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· 综述 ·

肠道黏膜、肠道免疫和微生物群在肠源性白念珠菌感染中的作用

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[摘要] 肠源性白念珠菌感染是指肠道内定植的白念珠菌在一定条件下发生易位, 突破肠道, 造成组织感染, 甚至引发侵袭性白念珠菌感染。肠道黏膜作为念珠菌第一接触位点, 是抵抗白念珠菌定植或侵入的第一道防线, 常通过物理屏障和激活宿主免疫抑制感染。作为另一种防御机制, 肠道内微生物群则通过调节 pH, 分泌抗菌肽和竞争黏附点共同抵抗白念珠菌侵袭感染。本综述总结肠道黏膜、肠道免疫和微生物群这三个关键因素在肠源性白念珠菌感染中的作用, 为肠道定植引发侵袭性白念珠菌病的科学研究提供新思路。

[关键词] 肠源性白念珠菌感染; 肠道黏膜; 肠道免疫; 肠道微生物群; 白假丝酵母菌

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Roles of intestinal mucosa, intestinal immunity and microbiota in enterogenic *Candida albicans* infection

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[Abstract] Enterogenic *Candida albicans* (*C. albicans*) infection refers to the translocation of intestinal colonized *C. albicans* under certain conditions, breaking through the intestinal tract, causing tissue infection or even invasive *C. albicans* infection. As the first contact point of *Candida*, the intestinal mucosa is the first line defending colonization or invasion of *C. albicans*, often inhibiting infection by physical barrier and activating host immunity. As another defense mechanism, the intestinal microbiota jointly resists the invasive infection of *C. albicans* through regulating pH, secreting antimicrobial peptides, and competing for adhesion points. This review summarizes the roles of three key factors, namely intestinal mucosa, intestinal immunity and microbiota, in enterogenic *C. albicans* infection, providing new ideas for scientific research on invasive candidiasis caused by intestinal colonization.

[Key words] enterogenic *Candida albicans* infection; intestinal mucosa; intestinal immunity; intestinal microbiota; *Candida albicans*

白念珠菌又称白假丝酵母菌, 为条件致病菌, 大部分以共生方式无症状定植在健康人体肠道。当人体内微环境发生改变, 菌群生态失衡, 以及免疫力下

降时, 白念珠菌会过度繁殖并改变生长方式, 突破肠道, 进入血液, 从而引起侵袭性感染^[1], 称为肠源性白念珠菌感染。由于广谱抗菌药物、抗肿瘤药物及

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免疫抑制剂的过度使用,白念珠菌感染发病率在临床上日益增高。尽管医疗技术发展迅速,白念珠菌感染仍然是发病率和病死率均较高的疾病之一^[2]。

研究^[3]发现,免疫系统被破坏,微生物失衡,以及肠炎引起的肠黏膜损伤是导致白念珠菌定植增加和通过肠道上皮进入血液的原因。患有溃疡性结肠炎、克罗恩病、结肠癌的患者,其机体免疫功能受损,体内微生物群整体多样性降低,但念珠菌属真菌含量升高^[4]。

肠道黏膜是白念珠菌易位进入血液的第一道防线^[5],当白念珠菌在肠道定植或感染时肠道免疫为宿主提供保护,而肠道微生物群也发挥着不容小觑的保护作用。本综述总结肠道黏膜、肠道宿主免疫和肠道微生物群在肠源性白念珠菌感染中的作用。

1 白念珠菌致病机制

一般情况下,白念珠菌为条件致病菌,但当肠道微生物群失衡,肠道黏膜受损,或免疫功能低下时,其毒力因子及其对环境的适应性调节能力可增强其在肠道定植及易位的能力。

1.1 白念珠菌毒力因素 白念珠菌形态的多样性可使其适应不同的生长条件。不同环境下,白念珠菌可以在酵母形态、假菌丝形态和菌丝形态之间进行可逆切换。白念珠菌酵母形态被认为是肠道共生的主要形式,可在肠道浅表共生定植;而菌丝形态则是通过肠道屏障侵入组织的主要形式^[5-6]。可利用白念珠菌形态转变区分定植和感染,通过免疫和肠道菌群识别并清除白念珠菌菌丝形态,降低其感染程度^[7]。

白念珠菌黏附和侵袭是加重其感染的关键。白念珠菌黏附于宿主细胞表面刺激菌丝生长引发生物膜形成。生物膜形成后促进菌丝形态向酵母形态转变,有利于白念珠菌的释放和扩散,且不易被免疫系统识别,从而促进真菌传播^[8]。感染肠道黏膜期间,白念珠菌通过诱导内吞和主动渗透两条途径入侵肠上皮细胞。诱导内吞作用由白念珠菌黏附素(Als3)和侵袭素(Ssa1)介导穿透上皮细胞质膜实现入侵。主动渗透则通过白念珠菌菌丝生长到宿主组织中实现入侵^[9]。

1.2 白念珠菌适应性调节 白念珠菌的适应性调节不是直接通过宿主相互作用,而是通过代谢调节、抗逆性及免疫逃避来增强自身毒力。白色念珠菌表现出高度的代谢灵活性,在葡萄糖限制条件下,

白念珠菌可以利用多种碳替代途径,迅速适应不同环境^[10]。当白念珠菌暴露后,宿主免疫细胞施加的应激源可诱导白念珠菌通过应激反应快速适应。针对 pH 值、渗透压、亚硝化应激等应激源,白念珠菌可通过热休克蛋白调节丝裂原活化激酶,活化蛋白激酶或蛋白磷酸酶增强对应激源的抗逆性^[11]。而针对免疫细胞的识别和清除,白念珠菌通过掩盖细胞壁成分等方式最大限度逃避免疫识别,还可通过将 O_2^- 转化为 O_2 和过氧化氢逃避免疫细胞的氧化杀伤^[12]。

2 肠道黏膜

2.1 肠道结构 肠道是人体最主要的消化器官和最大的免疫器官,是机体抵御病原体侵犯、维持内环境稳定的重要器官,主要由肠黏液质层、肠黏膜上皮细胞组成的单细胞层和肠道固有层组成^[13],其中,黏液层和肠上皮细胞之间的紧密连接对机体抵御有害物质突破肠道起到关键作用。肠道作为白念珠菌存在最多的载体,其黏膜的完整性和内环境对白念珠菌的生长定植影响很大。

2.2 肠道黏膜作用及其意义 肠黏液质层主要由肠上皮细胞分泌的黏蛋白-2 通过二硫键介导形成特殊分子结构,并与不同浓度的抗菌物质共同构成^[14]。白念珠菌对上皮细胞的黏附是定植的先决条件,其对黏蛋白的黏附程度与自身毒力密切相关。白念珠菌的毒力特性包括形态转变、对肠上皮的黏附、生物膜的形成、细胞外酶的分泌和逃避宿主防御的能力^[15]。肠源性白念珠菌感染的关键机制之一是白念珠菌通过高强度真菌负荷,促使菌丝分泌念珠菌溶血素与侵入部位上皮细胞结合,引起黏蛋白裂解,导致肠道上皮细胞间的紧密连接受损,屏障通透性增加,上皮完整性被破坏,从而突破肠道上皮细胞屏障^[16]。

肠上皮细胞在物质转运中分化出多种上皮细胞亚群:杯状细胞、潘氏细胞、簇状细胞、肠内分泌细胞等,它们通过紧密连接、黏附连接、间隙连接和桥粒连接的方式共同形成一个复杂的上皮层,以此确保肠上皮细胞间的内聚力和结构的稳定,维持肠道的完整性^[17]。白念珠菌常通过肠上皮细胞易位及使其坏死的方式穿过肠上皮屏障。一方面,白念珠菌可通过促进自身菌丝生长^[18],拉伸和破坏肠上皮细胞的细胞膜;另一方面,宿主修复自身细胞膜损伤^[19],两者相互作用,形成“入侵袋”,入侵的菌丝和其他毒力

因子被宿主细胞膜包围,从而对宿主造成进一步损伤。此外,“入侵袋”里还包含白念珠菌分泌的水解酶(如磷脂蛋白酶、脂肪酶、天冬氨酸蛋白酶)和念珠菌溶血素^[20-21],它们会降解宿主的细胞膜蛋白和释放到细胞外基质的营养物质。其中,白念珠菌分泌的天冬氨酸蛋白酶可选择性表达,分解黏蛋白并促进白念珠菌利用疏水作用与黏蛋白的 118 kDa C 端糖肽的蛋白质骨架结合^[22],使自身更好地黏附上皮层达到穿过肠黏膜屏障的目的,并加速白念珠菌侵袭其他组织细胞。由此可见肠上皮细胞在宿主黏膜抵御白念珠菌和降低宿主对白念珠菌的易感性中发挥重要作用。

除肠黏膜自身能对白念珠菌产生诸多影响外,肠黏膜所营造的内环境的改变也会对白念珠菌的致病性产生影响。不同肠道环境下,白念珠菌在共生性和致病性之间的转化还受白念珠菌代谢状态的影响。如白念珠菌刺激肠道上皮细胞促进 *Wor1* 调节因子表达,形成特殊的酵母形态,该调节因子可与白念珠菌菌丝相关毒力因子 *Efg1* 一起控制其形态转变^[23],并使其适应肠道新陈代谢。其次,葡萄糖是白念珠菌首选的碳源,当肠道中葡萄糖水平较低时,白念珠菌会通过多途径寻找替代碳源^[10],如氨基酸或 N-乙酰氨基葡萄糖等,且白念珠菌同时对氮代谢、磷酸盐和微量营养素同化具有适应性^[24],其中微量营养素对白念珠菌结构的完整性很重要,同时也会随 pH 值进行调节,通过对多胺和氨基酸的分解主动释放氨气碱化环境^[25],以此加强白念珠菌在肠道定植的能力。

3 肠道宿主免疫

为防止白念珠菌在肠道上皮过度定植和侵入组织,宿主通过固有免疫和适应性免疫相互作用以保护肠道黏膜上皮^[26]。其中固有免疫系统是抵御白念珠菌感染的第一道防线,对平衡肠道微生物在宿主体内稳态,防御病原体起重要作用。肠上皮细胞通过特定模式受体识别病原物相关分子达到抗菌作用,同时消化病原体的抗原,激活适应性免疫,促进 T 细胞活化,改善固有免疫功能,平衡炎症,保护受损肠上皮表面的完整性。

3.1 肠道固有免疫 固有免疫系统作为抵御白念珠菌感染的第一道防线,通过肠道上皮细胞与固有免疫细胞结合,并以此识别白念珠菌来启动白念珠菌免疫。其中巨噬细胞和中性粒细胞是固有免疫反

应的主要细胞^[27-28]。白念珠菌感染肠道促进巨噬细胞大量聚集并分化,使白念珠菌被吞噬,并消除炎症,维持肠道稳态^[29]。虽然白念珠菌菌丝形态对吞噬具有抗性,但巨噬细胞仍可以吞噬部分菌丝态白念珠菌,并释放出 IL-1 β 等炎性因子,抑制菌丝形成^[30]。白念珠菌毒力因子的表达和形态转变可诱导中性粒细胞形成中性粒细胞胞外陷阱(NET),胞外陷阱中的染色质将白念珠菌包围并捕获,通过颗粒蛋白、抗菌肽等杀灭真菌,达到抗感染作用。研究^[31]发现白念珠菌毒力因子—分泌型天冬氨酸蛋白酶和磷脂酶,通过 Syk-PKC-ROS 途径对中性粒细胞产生趋化作用。除此之外,白念珠菌形态转变对 NET 的形成具有很大影响,酵母形态和菌丝形态在诱导 NET 数量及动力学机制上也有所不同。研究^[32]发现,酵母态白念珠菌与中性粒细胞共培养,15 min 内白念珠菌可以通过自噬和 ROS 途径诱导 NET 形成,15 min 后则无法诱导 NET 形成;而菌丝态白念珠菌与中性粒细胞共培养,在 15 min 内则主要通过自噬快速诱导 NET 形成,15 min 后则以自噬和 ROS 途径诱导 NET 形成。

骨髓细胞使用特殊的模式识别受体来识别病原体相关分子模式,这些受体主要有 Toll 样受体、C 型凝集素受体、核苷酸结合寡聚结构域样受体和维甲酸诱导基因 I 样受体,其中 C 型凝集素受体^[33]中的树突细胞相关凝集素 1(dectin-1)、树突细胞相关凝集素 2(dectin-2)、巨噬细胞诱导型 C 型凝集素(mincle)、树突细胞特异性丙型凝集素(DC-sign)和甘露糖受体可以识别白念珠菌 β -葡聚糖和 α -甘露聚糖,激活炎症小体和诱导细胞吞噬。Toll 样受体中的 TLR4 和 TLR2 识别甘露糖蛋白,核苷酸结合寡聚结构域样受体中的 NOD2 和 TLR9 识别白念珠菌细胞壁成分,并且降低炎症反应^[34-35]。肠道上皮细胞对白念珠菌 β -葡聚糖的识别感知主要通过 *EphA2* 激活丝裂原活化蛋白激酶(MAPK)和转录激活因子 3(STAT3)信号通路^[36],以此诱导上皮细胞分泌炎性细胞因子和抗菌肽。念珠菌溶血素则与白念珠菌从共生到致病状态的转变相关。念珠菌溶血素在菌丝生长过程中产生,可破坏上皮细胞,损伤上皮屏障;同时,上皮生长因子受体被激活,并激活 p38/cFos 和 ERK/MKP1 信号传导^[37],是上皮细胞对白念珠菌菌丝形成的特殊反应。上皮细胞还可以分泌抗菌肽、IL-37、组氨酸和 β -防御素^[38],通过与白念珠菌细胞壁结合或使白念珠菌质膜透化发挥抗菌作用。

3.2 肠道适应性免疫 适应性免疫是通过免疫记忆对机体建立的长期保护机制^[39],主要涉及 B 细胞和 T 细胞。病原微生物抗原可以刺激 B 细胞产生抗体。白念珠菌生物膜的补体受体 3 相关蛋白可诱导机体生成和分泌浆细胞,并与白念珠菌结合,减少其数量并降低其黏附能力,使其在肠腔中被清除^[40]。T 细胞则是宿主黏膜防御的关键,其中 Th17 细胞对抵御白念珠菌在肠道黏膜定植至关重要。白念珠菌中的甘露聚糖和葡聚糖- β 会诱导 T 细胞分化为 Th17 细胞^[41],Th17 细胞通过释放 IL-17A/F、IL-22 等炎症因子促进对白念珠菌的清除。

在肠道黏膜对白念珠菌的作用下,Th17 细胞产生 IL-17 效应细胞因子家族 IL-17A、IL-17F 和 IL-22,可诱导上皮细胞表达抗菌和修复组织相关基因,如生成 β -防御素,抑制白念珠菌定植,减少其对肠道的损伤^[42]。在体内,CD4⁺ T 细胞是 Th17 细胞的主要来源,但缺乏 CD4⁺ T 细胞时,CD8⁺ T 细胞也可以代偿性分泌 IL-17,抑制白念珠菌菌丝生长,达到保护机体的作用^[43]。IL-17 还可以促进中性粒细胞向白念珠菌感染位置聚集^[44-45]。IL-17A 与 IL-17F 作用相似^[46-47],IL-22 则主要通过调节上皮细胞对 IL-17A 进行反应^[48]。Th17 细胞也可以产生 Th1 细胞相关的细胞因子 IFN- γ ,从而影响白念珠菌菌丝及生物膜形成。白念珠菌细胞壁成分甘露聚糖和 β -1,3-葡聚糖等,会促进 IL-23、IL-6、IL-1 β 等表达^[49],其中 IL-6 和 IL-1 β 与 TGF- β 一起驱动 Th17 细胞分化,而 IL-23 通过 STAT3 和 ROR γ t 通路来促进 Th17 细胞分化。目前已知 Th17 细胞免疫对白念珠菌长期定植在肠道黏膜,对肠道组织具有重要意义,但其对机体的抗菌防御功能及维持宿主肠道与白念珠菌之间的稳态机制还不清楚。

4 肠道微生物群

肠道微生物群主要由细菌、真菌、病毒等组成,目前被认为是宿主体内最大的虚拟免疫代谢器官^[50],对宿主免疫的激活和维持,以及保护宿主免受白念珠菌的侵害发挥着重要作用。

4.1 肠道微生物群的构成 肠道中的主要细菌门类为拟杆菌门、厚壁菌门、放线菌门、变形菌门和疣微菌门。不同肠道部位孕育着不同的微生物群落^[51]。小肠由于受氧气、pH 梯度、胆汁酸及抗菌物质的影响,主要以兼性厌氧菌为主,乳酸杆菌科和肠杆菌科占优势地位,其中小肠内的胆汁酸可以显著降低白

念珠菌对唑类抗真菌药物的耐药性,有利于抗菌药物药效的发挥。盲肠利于厌氧菌的生长,其中以厚壁菌门和拟杆菌门为主。结肠的结构具有两层,其内部黏液层几乎无菌,外层则定植了高载量细菌,主要为类杆菌科、普氏菌科、理肯氏菌科、毛螺菌科和瘤胃球菌科。

真菌仅占肠道微生物群的 0.1%^[52]。健康肠道中的优势真菌门类是子囊菌门和担子菌门,最常见的菌属则是念珠菌属、酵母菌属、半乳糖菌属。肠道中真菌的多样性和数量不如细菌丰富。白念珠菌可以在小肠、盲肠、结肠中定植。

4.2 肠道微生物群稳态的作用及重要性 肠道菌群的稳态会降低白念珠菌在肠道的定植,不同菌群发挥不同的作用来调节白念珠菌在肠道定植程度^[53]。肠道微生物群主要依靠分泌抑菌物质杀灭真菌,如乳酸杆菌在肠道内通过产生过氧化氢、有机酸和短链脂肪酸等物质使局部酸化,抑制白念珠菌形态改变,减少白念珠菌侵入^[54-55]。其次,含有色氨酸的菌群可以促进细菌基因的局部转录,通过刺激 IL-22 表达发挥抗菌作用^[56-57],沙门氏菌通过 *SopB* 转位酶效应物诱导清除白念珠菌菌丝^[50],粪肠球菌可产生细菌素抑制剂阻断菌丝和生物膜形成^[58],链球菌通过扩散因子抑制白念珠菌菌丝形成^[59]。再者,部分菌群与白念珠菌争抢黏附位点,叫噪及其衍生物作为细菌信号分子可抑制 NRG1 基因,从而抑制白念珠菌菌丝转化和生物膜形成^[60],减少其在肠道上皮细胞的黏附。此外,鼠李糖杆菌也被发现可以诱导白念珠菌定植的上皮屏障脱落以减少其侵入组织^[61]。

目前造成菌群失衡的原因有很多:环境因素,如污染的大气^[62]、水源^[63]以及装修房屋时产生的甲醛和苯^[64]均会降低肠道微生物的多样性;饮食因素,如高膳食纤维饮食的人肠道内含有更多厚壁菌门^[65],而高蛋白高油脂饮食则会促进嗜胆菌属和拟杆菌属生长^[66];精神因素,长期高强度高压或抑郁也会降低肠道微生物的多样性^[67],可导致肠道内部分益生菌如乳酸杆菌数量大幅减少;药物的过度使用,如长期使用抗菌药物会破坏肠道内细菌的多样性^[68];肠道疾病也会影响菌群变化,疾病状态下大部分微生物群多样性降低^[69]。肠道菌群稳态的失衡会促进白念珠菌在肠道的定植,是目前已知导致白念珠菌毒力增强,突破肠道屏障,易位侵袭组织的主要因素,最终导致肠源性白念珠菌感染向侵袭性白念珠菌感染转变^[70]。

5 未来展望

肠道是侵袭性白念珠菌感染的重要病原菌来源和关键因素。肠黏膜屏障损伤、免疫损伤、肠道菌群失衡是白念珠菌突破肠道进入血液发展成侵袭性感染的必要条件^[1]。肠道在肠源性白念珠菌感染中的作用机制逐渐明晰,有利于临床开发新型预防和治疗肠源性白念珠菌感染的药物,并可为临床研究肠道定植引发的侵袭性白念珠菌感染提供新思路,如近年来流行的包括治疗性抗体、重组细胞因子和重建免疫细胞^[71]在内的辅助免疫疗法,以及粪菌移植。通过以上治疗方法,增强机体免疫力,调节菌群平衡,刺激肠道运动,以减少白念珠菌定植及感染^[72-73]。上述方法都是未来临床治疗的重要方向。

肠源性白念珠菌感染仍然威胁着人类健康,是一个全球性的挑战,临床仍需对其进行深入研究,具体了解肠道微环境、肠道免疫与病原微生物的相互关系,以攻克肠源性白念珠菌感染治疗的难题。

利益冲突:所有作者均声明不存在利益冲突。

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