与干细胞相间分布, 在维持肠道稳态方面起着关键的作用。PC能分泌多种抗菌肽(antimicrobial peptides, AMPs)及信号分子, 具有塑造肠道菌群、促进再生和控制炎症等多种功能[3]。

1 PC的概述

PC位于各种动物小肠Lieberkühn隐窝的底部, 并散布在肠道干细胞(intestinal stem cell, ISC)中, 可在多种信号的调控下由干细胞分化而来[4]。其他ISC分化上皮细胞类型(如杯状细胞、肠内分泌细胞、簇状细胞和肠细胞)从肠隐窝迁移出并分布于肠上皮的不同部位, 而PC仍留在隐窝基底内[5]。此外, 其他上皮细胞类型的寿命为3~5天, 而PC则可以在肠隐窝中存活约一个月[6-7]。肠道细胞的分化由多种信号通路决定, 其中PC分化是在Notch信号和Wnt信号的共同调节下进行的[2]。Notch信号有利于干细胞向吸收细胞转化, 而Wnt信号则诱导干细胞向分泌细胞转化。Wnt信号转导在肠上皮细胞中起关键作用, 该信号通路的核心过程是β-catenin与转录因子T细胞因子(T-cell factor, TCF)的相互作用[8], 当肠上皮细胞释放的Wnt配体与细胞表面的Frizzled-5受体结合时, 经典的Wnt信号通路被启动, 从而促进PC的分化和成熟[9], 过表达一种Wnt信号抑制剂——Dkk1的转基因小鼠表现出所有分泌细胞(包括PC)的缺失[10]。此外, 其他因素也参与驱动分泌祖细胞向PC转变, Math1、Gfi1和Sox9都是PC分化所必需的[11-12]。

PC位于肠隐窝的基底部, 从广义上讲, 可以将PC的功能概括为: 为小肠上皮屏障提供重要的支持作用, 维护其正常结构和功能。PC由ISC分化而来, 而实际上, PC在肠隐窝的稳态以及ISC的生态位维持中也起到重要作用[13]。PC通过分泌EGF、Wnt3、TGF-α、Notch配体Dll4等因子向其相邻的ISC提供必要的生态位信号来维持上皮细胞的物理屏障[14], 同时PC清除隐窝中的凋亡细胞可防止炎症的发生[7]。此外, PC分泌大量抗菌肽, 在调控共生菌组成和防御病原菌方面发挥着重要作用(图1)。接下来我们讨论PC分泌的抗菌肽种类及其主要功能。

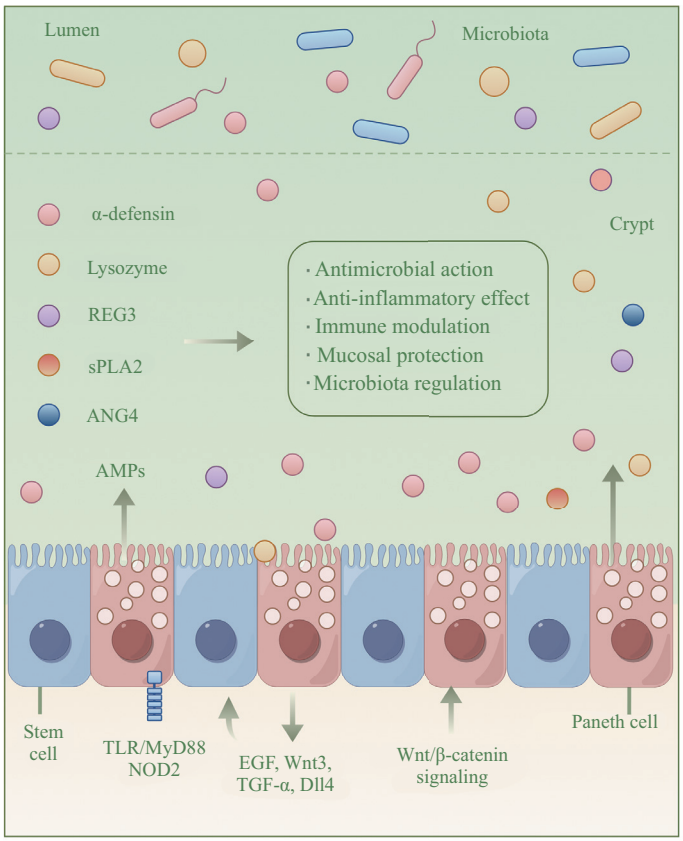
2 PC分泌的抗菌肽

肠道中共生着数以万计的微生物, 其中大部分是与机体互利共生的, 协助宿主代谢及产生营养物质、维持肠道的稳态、抵抗病原菌的入侵[15], 然而当机体的免疫力下降、肠道稳态被破坏时, 病原菌就可能增殖并引发疾病。PC是肠道中丰富的AMPs的主要来源, 其顶部细胞质中的颗粒中包含大量的AMPs, 在控制共生菌组成和防御病原菌方面发挥着重要作用, 因此可以认为PC是肠道先天免疫的重要组成成分。PC衍生的AMPs主要包括α-防御素(α-defensin, DEFA, 小鼠中的cryptdin)、溶菌酶(lysozyme, LYZ)、分泌型磷脂酶A2(secretory phospholipase A2, sPLA2)和再生家族成员3α(regenerating family member 3 alpha, REG3α)[小鼠中的REG3γ(regenerating family member 3 gamma)][3]。这些AMPs表现出相似的杀菌能力[16], 它们通过与细菌结合, 导致细菌质膜穿孔、透性增加(表1)。

2.1 α-防御素

α-防御素占PC分泌的所有AMPs的70%[17]。哺乳动物的α-防御素长度为30~40个氨基酸, 人类PC含有2种α-防御素, α-防御素-5(α-defensin-5, HD5)和HD6[18], 而小鼠的α-防御素则有更多分型, 且与品系相关。小鼠的防御素也被称为"隐窝素"(cryptdin)。CASTILLO等[19]提出了一种方法精确地确定C57BL/6小鼠小肠中α-防御素(*Defa*) mRNA的表达水平, 并鉴定出了8个*Defa*基因的亚组(表2)。*Defa*基因的表达与PC的分布一致, 在远端小肠多于近端, *Defa3*、*Defa5*、*Defa23*、*Defa24*和*Defa26*在整个小肠中的表达分布相对均匀。其中, *Defa24*表现出显著的高表达, *Defa20*的表达量也很高, 但是后者表达量在不同肠段出现了明显的差异, 因此在进行相应的研究时要更重视取材的区域。

与普通小鼠相比, 在无菌条件下饲养的小鼠先天和后天免疫都发生了较大的变化, 已有研究表明, PC分泌的另一种防御素REG3γ在无菌鼠中的表达量明显减少[20], 而α-防御素的表达对常规微生物群的依赖性较小[21-22]。α-防御素的表达是组成型的, 微生物刺激会促进其分泌, 细菌和细菌抗原[如脂多糖(lipopolysaccharide, LPS)、脂磷壁酸、脂质A和胞壁酰二肽]会刺激PC分泌防御素, 同时防御素的分泌量与刺激的时间和剂量相关[17]; 同时有研究表明, 核



AMPs: 抗菌肽; ISC: 肠道干细胞; TLR: Toll样受体; NOD2: 核苷酸结合寡聚化结构域样受体2; sPLA2: 分泌型磷脂酶A2; REG3: 再生家族成员3; ANG4: 血管生成素4。

AMPs: antimicrobial peptides; ISC: intestinal stem cell; TLR: Toll-like receptor; NOD2: nucleotide-binding oligomerization domain-containing 2; sPLA2: secretory phospholipase A2; REG3: regenerating family member 3; ANG4: angiogenin 4.

图1 潘式细胞及其分泌的抗菌肽(本图由Figdraw绘制)

Fig.1 Paneth cells and antimicrobial peptides (this image is drawn by Figdraw)

表1 潘氏细胞的抗菌肽

Table 1 Antimicrobial peptides secreted by Paneth cell

抗菌肽名称 Name of antimicrobial peptides	功能 Function	抗菌机制 Antibacterial mechanism
α-defensin	Broad-spectrum antibacterial effects, maintaining intestinal homeostasis, antifungal, antiviral [27-28]	Destroy the membrane of bacteria, change membrane permeability and conductivity [26]
Lysozyme	Primarily anti Gram-positive bacteria, regulates intestinal flora, alleviates inflammatory responses [3,35]	Hydrolyze bacterial cell wall [3]
sPLA2	Primarily anti Gram-positive bacteria [37-38]	Hydrolyze cell membrane phospholipids [37-38]
REG3α (human) REG3γ (mice)	Antibacterial; antifungal, supports the function of intestinal stem cells [41]	Bind with peptidoglycan [41]
ANG4 (mice)	Antibacterial, antiviral, induces the expansion of stem cells and apoptosis of intestinal epithelial cells [45,47]	Degrade bacterial RNA [45]
PYY	Anti-Candida albicans infection [48]	Change the intestinal environment, directly antifungal [48]

sPLA2: 分泌型磷脂酶A2; REG3: 再生家族成员3; ANG4: 血管生成素4; PYY: 肽YY。

sPLA2: secretory phospholipase A2; REG3: regenerating family member 3; ANG4: angiogenin 4; PYY: peptide YY.

苷酸结合寡聚化结构域样受体2(nucleotide-binding oligomerization domain-containing 2, NOD2)的功能缺失会降低α-防御素的表达水平[23-24], 表明其在PC信号转导中的重要性。

防御素在抵抗细菌方面起到重要作用, 但值得注意的是α-防御素只有在分泌后被裂解为活性形式时

表2 C57BL/6小鼠α-防御素(*Defa*)基因的亚组

Table 2 *Defa* paralog subgroups of C57BL/6 mice

*Defa*基因亚组 *Defa* paralog subgroup	包含成员 Members
Defa3	*Defa3*, *Defa17*
Defa5	*Defa5*, *Defa34*, *Defa35*, *Defa36*, *Defa37*
Defa20	*Defa20*, *Defa32*, *Defa33*, *Defa2*
Defa21	*Defa21*
Defa22	*Defa22*
Defa23	*Defa23*, *Defa27*, *Defa31*
Defa24	*Defa24*, *Defa30*
Defa26	*Defa26*, *Gm15292*

才会表现出抗菌能力, 而这一裂解过程在人类中由胰蛋白酶催化完成, 在小鼠中由基质金属蛋白酶7(matrix metalloproteinase 7, Mmp7)催化完成[25]。Mmp7与α-防御素共定位, 其本身不具备抗菌活性, 并且其缺陷也不会影响防御素的表达, 但是将*Mmp7*基因敲除会导致防御素的前体增多且无法转变为活性形式, 造成感染更为严重。防御素对革兰氏阴性和阳性菌均具有活性, 其可以通过破坏细菌的外膜、改变膜通透性及电导率来起到杀菌作用[26]。还有研究表明, 防御素有抗病毒和抗真菌功能[27-28], 但WILSON等[29]证明α-防御素在体外会增强腺病毒2(MAdV-2)的感染, 且防御素在某些条件下可以驱动病毒的进化[30]。因此防御素在体内的功能是多样的, 且取决于环境。

2.2 溶菌酶

PC分泌的另一种重要的抗菌肽是溶菌酶, 溶菌酶在小鼠中是被广泛使用的PC标记物; 在哺乳动物中, 溶菌酶还大量存在于血液和肝脏、分泌物(包括眼泪、尿液、唾液和乳汁)、黏膜表面(浓度可高达1 mg/mL)以及吞噬细胞(包括巨噬细胞、中性粒细胞和树突状细胞)中[31]。小鼠中存在两种溶菌酶, *Lyz1*(由PC表达)编码的P型溶菌酶和*Lyz2*(由巨噬细胞表达)编码的M型溶菌酶[3]。溶菌酶的表达与防御素一样, 也是组成型的。NOD2受体并不会影响溶菌酶基因的表达, 然而其能影响溶菌酶的分选和分泌。溶菌酶分选是一种促进其分泌的特异性过程。在无菌小鼠中, 缺乏细菌胞壁酰二肽(muramyl dipeptide, MDP)和LPS的刺激, 溶菌酶并不会被分选, 而是发生降解。在SPF小鼠的肠道中, NOD2感知肠道细菌后, 通过募集富亮氨酸重复激酶2(leucine-rich repeat kinase 2, LRRK2)、Ras相关蛋白Rab-2A(Ras-related protein Rab-2A, RAB2A)和受体相互作用蛋白2(receptor interacting protein 2, RIP2)形成复合物促进溶菌酶分选以及随后的释放[32]。

溶菌酶在杀伤细菌方面同样起着重要的作用, 特别是针对革兰氏阳性菌[3]。溶菌酶通过对细菌细胞壁的靶向水解引起细菌细胞裂解, 主要的机制是靶向细胞壁的肽聚糖(peptidoglycan, PG)。同时, 溶菌酶降解细菌后, 细菌降解产物如MDP是模式识别受体(pattern recognition receptors, PRRs)的重要激动剂, PRRs包括NOD1和NOD2受体以及Toll样受体(Toll-like receptors, TLRs)等[33-34], 降解产物与PRRs作用增强了随后的炎症反应。同时溶菌酶在限制炎症方面也发挥一定作用[35]。因此, 溶菌酶的产生和释放需要保持平衡, 以更好地调节感染过程中的免疫反应。

2.3 其他抗菌肽

PC颗粒含有sPLA2, 它主要为组成型表达, 类似于α-防御素和溶菌酶, 同时也有一部分磷脂酶是分泌型的。sPLA2催化膜磷酸甘油酯甘油骨架sn-2位置脂肪酸酯键的水解, 细菌细胞膜富含磷脂酰乙醇胺和磷脂酰甘油, 二者是sPLA2催化的底物[36]; 其中一些磷脂酶对细菌膜具有选择性活性, 其可杀伤革兰氏阳性杆菌[37-38]。

还有一种AMP是C型凝集素。人PC中的主要凝集素是REG3α(也被称为HIP和PAP)[39], 在小鼠中人REG3α的同源物是REG3γ[40], 这两种蛋白质都可与肽聚糖结合, 并且对革兰氏阳性菌具有杀伤作用[41]。这些C型凝集素的前肽被胰蛋白酶加工, 胰蛋白酶激活了它们的结合和杀菌活性[42-43]。REG3α与REG3γ是分泌型的AMPs, 当受到微生物刺激后二者的表达水平会增加, 同时有研究表明, IL-22也可以增加肠道REG3凝集素的表达水平[44]。

小鼠血管生成素4(angiopoietin 4, ANG4)属于

具有抗菌和抗病毒活性的RNase亚家族, 主要由PC和杯状细胞分泌[45]。ANG4作为一种内源性抗菌蛋白发挥作用, 并与其他分泌成分(如溶菌酶、REG3β和REG3γ)一起被分泌到肠腔中起到杀菌作用[46], 同时它也是一种双功能蛋白, 可诱导$Lgr5^+$干细胞的扩增和IEC凋亡[47]。近年来也有学者提出PC可以分泌肽YY(peptide YY, PYY), 抵抗白色念珠菌的感染, 以往研究表明PYY肽主要由肠内分泌细胞分泌[48]。总的来说, 这些人和小鼠的AMPs对细菌、病毒和原生生物均具有广泛的抵抗活性。

3 PC及其分泌的抗菌肽在疾病中的重要作用

3.1 肠道感染

由于PC是抗菌肽的主要来源, 因此其在宿主免疫反应以及对病原菌的抵抗方面起到重要的作用, PC功能受损会增加宿主对肠道感染的易感性。PC对肠道微生物(主要包括细菌、病毒和寄生虫)敏感。肠道细菌通过TLR/MyD88轴直接刺激AMPs的表达[49]。PC细胞维持肠道菌群的稳态, PC缺失会导致肠道微生物失调, 使机体对病原菌的抵抗力下降[50]。肠道防御素可以降低小鼠肠道伤寒沙门氏菌感染的死亡率以及细菌负荷[51], 小鼠中*Nod2*或X-盒结合蛋白1(X-box binding protein 1, *Xbp1*)敲除导致小鼠对李斯特菌感染的易感性增加。PC功能异常对病毒和寄生虫感染的影响尚不明确, 但有研究表明防御素可以在包膜和非包膜病毒生命周期中起作用, 包括抑制病毒与宿主受体结合和融合[52-53], PC的自噬相关基因*Atg5*特异性缺失可导致严重的肠炎、PC变形以及弓形虫感染的急性死亡率增加[54]。

3.2 炎症性肠病(inflammatory bowel disease, IBD)

IBD主要包括克罗恩病(Crohn's disease, CD)和溃疡性结肠炎(ulcerative colitis, UC), CD是一种复发性全身性炎症性疾病, 主要累及胃肠道, 伴有肠外表现和相关的免疫疾病, 其发病原因是多样的, 主要是遗传因素与环境因素[55]。全基因组关联研究中发现的几种CD风险因素与PC功能障碍有关, 自噬相关16样蛋白1[56-57](autophagy-related 16-like 1, *ATG16L1*)、*XBP1*[52]、*LRRK2*[58]和*NOD2*[59], 这几个PC功能障碍相关等位基因参与自噬、未折叠蛋白反应和线粒体功能调节等过程。自噬功能障碍被认为是IBD发病的重要因素, 可能与抗菌能力损害有关, PC的自噬参与调节与IBD发病相关的多种过程, 包括内质网应激(endoplasmic reticulum stress, ERS)、活性氧(reactive oxygen species, ROS)的积累以及肠道菌群的失调, 从而在缓解IBD的症状中发挥重要作用[60]。PC表现出连续的AMPs合成和释放, 因此需要功能性线粒体来提供能量。最近有研究报道, 活动性CD与PC中的线粒体异常有关, 从而损害PC功能[61], 而线粒体的功能障碍同样会引发PC缺陷和自发性回肠炎[62]。

PC在维持肠道菌群稳态中起到关键的作用, 其缺陷可能会诱导肠道生态失调, 而免疫失调也是IBD的病因及加重因素之一[55]。PC与肠道微生物群之间的相互作用被认为是CD发病的关键因素之一[63], 有诸多研究报道CD患者的肠道菌群多样性减少且丰度发生改变[64-66]。*Lyz1*缺乏症降低了肠道对细菌的免疫反应, 并导致了溶菌酶敏感的黏液溶解细菌(如一种与CD相关的致病菌格纳瘤胃球菌)的扩增。结肠上皮细胞中异位溶菌酶的产生抑制了溶菌酶敏感细菌的生长并加剧了结肠炎[33]。在CD患者中回肠HD5和HD6含量均减少[24,67], 并且PC会出现异常形态[59], 同样也有动物实验表明α-防御素错误折叠与克罗恩病模型小鼠的肠道菌群失调和回肠炎相关[68]。IBD患者的PC存在功能缺陷, 而PC功能障碍可能导致菌群失调, 这反过来又可能促进CD的发展。近年来也有学者认为, 肠道菌群失调先于肠道炎症的发生以及随后的PC功能障碍[69]。总之, PC功能异常与IBD的发生发展之间存在复杂的串扰, 但毋庸置疑, PC功能的正常对维护肠道稳态以及IBD病情的稳定十分重要。

3.3 新生儿坏死性小肠结肠炎(necrotizing enterocolitis, NEC)

NEC是早产儿中最常见的胃肠道急症之一, 其特征是肠道缺血性坏死[70]。功能失调的PC被认为在NEC的多因素发病机制中起作用。人类在妊娠22~24周时胎儿PC才开始出现并发育, 而小鼠PC则在出生后才开始发育, 早期PC并不具有成熟颗粒中包含的所有成分, 因此早产儿没有足够的时间发育出具有完整功能的PC[71], 同时在NEC新生儿肠道中的PC会发生增生和化生[72]。由于PC有助于调节肠道菌群的稳态, 而NEC的肠道损伤由细菌来诱导, 因此正常PC功能的破坏, 特别是在未成熟的肠道中, 很可能与NEC表型的发展有关。有研究人员

用化学制剂双硫腙(Dith)或PC特异性基因敲除的方法破坏或消除肠道PC, 随后用细菌灌胃模拟肠道感染诱导小鼠NEC模型[73-75], 这些实验表明未成熟小肠中NEC样损伤的发展是PC的破坏及其功能丧失导致的, 而不是因为PC的缺失。同时, 一项机制研究证明对新生小鼠进行抗生素治疗会破坏PC, 并增加小鼠对NEC的易感性[76], 因此在治疗中要更加注意抗生素的使用。值得注意的是, 前文提到PC通过产生EGF、Notch和Wnt来维持干细胞的生态位[9], 健康的干细胞对于诱导损伤后的上皮修复至关重要[77], 因此PC也可以通过这一方面影响NEC的发生发展。综上, PC破坏在机制上与NEC样损伤的发展相关, 对PC更深入的理解可能为进一步阐明NEC的发展以及提出新的治疗方案提供一条重要的新途径。

3.4 其他疾病

移植物抗宿主病(graft-versus-host disease, GVHD)是同种异体造血干细胞移植的潜在并发症, 是一种多系统疾病, 常累及胃肠道和肝脏, 表现为腹痛和腹泻[78]。GVHD的组织学特征是上皮细胞凋亡、隐窝炎和隐窝破坏[79]。有研究表明, 较少的十二指肠PC数量与临床上更严重的GVHD相关, 并且比经典的病理分级更能预测疾病严重程度[80]。较低的PC数量也与患者对治疗的反应性降低有关, 从机制上讲PC数量减少可促进GVHD肠道菌群失调, 而菌群平衡与GVHD的严重性相关[81]。同时, *HD5*中的单核苷酸多态性也参与GVHD发病机制[82]。鉴于PC在GVHD中的关键作用, 针对PC的治疗可能是减轻GVHD严重程度的有效方法。

急性胰腺炎(acute pancreatitis, AP)是一种常见的急腹症, 在AP患者中PC的功能下降, 表现为分泌溶菌酶、HD5、REG3和Wnt3a的减少[83]。在动物模型中, 急性坏死性胰腺炎(acute necrotizing pancreatitis, ANP)大鼠肠道损伤更为严重, 防御素与溶菌酶的水平降低, 同时肠道中的致病菌会扩张[84]。Dith对PC的瞬时消融会加重AP大鼠和小鼠的胰腺和肠道损伤[83,85], PC的长期功能障碍加剧了AP的严重程度, 这与肠道菌群紊乱有关, 补充溶菌酶有助于缓解疾病。肠道微生物参与了AP的病理过程, 在AP发展中发挥重要作用[86], 而PC作为调节肠道菌群的重要细胞在AP的发生发展中也起到不可忽视的作用, 为临床治疗提供了新的见解。

4 总结与展望

PC是一种位于小肠腺底部的分泌型肠上皮细胞, 由相邻的Lgr5阳性ISC分化而来, 其细胞质中存在丰富的颗粒, 颗粒中包含防御素、溶菌酶、REG3γ等多种AMPs。在肠道黏膜免疫防御机制中, PC通过分泌AMPs, 为肠隐窝营造一个相对无菌的微环境, 并且通过提供生长因子及代谢产物来维持ISC的功能。鉴于PC在维持肠道稳态中扮演的关键角色, 它们的数量和功能的改变与多种胃肠道炎症性疾病(如IBD、肠道感染、GVHD、NEC等)的发病机制密切相关。然而, 目前尚不明确PC的这些改变究竟是炎症过程的继发性结果, 还是炎症反应的始动因素, 因此需要进一步的研究来阐明其间的因果关系。理论上用AMPs治疗能降低细菌耐药性的风险, 并可能对肠道菌群失衡起到缓解作用。因此深入探究PC的生物学特性及其分泌的抗菌肽在肠道黏膜屏障中的作用, 有助于开发针对PC的新型疗法以优化肠道黏膜屏障功能并预防慢性炎症反应。同时, 需要进一步研究重组AMPs在预防和治疗肠道菌群失调和感染方面的应用潜力。

总而言之, PC及其分泌的AMPs在肠道黏膜免疫防御中起着至关重要的作用。未来的研究应当关注PC在炎症性疾病中的变化及其作用机制, 以及如何利用AMPs开发新型疗法以改善肠道健康状态并预防相关疾病的发生。

作者贡献

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