· 综述 ·

慢性萎缩性胃炎发病机制的研究进展*

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[摘要] 慢性萎缩性胃炎属于胃癌的癌前疾病状态，是炎-癌转化的发生关口，近年来患病率呈上升且有年轻化趋势，严重威胁人类生活健康。目前慢性萎缩性胃炎的发病机制尚未明确统一，研究发现慢性萎缩性胃炎发病与幽门螺杆菌感染、自身免疫反应异常、胆汁反流和胃内非幽门螺杆菌菌群等相关。笔者查阅国内外相关文献资料，整理慢性萎缩性胃炎的相关发病机制，以供学习交流。

[关键词] 慢性萎缩性胃炎；发病机制；幽门螺杆菌；自身免疫反应异常；胆汁反流；胃内非幽门螺杆菌菌群
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Advances in the pathogenesis of chronic atrophic gastritis

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Abstract Chronic atrophic gastritis is a precancerous disease state of gastric cancer, which is the key to the occurrence of inflammatory-cancer transformation. In recent years, the prevalence rate is on the rise and tends to be younger, which seriously threatens human life and health. At present, the pathogenesis of chronic atrophic gastritis has not been clearly unified. Studies have found that the pathogenesis of chronic atrophic gastritis is related to helicobacter pylori infection, abnoral autoimmune reaction, bile reflux and non-helicobacter pylori flora in the stomach. The author consulted relevant literature at home and abroad to sort out the pathogenesis of chronic atrophic gastritis for learning and communication.

Key words chronic atrophic gastritis; pathogenesis; Helicobacter pylori; abnoral autoimmune reaction; bile reflux; non-Helicobacter pylori Helicobacter

慢性萎缩性胃炎(chronic atrophic gastritis，CAG)是指胃内腺体萎缩，原始腺体被肠化生、假幽门化生和(或)纤维化所替代[1-2]。患病人群以中老年为主[3]，但具有年轻化的倾向[4]。CAG 患病率因检测方式和病检位置不同有所差异[2]，每年的变化率在 0～10.9%[5]。CAG 多无特征性临床表现，意大利胃肠病学家称其为一种诊断不足的疾病，超越了严格意义上的胃肠病学特征，同时具有胃内和胃外的症状体征。CAG 临床常见餐后饱胀不适、嗳气等消化不良症状，或伴免疫性胃炎引起的贫血、维生素 B_{12} 缺乏相关神经精神症状或合并其他自身免疫疾病[1-2,6-9]。悉尼系统、OLGA/OLGIM 分级风险评估和组织病理检测是 CAG 诊断的最佳标准，胃泌素 17 和胃蛋白酶原等血清学检测可作为侵入性检查前的辅助手段[1-2,10-11]。CAG 作为 Correa 级联反应模式中慢性胃炎发展成胃癌的重要一环[12]，是炎-癌转化的关口。然而，CAG 和炎-癌转化的发生、发展是多环节、多作用位点交叉的复杂机制，目前尚无明确统一的结论。幽门螺杆菌感染(Helicobacter pylori，Hp)和自身免疫性胃炎是 CAG 发病机制的两大主要研究背景，胆汁反流和胃内非 Hp 菌群引起的信号通路的异常激活、炎症因子的过表达也是 CAG 发病机制的研究热点和预防炎-癌转化研究的重要靶点。

1 Hp 感染与 CAG

Hp 是一种微需氧革兰阴性杆菌，是世界卫生组织认定的细菌致癌物[13]，是目前研究宿主-病原体相互作用和细菌诱导炎癌机制的典型生物模型[14]。Hp 感染会释放相关毒性因子，干扰胃内环境稳态平衡，诱导黏膜细胞形态功能改变和死亡，最终诱发萎缩、肠化等癌前病变甚至肿瘤发生。研究发现，Hp 阳性的 CAG 发病率为 Hp 阴性的

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2.4～7.6 倍[15]，而且在 CagA 表达的 Hp 感染中，轻、中度和重度的 CAG 受试者胃癌发病率分别增加 6.4 倍和 11.8 倍[16]，表明 Hp 感染与和胃癌前病变和肿瘤的发病密切相关。

Hp 发病机制主要归于定植和毒力因素。Hp 通过转化生长因子下调细胞碳酸氢盐转运蛋白的表达，诱导黏膜碳酸氢盐分泌减少，并通过调节脲酶活性等升高胃内环境的 pH 值；又可通过表面黏附素介导、鞭毛运动、多种趋化受体介导的定向运动和 γ-谷氨酰转肽酶、RhpA（一种 RNA 解旋酶蛋白）等定植毒力因子作用定植于胃黏膜，从而干扰宿主代谢途径，诱导胃屏障稳态的下调[14,17-18]。细胞毒素相关抗原（Cag A）和空泡细胞毒素（Vac A）是 Hp 的主要致病毒性因子。Cag A 通过 cag 致病岛编码的Ⅳ型分泌系统注入宿主细胞后被宿主磷酸化，以磷酸化依赖和非磷酸化的方式改变宿主细胞的信号传导通路和炎症因子表达[18-20]。Vac A 通过促进胃上皮细胞胞质中酸性空泡的形成，破坏线粒体、细胞质膜和内膜结构的完整性，致使细胞结构不稳定而崩溃[19-20]；又可诱导细胞凋亡途径引起胃上皮细胞死亡；破坏自噬体的成熟，导致有缺陷的自噬体形成，使得自噬体清除细菌和潜在遗传毒性物质的能力减弱。同时，Vac A 又被称为免疫调节毒素，可抑制 T 细胞、B 细胞的活化与增殖，以及抑制巨噬细胞对 Hp 的内化、吞噬等，从而导致免疫清除和 Hp 持续感染[19-20]。研究发现，Hp 感染可诱导胃细胞中坏死性凋亡关键调节因子—蛋白激酶 3 阳性数量表达增加[21]；操纵炎症小体 NLRP3 的激活和形成，分泌大量成熟 IL-1β，使得炎症反应和细胞焦亡持续存在[22]。这表明慢性 Hp 感染通过释放毒性因子，抑制免疫细胞功能，释放炎症递质，触发黏膜炎症级联反应，而诱导壁细胞坏死和丢失。

2 免疫反应异常与 CAG

自身免疫性胃炎（autoimmune gastritis，AIG）是发病主要在胃体，病灶呈弥漫性分布的 CAG 的一种类型，又称 A 型胃炎；是一种自身免疫异常介导的器官特异性疾病，以 H^+K^+-ATP 为靶抗原，抗壁细胞抗体（parietal cell antibody，PCA）选择性介导的壁细胞破坏所致[23-24]，是 H^+K^+-ATP 酶、抗壁细胞抗体和 T 细胞之间免疫失调复杂作用的结果[25-26]。激活的自反应性 T 细胞可通过 Fas-Fas 配体和穿孔素颗粒酶机制产生许多促炎细胞因子，放大免疫反应，导致壁细胞破坏，泌酸功能受损、微量元素吸收障碍和黏膜萎缩重塑，以及 G 细胞分泌胃泌素去抑制引起高胃泌素血症，刺激肠嗜铬样细胞增殖，使得Ⅰ型神经内分泌瘤和胃腺癌的发生风险增加[23-25,27]。

目前关于 AIG 的免疫介导引起免疫级联和黏膜损伤的初始事件发生机制尚不明确[25,28]。现有两种可能假设[25,29]：一是 Hp 感染相关，Hp 通过分子模拟机制诱导自身免疫耐受性丧失[30-32]；宿主遗传、接触微生物和环境化学物质等均可诱发分子模拟，当外源肽和自身肽具有相似性，可利于易感个体中外源性抗原激活自身反应性免疫细胞而导致自身免疫性疾病发生[32]。Amedei 等[33]对 Hp 蛋白进行交叉反应性表位鉴定，发现交叉反应性 Hp 肽与 H^+K^+-ATPase 表位具有同源性。多项研究发现，在 AIG 患者中经常检测到 Hp 现症或既往感染迹象，表明 Hp 可能在 AIG 的发生、发展中起着诱导和支持作用[34-35]。二是“原发性”自身免疫性疾病。Zhang 等[36]的研究表明，相较 Hp 阳性受试者，PCA 和 CAG 的相关性在 Hp 阴性受试者中更强烈，表明 Hp 感染和 PCA 介导的 AIG 在很大程度上可能是独立的、不同的发病途径；有研究表明，可能基于宿主遗传的作用，Hp 感染后具有某些 Toll 样受体多态性的个体相较不具有者可能更易患 AIG[37]；一项荟萃分析表明，Hp 感染对 AIG 具有预防作用[38]。综上研究表明，关于 AIG 的免疫发病机制以及 AIG 与 Hp 感染的关系仍存在矛盾和争议，因此需要未来进一步研究阐明。

3 胆汁反流与 CAG

胆汁反流是除 Hp 感染之外的 CAG 的又一大常见病因[39-40]。十二指肠反流是胃窦与十二指肠运动失调引起胆汁反流的常见慢性胃黏膜病变，多见于原发性胃十二指肠运动障碍或术后胃十二指肠结构功能继发改变等，引起胆汁、胰液等十二指肠内容物反流胃部而导致的胃黏膜病变。胆汁酸作为胆汁的主要成分之一，首先在肝脏中合成初级胆汁酸，后由肠道细菌转化为次级胆汁酸。胆汁酸的亲水性与疏水性使其发挥不同的生物功能，如熊去氧胆酸、牛磺熊脱氧胆酸等亲水性胆汁酸具有细胞保护性；而鹅去氧胆酸和脱氧胆酸等疏水性胆汁酸具有细胞毒性[41]。研究发现，胆汁酸暴露时间的长短与胃黏膜病变的严重程度呈正相关[42]，胆汁反流会损坏胃上皮细胞间的紧密连接，引起黏膜炎症反应，破坏胃黏膜屏障的防御功能，反而促进 Hp 定植、诱导细胞增殖和凋亡[43]。持续性胆汁反流会造成黏膜深部损伤，无法如急性浅表黏膜损可以“恢复原状”[44]，而是通过机制不明的再生性病变和具有癌前病变性质的解痉多肽表达化生来修复损伤[45-46]，从而最终导致胃黏膜萎缩、化生。

近年来，多项研究表明，胆汁反流是肠化生等癌前病变和胃癌发生的危险因素[47-49]。尾型同源框核转录因子 2（caudal-related homeobox transcription factor 2，CDX2）作为一种肠特异性转录因子，参与肠上皮细胞的形成、增殖分化和肠表型的维持。研究发现，胆汁酸可能通过激活 FXR/

NF-κB 信号通路，上调胃上皮细胞中 CDX2 和 MUC2 的表达而促进肠化生[50]；同时，胆汁酸可通过剂量依赖性方式诱导 microRNA-21 表达来抑制 SOX2 表达，从而诱导 CDX2 及其靶基因的表达，最终发挥胆汁酸在诱导肠化生中的重要作用[51]。胆汁反流也可通过影响胃内环境而改变胃内菌群丰富度和均匀度。研究发现，在无 Hp 感染的情况下，胆汁反流阳性患者胃内菌群的丰富度和多样性明显高于阴性，并且二者的微生物群结构存在显著差异[52]。脱氧胆酸作为疏水性胆汁酸主要组成部分，可通过干扰胆汁酸的代谢而促使乳酸杆菌的丰富度明显增加[53]，乳酸杆菌通过定植于胃黏膜，将乳糖代谢成乳酸而酸化胃黏膜层，进而抑制壁细胞和 G 细胞的生理功能，这可能会加速胃黏膜的萎缩、肠化生和肿瘤发生。

4　胃内非 Hp 菌群与 CAG

人体胃肠道是一个复杂的微生态系统。随着 16S rRNA 基因测序技术的发展应用，发现人体胃内微生物以变形菌门、厚壁菌门、拟杆菌门等为主[54-56]。在对 Hp 相关的 CAG 研究的同时，研究人员发现单独根除 Hp 不能完全阻止萎缩、化生及肿瘤的发生，说明胃内非 Hp 细菌（non-helicobacter pylori helicobacter，NHPH）在胃癌前病变和肿瘤中扮演着不可忽视的作用[55,57-58]。研究发现，抑酸药物的使用和壁细胞损伤相关的胃酸分泌减少可为 NHPH 的胃内定植、过度生长提供环境支持[56,59]，而胃内微生物的过度生长反会增强炎症反应和降低机体免疫力[60]，而加速萎缩、化生和肿瘤的发生。

NHPH 可通过抑制胃酸分泌和细菌趋化性引起胃肠道菌群结构和功能变化[61]。研究发现，在根除 Hp 治疗 1 年后，持续炎症的受试者胃内的鲁氏不动杆菌、咽峡炎链球菌、罗尔斯顿菌、厄氏菌和普雷沃菌富集，并且与萎缩、肠化相关的潜在致病菌如肉芽肿菌、消化性链球菌、链球菌等丰度增加；在根除 Hp 后，萎缩、肠化组织中 NHPH 的氨基酸代谢和肌醇磷酸盐代谢等功能通路表达增多，而叶酸生物合成和 nod 样受体信号减少，表明 NHPH 可能通过抑制宿主免疫，向宿主细胞传递效应分子，进而促使癌前病变发生[62]。NHPH 在胃癌发病中也发挥关键作用，多项研究发现，链球菌不仅在慢性胃炎患者胃内丰度的明显增加[56,63]，而且在胃癌患者的胃内富集[64]，表明链球菌与胃癌的发生密切相关[65]。同时，研究表明 NHPH 可通过在人体内产生氧化还原蛋白诱导炎症反应、调节免疫细胞形成免疫抑制微环境以及产生活性氧等途径促使胃癌的发生[66-68]。

5　结束语

CAG 作为一种年龄相关的胃黏膜退行性病变，但 Hp 感染、饮食及肥胖等因素使得 CAG 患病人群逐渐年轻化[4]，同时因临床疗效欠佳和癌症恐惧心理引起的 CAG 相关的焦虑抑郁问题愈发明显[69-70]，严重影响人们的生活健康、降低人们的生活质量。所以明悉 CAG 的发病机制，前移炎-癌转化关口显得刻不容缓。

目前人们关于 Hp 感染相关 CAG 的发病机制研究已初见光明，杀菌治疗成为根除 Hp 的首要疗法[11,71]，但抗生素耐药又成为抑制 Hp 相关的 CAG 的一大障碍[72]，所以规范抗生素使用十分必要。自身免疫相关 CAG 可具有胃肠病学、血液学、神经精神学和自身免疫疾病学等胃内胃外多种症状表现，目前尚未形成统一规范的诊断评估标准，临床中又因疾病重叠而常导致 AIG 延迟诊断和治疗[73-74]。胆汁反流相关的 CAG 临床常予质子泵抑制剂、胃黏膜保护剂等治疗，但长期使用质子泵抑制剂治疗可能增加肺部和肠道感染、骨折、肾损伤、微量元素吸收障碍、心血管事件以及胃癌前病变、肿瘤发生的风险[75]。目前改善黏膜防御和促进黏膜修复成为治疗胆汁反流破坏胃黏膜屏障的新靶点[76]。研究发现陈皮、香附、高良姜等中药和艾灸、电针等中医外治技术具有促进胃黏膜修复的良好作用[77-82]，值得临床应用和推广。胃内非 Hp 菌群相关的 CAG 是目前新兴的 CAG 发病机制研究热点，研究表明胃内非 Hp 菌群有望成为预防 CAG 和肿瘤发生、发展及扭转炎-癌转化关口的治疗新靶点[56,62]，其研究前景值得期待。

利益冲突　所有作者均声明不存在利益冲突

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