结肠炎癌转化调控机制和化学干预的研究进展

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摘要: 结直肠癌是消化道常见恶性肿瘤, 炎症性肠病发展为结直肠癌的风险显著增加。免疫信号通路 NF-κB、IL-6/STAT3、COX-2/PGE2、IL-23/Th17、TLRs 等已被证实能够促进结肠炎向结直肠癌转化的进程, NOD2 与肠道微生物的作用也参与炎癌转化的调控。慢性炎症作为结直肠癌的潜在风险, 抑制炎症的药物可能起到化学预防的作用。本综述对结肠炎癌转化过程相关的信号通路进行了总结, 并对用于结肠癌化学预防的药物进行了概述。

关键词: 炎症性肠病; 结直肠癌; 炎症信号通路; 炎癌转化; 化学预防

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Advances in mechanisms for inflammation-associated colon carcinogenesis and chemoprevention

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Abstract: Colorectal cancer is a common malignant tumor of digestive tract, and the risk of inflammatory bowel disease developing into colorectal cancer is significantly increased. Immune signaling pathways NF-κB, IL-6/STAT3, COX-2/PGE2, IL-23/Th17 and TLRs have been confirmed to promote the transformation from colitis to colorectal cancer. NOD2 and intestinal microbes also participate in the regulation of inflammation mediated carcinogenesis. Chronic inflammation is a potential risk for colorectal cancer, and anti-inflammatory drugs may play a chemical preventive role. In this review, we summarize the signaling pathways involved in inflammation-associated colon carcinogenesis and evaluate the chemoprophylaxis of colon cancer.

Key words: inflammatory bowel disease; colorectal cancer; inflammatory signaling pathway; inflammatory carcinomatosis; chemoprevention

炎症性肠病 (inflammatory bowel disease, IBD) 是病因不明的慢性、复发性的导致肠道结构破坏的炎性疾病, 其发病机制是复杂和多因素的。临床上定义的 IBD 主要为溃疡性结肠炎 (ulcerative colitis, UC) 和克罗恩病 (Crohn's disease, CD)。

结直肠癌 (colorectal cancer, CRC) 是常见的消化道恶性肿瘤。据世界卫生组织国际癌症研究机构 (IARC) 发布的 2020 年全球最新癌症负担数据显示, 结直肠癌是全球第三大常见癌症, 占全部诊出癌症的 9.7%[1]。结直肠癌主要分为两种类型: 结肠炎相关的结直肠癌 (colitis associated colorectal cancer, CAC) 和散发性结直肠癌 (sporadic colorectal cancer, SCRC)。

目前, 70% 以上的结直肠癌为散发性, 发病机制与家族遗传和环境因素等密切相关。而炎症性肠病的患者具有更高的结直肠癌风险, 与普通人群相比, 这类患者结直肠癌的发生率可增加 60%[2]。并且由 UC 和 CD 发展为结直肠癌的患者具有更高的死亡率[3]。但是,

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目前由炎症性肠病发展为结直肠癌的机制尚不完全清楚。本综述对炎症性肠病向结肠癌转化过程的调控机制以及化学干预策略进行总结。

1　结肠炎癌转化调控机制

1.1　NF-κB 信号通路　NF-κB 是参与先天免疫和炎症的关键转录因子, 也参与肿瘤的发生和发展。哺乳动物 NK-κB 家族主要由 p50、p52、p65 (RelA)、c-Rel 和 RelB 五种蛋白组成[4]。NF-κB 信号通路可由脂多糖 (LPS)、促炎细胞因子如 TNF-α 和 IL-1、病毒和 DNA 损伤剂等刺激激活[5]。

NF-κB 信号通路的激活包括经典激活途径和非经典激活途径。结合于 NF-κB 的 IκB (NF-κB 抑制剂) 可被 IκB 激酶 (IKK) 复合物磷酸化。在典型的激活途径中, IκB 在细胞因子、生长因子和微生物等刺激下降解, NF-κB 同源或异源二聚体可以转移到细胞核并激活靶基因的转录[6]。在非典型途径中, NF-κB 由 TNF 家族细胞因子激活, 选择性参与 B 细胞成熟和淋巴器官的发育[7]。下游分子 BAFFR、CD40、RANK 或 LTβR 等导致 NF-κB 诱导激酶 (NF-κB-inducing kinase, NIK) 活化并激活 IKKα[8]。IKKα 磷酸化 p100 使其随后被蛋白酶体加工为 p52, p52/RelB 进入细胞核激活靶基因的转录[9]。

NF-κB 作为炎症反应的核心调节因子, 参与包括 IBD 在内的多种炎症反应的发病过程, 诱导炎症细胞因子的表达和促进炎症相关的组织损伤。在 IBD 患者中观察到 NF-κB 表达和激活的增加, 特别是黏膜巨噬细胞和上皮细胞中, 伴随促炎细胞因子如 TNF-α、IL-1 和 IL-6 的产生[10]。靶向巨噬细胞的 NK-κB 通路抑制药物可有效地缓解小鼠结肠炎[11]。NF-κB 还参与了肿瘤的增殖与发展过程, 抑制细胞凋亡, 促进细胞的侵袭和迁移[12]。NF-κB 通路的靶基因编码抗凋亡调节因子, 包括生长抑制 DNA 损伤基因 (growth arrest and DNA-damage-inducible gene 45, Gadd45)、B 细胞淋巴瘤相关蛋白 (BFL1) 等, 这些抗凋亡基因的表达促进肿瘤细胞的增殖和存活[12,13]。此外, NF-κB 的活化还可促进血管内皮因子 (VEGF)、COX-2 和 IL-8 的表达, 促进血管生成, 从而促进肿瘤的侵袭[14,15]。

与野生小鼠相比, IKKβ 失活的小鼠可以减少炎症相关结肠癌的发生和发展。在肠上皮细胞中, IKKβ 通过抑制细胞凋亡促进肿瘤的增殖, 而在髓系细胞中, IKKβ 参与肿瘤生长所需炎症介质的产生[16]。非典型激活途径也参与了 CAC 的发展。NOD 样受体 12 (Nod-like receptor 12, NOD12) 是 NF-κB 非典型活化途径的负调控因子。NOD12 敲除小鼠经过 AOM/DSS 处理后表现出更为严重的结肠炎, 炎症相关肿瘤细胞的比例更高[17]。在 DSS 处理的 CAC 小鼠模型中, p53 的突变也会通过经典途径激活 NF-κB, 提高促炎细胞因子的水平, 如 IL-6 和 IL-8, 因此对早期 IBD 患者进行 p53 基因突变的筛查, 进一步研究 p53 与 NF-κB 的关系是必要的[18]。

NF-κB 的活化可诱导 TNF-α 的产生, TNF-α 与其受体 TNFR1 和 TNFR2 结合后又可进一步活化 NF-κB。TNF-α 诱导 ROS 产生会造成 DNA 损伤。TNF-α 还通过刺激促血管生成趋化因子的表达来促进血管生成[19]。在 AOM/DSS 诱导的小鼠 CAC 模型中, TNF-α 的表达明显升高, TNF 拮抗剂能够显著抑制小鼠肿瘤生长。与野生型小鼠相比, TNFR1 敲除小鼠 CAC 细胞数量明显减少[20]。此外, 在 DSS 诱导的小鼠结肠炎中, 结肠上皮中 TNFR2 过表达[21]。因此, TNF-α 是 NF-κB 通路调控结肠炎相关结肠癌发生发展的关键细胞因子。

1.2　IL-6/STAT3 信号通路　促炎性细胞因子 IL-6 由免疫细胞和基质细胞分泌以调节肠上皮炎症和应对肠道损伤, 在炎症性肠病和结肠癌中起着重要的致病作用。IBD 和 CRC 患者血清和肠黏膜中 IL-6 的水平均明显升高, 且与炎症严重程度和肿瘤进展呈正相关[22,23]。IL-6 与其受体 IL-6Rα 结合形成复合物, 招募两个 gp130 亚基并诱导其形成同源二聚体, 触发 Janus 激酶 (Janus kinase, JAK) 的磷酸化[24]。激活的 JAK 进一步磷酸化 IL-6Rα, 使受体显示了转录激活因子 STAT3 的结合位点, 从而募集 STAT3 与之结合, 与受体结合的 STAT3 被 JAK 磷酸化后形成二聚体, 进入细胞核调控细胞增殖、生存和血管生成[25]。在 AOM/DSS 处理的小鼠结肠癌模型中, IL-6 主要由肿瘤浸润的巨噬细胞、树突状细胞和 T 细胞产生, 刺激肠上皮细胞的增殖并调节肿瘤的发生[26]。在这一过程中, STAT3 诱导鞘氨醇-1-磷酸酯受体 1 (sphingosine-1-phosphate receptor 1, S1PR1) 表达, 肿瘤和相关免疫细胞中的 S1PR1 又将持续激活 STAT3, 促进肿瘤的发生发展。上调 S1PR1 可诱导肿瘤浸润的巨噬细胞和树突状细胞促进 IL-6 的分泌[27,28]。

IL-6 信号通路在肿瘤细胞抗凋亡中也至关重要。IL-6 的缺失能抑制肿瘤细胞增殖, 降低肿瘤数量、大小和肿瘤多样性。利用阿司匹林抑制小鼠 IL-6 的表达, STAT3 磷酸化水平降低, 下游调控细胞凋亡基因 Bcl-2 和 Bcl-xL 的表达也降低[26]。IL-6 敲除小鼠肠上皮细胞增殖减少, 凋亡程度升高, STAT3 信号转导的细胞增殖相关基因的表达也显著下调, 如 cyclin D 和 PCNA[29]。在 STAT3 敲除的小鼠中也得到了相似的结果, 小鼠肿瘤生长受到抑制[30]。STAT3 可调节下游抗凋亡蛋白

Mcl-1的表达, 抑制STAT3能促进肿瘤细胞的凋亡[31]。因此, IL-6在结肠炎相关结肠癌中是重要的肿瘤启动因子, 而STAT3作为下游分子在信号转导中是必不可少的。

1.3 COX-2/PGE2信号通路 环氧化酶 (cyclooxygenase, COX) 是催化花生四烯酸转化为前列腺素 (prostaglandin, PG) 的关键酶, 是血管生成、炎症和癌变的重要调节因子, 包括COX-1、COX-2、COX-3三种亚型[32]。COX-1是一种满足前列腺素基本需求的管家酶。COX-3是中枢神经系统内COX-1的变体[33]。而COX-2在结直肠、肾脏、生殖器官等多种组织中表达, 在肿瘤发生过程中可不断上调。促炎细胞因子TNF-α、IL-1等诱导COX-2和PGE2的表达, 参与血管舒张, 从而加重炎症[34]。约有85%的结肠癌患者中可观察到COX-2表达的升高, 并伴有较差的生存情况[35]。在结肠炎患者中同样可检测到COX-2的过表达[36]。人群研究和动物实验证明非甾体抗炎药物 (nonsteroidal anti-inflammatory agents, NSAIDs) 对结肠癌具有保护作用[37]。NSAIDs可以抑制COX-2活性, 长期使用非甾体抗炎药阿司匹林可降低结直肠癌风险40%～50%[38,39]。COX-2编码基因*Ptgs2*突变小鼠肿瘤发生率明显降低, 使用COX-2抑制剂处理也得到了相似的结果[40,41]。此外, COX-2还可通过诱导BCL-2等抗凋亡蛋白的表达导致细胞凋亡抵抗, 从而促进肿瘤生长[42]。

COX-2的下游产物PGE2是一种具有多种激素功能的活性脂类化合物, 介导COX-2在IBD和CRC中的作用[43,44]。COX-2以花生四烯酸为底物合成前列腺素G2和前列腺素H2, 然后合成前列腺素D2、E2、F2α、I2和血栓素A2, 并通过G蛋白偶联受体发挥作用[45]。PGE2通过特定的细胞表面受体 (prostaglandin E receptor, EP) 发挥作用, 该受体由EP1、EP2、EP3和EP4四种亚型组成[46]。PGE2的主要信号转导包括通过EP1提高细胞内游离钙离子浓度, 降低细胞内cAMP浓度和通过EP3抑制亚基Gi激活ERK, 以及cAMP浓度升高, 随后EP2和EP4亚基Gs激活蛋白激酶PKA[47]。其中, PEG2的促炎作用主要由EP1和EP3介导。最近也有研究表明高水平PGE2通过EP2和EP4激活树突状细胞表达IL-23和促进T细胞向Th17分化来维持炎症[48]。在IBD发病过程中, PGE2可能具有双重作用。一方面, 高水平的PGE2会加剧炎症反应。PGE2产生缺陷降低了小鼠结肠炎的发病潜力, EP4受体缺失可显著缓解小鼠结肠炎[49]。另一方面, PGE2可增强上皮细胞的存活和再生, 在抑制结肠炎和维持肠上皮完整性方面是必需的[50]。此外EP4促进上皮细胞增殖的同时可起到促肿瘤的作用。EP4激动剂可与PGE2同等水平地促进结肠癌细胞生长。敲除EP4或使用EP4拮抗剂处理AOM处理的小鼠可减少癌前病变和肠道息肉数量[51]。因此, EP4可介导PGE2在结肠癌中促癌作用。

此外, PGE2还可通过诱导促血管生成的趋化因子CXCL1的表达, 其可诱导微血管内皮细胞的迁移和血管的形成, 促进肿瘤生长和侵袭[52]。CXCL1的受体CXCR2可诱导CAC小鼠骨髓源抑制细胞 (myeloid-derived suppressor cells, MDSCs) 浸润。髓系抑制细胞通过抑制CD8$^+$ T细胞的细胞毒性加速肿瘤的增殖, 说明它们在肿瘤免疫逃逸中的重要作用[53]。

1.4 IL-23/Th17信号通路 IL-23由树突状细胞和其他抗原呈递细胞产生, 由p19和p40两个亚基组成, 其受体IL23Rs包括IL-12Rβ1和IL-23Rα[54,55]。TGF-β和IL-6可诱导Th17细胞上的IL-23受体表达, 介导IL-23驱动Th17分化的作用[56]。IL-23与其受体结合后, 激活激酶JAK2和Tyk2, 随后转录激活因子STAT3和STAT4被激活, 促进下游靶基因表达[57]。IL-23受体对于Th17细胞的分化具有关键作用。利用中和抗体阻断IL-23信号通路, 可导致Th17细胞的凋亡, 减轻CD4$^+$ T细胞转移至SCID小鼠引起的实验性结肠炎[58]。

IL-23促进表达IL-23受体的记忆T细胞大量增殖, 随后记忆T细胞产生Th17细胞因子, 包括IL-17A、IL-17B、IL-17C、IL-17D、IL-17E和IL-17F[59]。IL-17通过诱导内皮细胞和巨噬细胞产生的细胞因子和趋化因子以及募集中性粒细胞来驱动肠道炎症[60]。IL-23/Th17通路在CRC发病过程中同样具有重要作用。在APC突变小鼠结肠癌模型中, IL-23和IL-17A的表达显著上调。抗体中和IL-23及其受体后抑制了IL-17A的表达, 并且降低了细胞增殖和肿瘤负荷[61]。IL-17与内皮细胞上的受体结合, 刺激内皮细胞产生VEGF, 促进血管生成, 并且产生IL-17的细胞数量与肿瘤内微血管密度呈正相关[62]。此外IL-17A能促进小鼠结肠肿瘤中MDSCs的募集, 促进肿瘤的增殖。阻断IL-17A可提高PD-1抗体在小鼠CRC模型的治疗效果[63]。然而, IL-17家族的某些成员, 如IL-17F, 可抑制肿瘤组织血管的生成, 对结肠癌发展具有保护作用。IL-17F在结肠癌患者组织中的表达量降低。将过表达IL-17F的结肠癌细胞移植至裸鼠时, VEGF表达水平降低, CD131$^+$细胞数量减少, 肿瘤生长受到抑制[64]。

此外, Th17细胞还产生其他调控肠道免疫反应的细胞因子如IL-21和IL-22等。IL-6通过STAT3依赖的

方式诱导 Th17 细胞表达 IL-21, IL-21 也可通过激活 STAT3 和上调 IL-23R 放大 Th17 细胞的免疫反应[65-67]。IL-21 在结肠炎相关结肠癌患者中过表达。IL-21 的缺失导致 T 细胞浸润减少、STAT3 的激活以及 IL-6 和 IL-17A 的产生受到抑制, 肠道炎症减轻。在 AOM/DSS 处理的小鼠结肠癌模型中, IL-21 缺失可减缓肿瘤发展[68]。IL-22 可由 Th1、Th17 和 Th22 等多种免疫细胞产生, 在结肠炎相关 CRC 肿瘤浸润的 T 细胞中表达上调[69]。IL-22 对肿瘤的发展具有双重作用。一方面, IL-22 可激活 STAT3 和诱导 BCL-xL 等抗凋亡因子的表达, 促进肿瘤的生长和转移[70]。另一方面, IL-22 刺激肠上皮细胞和上皮下肌成纤维细胞产生一系列抗炎、再生和组织保护蛋白[71]。在 DSS 诱导的结肠炎中, IL-22 表现出一定的保护作用, 可能是由于 IL-22 增加的肠壁黏液的产生, 从而减轻 DSS 对肠上皮的损伤[72]。因此, IL-22 在不同的肠道炎症和肿瘤中具有不同甚至矛盾的功能。

1.5　TLRs 信号通路　Toll 样受体 (Toll-like receptors, TLRs) 属于 1 型跨膜糖蛋白, 包括细胞外富含亮氨酸的重复序列和 Toll/白介素 1 受体 (Toll/IL-1 receptor, TIR) 信号域。TLRs 具有 5 种 TIR 接合蛋白: 髓样分化因子 MyD88、MyD88 适配体样蛋白 (TIR domain-containing adaptor protein, TIRAP)、诱导 IFN-β 的 TIR 结构域衔接蛋白 (TIR domain-containing adaptor, TRIF)、TRIF 相关接头蛋白 (TRIF-related adaptor molecule, TRAM) 以及包含 Sterile α 和 Armadillo 序列的接头蛋白 (sterile α- and armadillo-motif-containing protein, SARM)[73]。TLR 经典信号通路主要通过 MyD88 激活, 而 MyD88 又会招募 IRAKs 和 TRAF6。TRAF6 活化转化生长因子 β 激活激酶 1 (TGF-beta activated kinase 1, TAK1), 进而刺激 IKK 介导的 NF-κB, 最终导致 NF-κB 转位进入细胞核, 诱导 TNF-α、IL-1 和 IL-6 等细胞因子的产生。TLR3 的活化途径不依赖于 MyD88, 最终激活 TRAF3 和 IRF3, 诱导 I 型干扰素的分泌[74]。而上述两个通路都可以活化 TLR4[75]。

TLRs 信号对于肿瘤的发展具有典型的双重作用。TLRs 参与肠道上皮屏障完整性和调节 MyD88 蛋白的功能, 可控制肠道炎症的出现并降低炎症相关肿瘤的发生[76]。肿瘤细胞抗原提呈能力较差, 因此抗肿瘤免疫应答通常依赖于树突状细胞[77]。DCs 上 TLR5 的激活以及 TLR9 刺激浆细胞状 DCs 可有效促进抗肿瘤免疫[78,79]。TLR 还通过 IL-6 依赖的方式阻断 Treg 细胞的免疫抑制作用[80]。在人结肠癌异种移植小鼠模型中, MyD88 或 TLR5 缺失可促进结肠癌生长, 肿瘤细胞凋亡受到抑制, 而激活 TLR5 可显著促进肿瘤坏死, 导致肿瘤明显消退[81]。

另一方面, 肿瘤细胞中 TLRs 的表达也可能通过诱导慢性炎症介导的抑制性肿瘤微环境来促进肿瘤发生[82]。增强 NF-κB 信号是 TLRs 的主要促肿瘤作用之一。TLR 以 NF-κB 依赖的方式上调促炎性细胞因子 IL-1β、TNF-α、IL-6 等[83]。在结直肠癌中, TLR 诱导的 NF-κB 活化有利于肿瘤细胞的生存[84]。在小鼠结肠癌细胞系中, TLR4 的激活诱导了肿瘤细胞对细胞毒性 T 细胞介导的细胞死亡抗性, 有利于肿瘤的存活[85]。在 AOM/DSS 诱导的小鼠 CAC 模型中, TLR4 缺失显著减弱炎症和降低了肿瘤负荷[86]。在转基因小鼠模型中, 过表达组成型激活的 TLR4 表现出对 CAC 更高敏感性[87]。因此, TLR4 可开发作为预防和治疗结肠炎相关结肠癌的靶点。

1.6　NOD2 与肠道菌群　NOD2 是 NOD 样受体 (Nod-like receptors, NLRs) 家族的成员, 其编码基因位于染色体 16q12 上, 包括 C 端传感器结构域、中心核苷酸结合和寡聚结构域和 N 端效应结构域[88]。NOD2 参与识别外来微生物细胞壁成分, 通过识别细菌脂多糖和激活 NF-κB 在先天免疫中发挥重要作用[89]。肠上皮细胞中的 NOD2 可能通过促进潘氏细胞产生防御素等抗菌化合物调控肠道微生物群落[90]。NOD2 还可参与诱导自噬, 促进受损蛋白质和细胞器的清除[91]。*NOD2* 基因突变会导致识别、清除细菌病原体的功能丧失, 促炎细胞因子的增加, 进而导致慢性炎症的发生[92]。NOD2 与肠道微生物群的相互作用在慢性炎症反应中也是至关重要的, NOD 基因多态性与克罗恩病易感性增加密切相关[93]。对 CD 和 UC 患者的肠道样本进行 NOD2 风险等位基因分型, 发现 *NOD2* 复合基因型与微生物组成变化显著相关, 特别是粪钙杆菌和大肠杆菌的组成[94]。在 TNBS 诱导的小鼠结肠炎模型中, 唾液乳酸杆菌 Ls33 的保护能力依赖于 NOD2, 并与 IL-10 的产生有关[95]。NOD2 缺陷小鼠在 DSS 诱导的结肠炎中也表现出易感性增加。NOD2 在结肠炎相关结肠癌的进展中也发挥重要的作用, NOD2 缺失小鼠远端结肠肿瘤负荷增加。值得注意的是, 上述效果可以通过共住或交叉培养进行传播。与 NOD2 缺陷小鼠共同培养后, 野生型小鼠的发病率和死亡率显著提高, DCs 表达更高水平的 IL-6。粪便移植实验进一步证明, 无菌型野生小鼠接受 NOD2 缺陷小鼠的粪便后病情加重, 而无菌型 NOD2 缺陷小鼠接受了野生型小鼠的粪便菌群后肿瘤发展得到缓解[96]。因此, NOD2 及其与肠道微生物菌群的互作对于结肠炎和结肠癌具有重要的保护作用。

2　结肠炎癌转化的化学干预策略

化学预防策略是利用药物来降低恶性肿瘤的风险。目前已发现有多种治疗炎症性肠病的药物具有化学预防结肠癌的潜力。

2.1　美沙拉嗪 (5-aminosalicylic acid, 5-ASA)　5-ASA是临床治疗溃疡性结肠炎的常用药物。5-ASA能够负调控COX-2/PGE2信号通路, 抑制NF-*κ*B和Wnt信号通路[97]。5-ASA还可以抑制mTOR信号通路, 诱导细胞周期阻滞, 干扰结直肠癌细胞的增殖[98]。在对包括15 460名受试者进行的Meta分析中, 5-ASA对IBD患者发展为结肠癌有化学预防作用, 并且UC患者比CD患者具有更好的预防效果。5-ASA维持剂量每天1.2 g是降低IBD患者结直肠癌风险的有效治疗方法[99]。然而也有研究显示, 5-ASA的使用与IBD患者发生结肠癌风险降低无关[100]。虽然5-ASA对IBD患者结直肠癌风险的作用尚不清楚, 但目前仍然是治疗溃疡性结肠炎的主要药物, UC患者可考虑长期维持治疗。

2.2　TNF-*α*拮抗剂　在慢性炎症中, 肠上皮细胞NF-*κ*B通路的持续激活诱导结肠炎向结肠癌的转化。抗肿瘤坏死因子药物通过阻断TNF-*α*, 抑制NF-*κ*B炎症通路, 减少结直肠癌的发生。目前, 美国FDA和欧洲EMA共批准上市了5款TNF抑制剂, 分别是英夫利昔单抗、阿达木单抗、赛妥珠单抗、戈利木单抗和依那西普, 主要用于治疗类风湿性关节炎、强直性脊柱炎、银屑病和克罗恩病等自身免疫疾病[101]。英夫利昔单抗和阿达木单抗被广泛用于治疗溃疡性结肠炎, 理论上可以通过减少黏膜炎症起到预防结肠癌的作用。在一项荷兰的病例对照研究中, 接受TNF-*α*抗体治疗的IBD患者发生结直肠癌的风险较低[102]。而在另外两项人群研究中发现TNF-*α*治疗与结直肠癌的发病之间没有关联[103,104]。目前, 还没有足够证据证明使用生物制剂能够进行结直肠癌的化学预防。

2.3　IL-6/STAT3通路抑制剂　目前已有许多研究证明IL-6抑制剂对于癌症治疗有效。泮托拉唑可减少IL-6的分泌, 引起胃癌细胞特异性死亡。由于结直肠癌与胃癌的肿瘤进展机制相似, 因此它可能是治疗结直肠癌的潜在药物[105]。膳食多酚通过调节IL-6受体和SOCS3 (suppressor of cytokine signalling-3) 蛋白的表达来抑制血管生成, 可以起到抑制结直肠癌变的作用[106]。Olamkicept (TJ301) 由两个可溶性人gp130蛋白与人IgG的Fc片段融合而成, 是通过反式信号机制发挥作用的选择性IL-6抑制剂, 目前正处于临床试验阶段, 有潜力成为同类治疗溃疡性结肠炎的最佳药物[107]。

2.4　IL-23/Th17通路抑制剂　目前已上市的IL-23靶向药主要用于治疗银屑病, 用于治疗溃疡性结肠炎和克罗恩病的药物也在陆续获批或处于临床试验阶段。优特克单抗 (ustekinumab) 已获批治疗UC和CD。古赛库单抗 (guselkumab)、替拉珠单抗 (tildrakizumab) 和瑞莎珠单抗 (risankizumab) 用于UC和CD适应症的临床试验正在开展中[108]。

2.5　TLR激动剂　替拉莫得 (telratolimod) 是具有抗肿瘤活性的TLR7和TLR8激动剂, 已用于结直肠癌患者的治疗。TLR9激动剂cobitolimod在重度溃疡性结肠炎的临床试验中取得重大进展, 可在大肠局部起到抗炎的作用, 具有很高的安全性, 在临床缓解方面表现出显著的疗效[109]。

2.6　其他药物　阿司匹林、其他非甾体抗炎药、他汀类药物、维生素D和叶酸在其他疾病和散发性CRC中的抗炎作用已得到较为广泛的研究[110]。在阿司匹林和非甾体抗炎药的评估中, 8项涉及14 917例患者的研究和3项涉及1 282例患者的研究分别提供了服用非甾体抗炎药和阿司匹林的IBD患者结直肠癌风险的数据, 结果显示两种药物的使用与IBD相关结直肠癌风险之间没有显著相关性[111]。相反, 他汀类药物显示出具有预防IBD相关结直肠癌的作用。在一项涉及1 376例IBD患者的研究中, 9年随访期间, 接受过他汀类药物的患者结直肠癌的发病率较低[112]。同样, 适当补充维生素D和叶酸也有助于降低结直肠癌的风险[113,114]。

3　展望

炎症性肠病可显著增加结直肠癌的发病风险, NF-*κ*B、IL-6/STAT3、COX-2/PGEs、IL-23/Th17信号通路以及TLRs和NLRs在结肠炎症向癌症转化进程中发挥重要的调控作用 (图1)。促炎信号通路诱导炎症介质的表达, 造成炎症相关的组织损伤, 上调抗凋亡蛋白水平, 促进上皮细胞的增殖, 为肿瘤生长创造有利微环境。这些信号还诱导肿瘤内血管的形成, 进一步促进肿瘤的发展。而部分TLRs和NLRs能够缓解肠道炎症, 保护黏膜屏障完整性, 促进肿瘤细胞坏死。然而, 目前已上市的药物尚不能对炎症性肠病患者发展为结直肠癌起到很好的预防效果。因此, 通过探究结肠炎癌转化的调控机制, 寻找其中可进行干预的关键分子, 将为炎症性肠病相关结肠癌的预防和治疗提供有效靶点。

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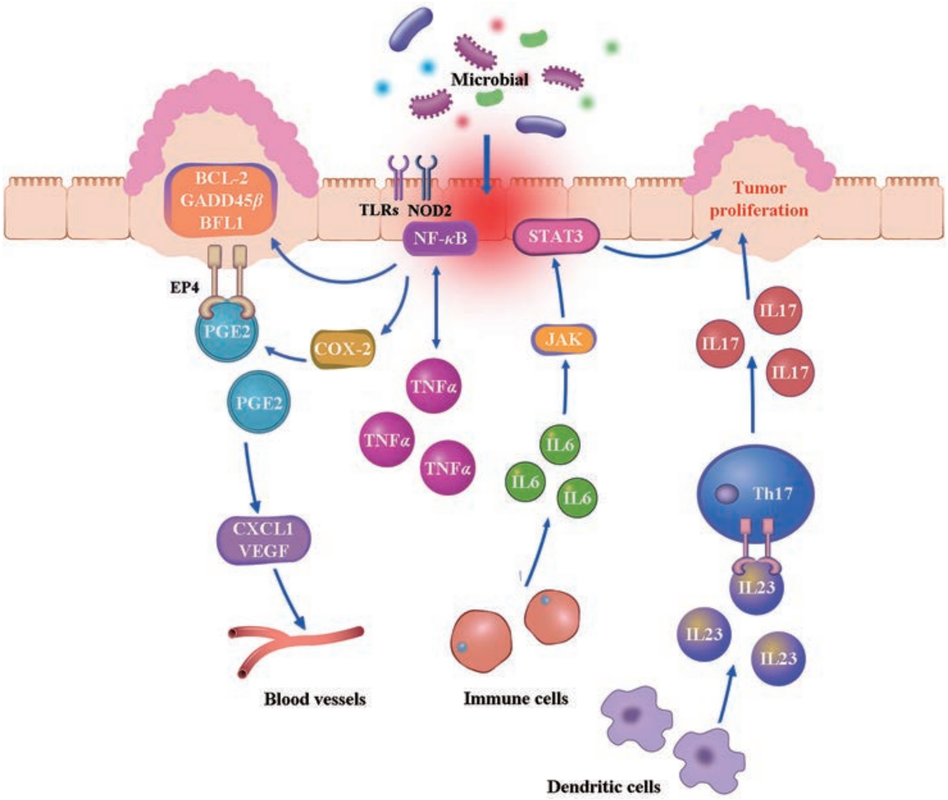

Figure 1 Regulation mechanism of the transformation from inflammatory bowel disease to colon cancer

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