白细胞介素-10在维持肠道稳态中的作用研究进展

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摘要 肠道稳态是宿主肠道黏膜和免疫屏障、肠道环境、营养物质和代谢产物等相互作用而形成的动态平衡状态。白细胞介素-10(interleukin-10, IL-10)是IL-10细胞因子家族的成员之一, 是免疫反应中重要的抗炎细胞因子, 在维持肠道稳态中发挥重要作用。该文从IL-10在维持肠上皮细胞稳态、肠屏障完整性、肠道菌群平衡以及在肠道中的抗炎作用四个方面对IL-10在维持肠道稳态中作用的研究进展作一综述, 并对IL-10在肠道疾病中的治疗前景进行展望。

关键词 白细胞介素-10; 肠道稳态; 肠上皮细胞; 肠屏障; 肠道菌群

Research Progress on the Role of Interleukin-10 in Maintaining Intestinal Homeostasis

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Abstract Intestinal homeostasis is a dynamic equilibrium state formed by the interaction of the host intestinal mucosa and immune barrier, intestinal environment, nutrients and metabolites. IL-10 (interleukin-10), a member of the IL-10 cytokine family, is an important anti-inflammatory cytokine in the immune response and plays an important role in maintaining intestinal homeostasis. This article reviewed the research progress of the role of Il-10 in maintaining intestinal homeostasis from four aspects: the maintenance of intestinal epithelial homeostasis, the integrity of intestinal barrier, the balance of gut microbiota and the anti-inflammatory effect in the intestine, the therapeutic prospect of IL-10 in intestinal diseases was prospected.

Keywords interleukin-10; intestinal homeostasis; intestinal epithelial cells; intestinal barrier; gut microbiota

肠道稳态是宿主(肠道黏膜和免疫屏障)、肠道环境(肠道菌群)、营养物质和代谢产物等相互作用而形成的动态平衡状态[1]。肠道稳态对于肠道的生理功能以及健康至关重要, 肠道稳态的失调可导致多种肠道疾病比如炎症性肠病(inflammatory bowel disease, IBD)、肠易激综合征(irritable bowel syndrome, IBS)、乳糜泻等的出现[2-3]。肠道的细胞结构以连续的单层肠上皮细胞(intestinal epithelial cells, IECs)为特征, 通过发挥抗原呈递、产生抗菌肽和黏液以及维持紧密的物理屏障等作用, 成为抵御环境和微生物攻击的第一道防御屏障。在肠道中, IL-10可以提高紧密连接蛋白的表达水平来维持肠屏障的

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完整性, 并且在肠道损伤后促进IECs的增殖进而加快伤口愈合[4]。IL-10的缺失导致了肠道菌群平衡的失衡, 进而促进了肠道疾病的发生[5]。此外, IL-10还可以抑制肠道中促炎因子的产生从而发挥其抗炎的作用。IL-10和IL-10受体(interleukin-10 receptor, IL-10R)缺陷导致人类严重的早期发病以及严重的婴儿小肠结肠炎, IL-10缺失的小鼠则会出现自发性结肠炎, 表明IL-10在维持肠道稳态中具有重要作用[6-7]。因此, 本文从IL-10在维持IECs稳态、肠屏障完整性、肠道菌群平衡以及在肠道中抗炎作用四个方面进行综述, 并对IL-10在肠道疾病中的治疗前景以及应用前景进行展望。

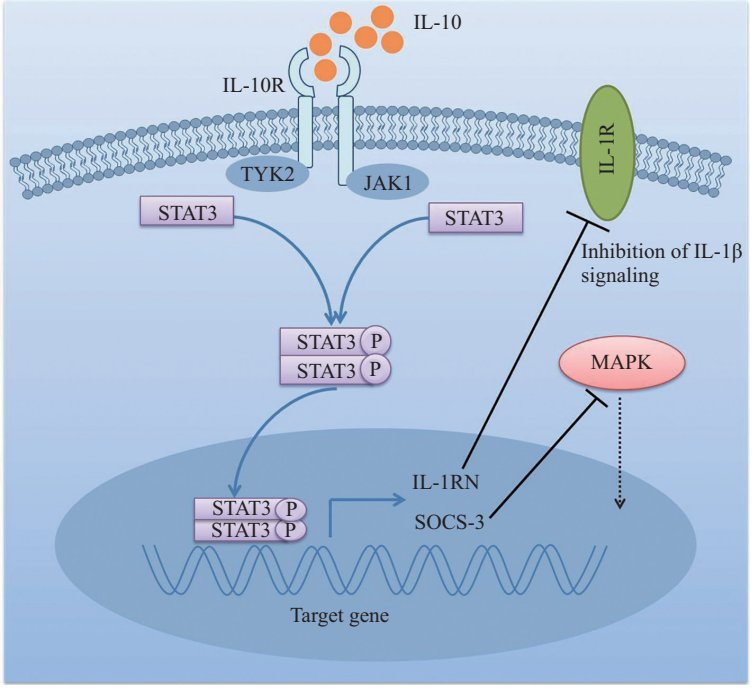
1 IL-10的生物学特性

1989年, MOSMANN等[8]发现Th2细胞可以产生一种抑制Th1细胞功能的因子, 这种因子后来被命名为IL-10。人类*IL-10*基因定位于染色体1q32上, 长4.7 Kb, 包含5个外显子和4个内含子, 人功能性IL-10蛋白是去除18个氨基酸信号肽后的160个氨基酸的二聚体[9]。小鼠*IL-10*基因位于染色体1E4上, 大小为5.1 Kb, 小鼠IL-10每条链由157个氨基酸组成, 其氨基酸序列与人类IL-10氨基酸序列有75%同源性[10]。

IL-10是免疫反应中重要的抗炎细胞因子, 树突状细胞、巨噬细胞、中性粒细胞、B细胞、T细胞以及上皮细胞等都可以合成和分泌IL-10[11]。IL-10通过结合IL-10R发挥作用, IL-10R是由IL-10R1(IL-10Rα)和IL-10R2(IL-10Rβ)分子构成的一种异二聚体。IL-10R1主要在T细胞、B细胞、巨噬细胞等免疫细胞和其他造血细胞中表达, IL-10R2几乎在所有细胞中均有表达[12]。IL-10信号可以激活STAT1、STAT3以及STAT5, 其中STAT3在IL-10信号转导中起主导作用。IL-10与其受体结合后激活JAK1和TYK2, 随后导致STAT3的磷酸化, 磷酸化后STAT3形成同源二聚体并进入细胞核, 进而与STAT3结合元件结合, 驱动抗炎介质比如IL-1受体拮抗剂(IL-1 receptor antagonist, IL-1RN)、细胞因子信号转导抑制因子3(suppressor of cytokine signaling-3, SOCS-3)等的表达, 从而阻断各种炎症通路[13](图1)。

2 IL-10在维持IECs稳态中的作用

IECs对维持肠道黏膜的正常消化和稳态至关重要, IECs每3~5天更新一次, 这种快速更新是由隐窝底部的肠道干细胞(intestinal stem cells, ISCs)维持的[14]。ISCs进行不对称分裂以及自我更新, 同时产



→: 信号通路的激活; ┤: 信号通路的抑制; ----->: MAPK的信号转导。P: 磷酸化。

→: activation of signaling pathway; ┤: inhibition of signaling pathway; ----->: signal transduction of MAPK. P: phosphorylation.

图1 IL-10信号转导导示意图

Fig.1 Schematic diagram of IL-10 signaling

生转运扩增细胞, 并进一步分化产生肠上皮中发现的所有细胞类型, 包括吸收性肠细胞、M细胞、肠内分泌细胞、簇状细胞、杯状细胞和Paneth细胞[15]。每种细胞类型都有特定的功能, 比如杯状细胞和Paneth细胞可通过产生黏液以及抗菌肽来确保肠屏障的完整性, 抵御微生物入侵。 因此, IECs是维持肠道稳态的重要部分。

人和小鼠IECs表达IL-10R, 因此IECs能够对IL-10的刺激产生细胞反应[16-17]。JENKINS等[17]在小鼠IECs中敲除IL-10R后发现Wnt信号异常、IECs过度增殖以及结肠隐窝深度增加, 这些是不典型增生以及结直肠癌发生的前兆[18-19]。小鼠IECs IL-10以及IL-10R缺失导致小鼠对结肠炎的易感性增加, 并且在葡聚糖硫酸钠(dextran sulfate sodium, DSS)诱导的结肠炎研究中发现, IL-10R缺失的小鼠出现更严重的结肠炎症状[20-21]。因此, 当IECs中IL-10R缺失不能接受IL-10信号后, IECs的稳态被破坏, 可能导致肠道疾病的发生, 表明IL-10信号在维持IECs稳态中发挥重要作用。

IL-10影响IECs的数量和功能, 与野生型(wild type, WT)小鼠相比, *IL-10*$^{-/-}$小鼠中杯状细胞数量减少, 黏蛋白2(mucin2, MUC2)的表达量显著降低, Paneth细胞中颗粒含量异常, 分泌的鼠隐窝素4(Cryptdin-4, Crp4)水平降低, 且隐窝底部有大量未成熟的Paneth细胞[22-23]。IL-10缺失后, Paneth细胞和杯状细胞的数量和功能异常, 表明IL-10在维持Paneth和杯状细胞数量及功能中发挥作用。上皮细胞数量和功能的异常可能是IL-10缺失后间接导致的结果, 有直接研究表明IL-10在ISCs自我更新中发挥作用。BITON等[24]使用WT小鼠的小肠类器官证明IL-10的刺激(10 ng/mL, 72 h)可以促进ISCs自我更新。与WT小鼠类器官相比, *IL-10*$^{-/-}$小鼠肠道类器官具有更多的DNA双链断裂, 而添加IL-10恢复了DNA双链断裂的数量[25]。简而言之, IL-10在维持IECs的数量和功能中发挥作用, 同时也促进ISCs的自我更新, 在维持肠道稳态中发挥作用。

IECs凋亡和坏死的增加与肠道炎症的严重程度密切相关, 而IL-10可以抑制IECs的凋亡[26]。早期的研究发现, IL-10的缺失导致干扰素-γ(interferon-γ, IFN-γ)和肿瘤坏死因子α(tumor necrosis factor α, TNF-α)的产生增加, 从而导致体内上皮细胞大量凋亡以及隐窝数量明显减少[27]。在恒河猴结肠外植体中阻断内源性IL-10, 导致固有层和隐窝中凋亡的细胞数量增加, 并且隐窝宽度显著扩大以及杯状细胞出现细胞质空泡变性[28]。DENNING等[29]利用Mode-K细胞证明IL-10(10 U/mL)可以逆转IFN-γ对细胞生长和活力的不利影响。另一项研究表明IL-10保护IECs免受Fas诱导的凋亡, 其机制是下调Fas蛋白、降低Caspase-3和Caspase-8活性以及上调FLIP(Fas-associated death-domain-like IL-1β-converting enzyme inhibitory protein)的表达[30]。粪肠球菌定植的*IL-10*$^{-/-}$小鼠IECs中半乳糖凝集素-3(galectin-3, Gal-3)表达水平减少, 这通常与cleaved Caspase-3的显著增加相关, 并且该研究还观察到核因子κB(nuclear factor kappa-B, NF-κB)依赖性的锌指蛋白Pw1在*IL-10*$^{-/-}$小鼠感染的IECs中上调, 这与p53介导的凋亡有关, 以上结果表明IL-10发挥了抗凋亡作用[31]。总之, IL-10通过上调抗凋亡基因表达、下调凋亡基因表达等多种方式来减少IECs凋亡。

内质网(endoplasmic reticulum, ER)功能紊乱影响蛋白质折叠, 当聚集在ER内的未折叠蛋白质或错误折叠蛋白质超过ER的负荷能力时, 将会引起ER平衡失调, 从而导致ER应激(endoplasmic reticulum stress, ERS)[32]。IECs中具有丰富的ER结构, 并不断受到肠道菌群、黏膜炎症等刺激, IECs过度的ERS可导致肠黏膜屏障功能受损, 甚至导致IBD的发生[33]。研究发现*IL-10*$^{-/-}$小鼠中ERS相关信号通路蛋白表达升高, 表明IL-10在抑制IECs中ERS发挥重要作用[33]。HASNAIN等[34]使用Winnie小鼠(MUC2错误折叠小鼠)和体外衣霉素处理的LS174T细胞来模拟ERS, 结果发现在给予IL-10(50 ng/mL, 24 h)后ERS持续减少, 而当IL-10或IL-10R中和后ERS加剧, 表明IL-10在抑制杯状细胞中的蛋白质错误折叠和ERS方面发挥重要作用。SHKODA等[35]使用炎症的*IL-10*$^{-/-}$小鼠和IBD患者的原发性IECs, 研究发现IL-10抑制激活转录因子6(activating transcription factor 6, ATF-6)募集到葡萄糖调节蛋白-78(glucose-regulated protein 78, *GRP78*)基因启动子, 以抑制炎症诱导的IECs内质网应激反应。总而言之, IL-10通过维持IECs数量及功能的正常、减少IECs凋亡、抑制IECs中的ERS反应, 来维持IECs的稳定状态。

3 IL-10在维持肠上皮屏障完整性中的作用

健康的肠道是通过黏膜免疫系统、腔内微生物

群落和肠上皮之间的平衡关系来实现和维持的。肠上皮形成了一个动态的半透性屏障, 允许吸收营养物质、电解质和水, 以及在免疫调节中发挥作用的抗原, 但它也保护宿主不受肠腔中致病性微生物以及潜在的有毒分子的影响。当肠上皮屏障被破坏后, 肠腔中的微生物(大多数为致病性)会移位进入肠道固有层, 进而引起炎症反应。因此, 肠屏障的完整性对于肠道稳态也至关重要。

上皮细胞通过各种连接蛋白连接, 其中最常见的是紧密连接蛋白(包括Occludin、Claudin-1和ZO-1), 在维持肠屏障完整性中发挥重要作用。小鼠IECs中IL-10R的缺失以及体外T84细胞中IL-10R表达降低都会导致肠屏障功能受损, 肠道通透性增加, 表明IL-10在维持肠屏障完整性中具有重要作用[20]。*IL-10*$^{-/-}$小鼠中Occludin、Claudin-1和ZO-1紧密连接蛋白表达水平显著降低, 肠屏障完整性受损[36-37]。QUIROS等[4]研究发现, 肠道创伤后1天内, 伤口部位的IL-10 mRNA和蛋白表达水平增加, 表明IL-10通过促进上皮Wnt1诱导信号蛋白-1(Wnt1-inducible signaling protein 1, WISP-1)的合成和分泌, 进而促进IECs的增殖和伤口愈合。MORHARDT等[38]发现在非甾体类抗炎药诱导小鼠小肠上皮损伤后, 巨噬细胞产生的IL-10在肠上皮损伤修复中发挥关键作用。MADSEN等[39]的早期研究表明, 在T84培养中外源性IL-10(100 ng/mL)可以减弱钠和氯的转运能力, 并在IFN-γ破坏后恢复屏障完整性。KOMINSKY等[20]利用IFN-γ诱导的T84细胞单层屏障破坏模型, 发现IL-10(10 ng/mL)可以恢复跨上皮电阻(transepithelial electrical resistance, TEER), 促进肠上皮屏障的恢复。这些研究表明了IL-10可以促进IFN-γ诱导的屏障破坏后上皮屏障的恢复, 在维持肠屏障的完整性中发挥重要作用。ZHENG等[40]发现, 丁酸盐和IL-10(10 ng/mL)处理T84细胞与单独使用丁酸盐处理的T84细胞相比, 丁酸盐联合IL-10处理后的上皮屏障的完整性增加更显著。SUN等[41]利用小鼠全肠外营养引起的上皮屏障功能障碍模型, 发现IL-10可以上调ZO-1、E-cadherin以及Occludin的表达水平。与WT小鼠相比, *IL-10*$^{-/-}$小鼠结肠的通透性显著增加以及TEER显著降低, 这可能与*IL-10*$^{-/-}$小鼠结肠中Claudin-1和Occludin的mRNA和蛋白水平均较低有关[42]。与WT小鼠类器官相比, KHARE等[43]发现在*IL-10*$^{-/-}$结肠类器官中E-cadherin的表达异常并且Desmoglein-2表达水平降低。上述研究表明, IL-10可以通过促进IECs的增殖以及提高紧密连接蛋白的表达水平来维持肠上皮屏障的完整性, 从而维持肠道的稳定状态。

4 IL-10在维持肠道菌群平衡中的作用

人类胃肠道被数万亿微生物定植, 它们与宿主相互作用以维持结构和功能的稳态。肠道是一个独特的器官, 其构成暴露在腔内无数病原性和非病原性微生物中。肠道菌群的失衡, 会破坏肠道稳态, 甚至可导致IBD和结直肠癌(colorectal cancer, CRC)等肠道疾病的发生[5]。IL-10是一种重要的抗炎细胞因子, 在维持肠道菌群稳态中至关重要(表1)。

IL-10在维持肠道菌群的平衡中的重要作用通过维持黏液层的功能得到体现。在黏膜组织中, 黏液是抵御共生微生物和入侵病原体的第一道防线。*IL-10*$^{-/-}$小鼠的结肠黏液层发生了改变, 虽然黏液层更厚, 但是更容易被细菌穿透[44]。在*IL-10*$^{-/-}$小鼠中, 杯状细胞分泌的黏液中MUC2的含量减少, 导致黏液对细菌的限制能力减弱, 使得致病菌进入肠道的可能性加大, 从而导致肠道菌群平衡失调[22]。此外, 肠固有层的浆细胞产生的分泌性IgA通过上皮细胞运输到黏液中, 在维持肠黏液功能以及避免潜在的有害免疫反应中发挥着重要作用[45]。有研究发现, IL-10促进肠固有层中产生IgA的B细胞数量的增加, 并且上调IgA的表达水平[46-47]。因此, IL-10通过维持黏液层的功能来抵御各种微生物的入侵, 从而使肠道菌群处于平衡状态。

IL-10的缺失破坏了肠道菌群的平衡状态, 导致肠道疾病的发生。几项研究报道了*IL-10*$^{-/-}$小鼠与WT小鼠之间肠道菌群差异(表2)。无菌的*IL-10*$^{-/-}$小鼠中定植粪肠球菌(*Enterococcus faecalis*, *E. faecalis*)、大肠杆菌(*Escherichia coli*, *E. coli*)或双歧杆菌(*Bifidobacterium*)均足以诱导肠道炎症, 而在无菌WT小鼠中不会出现肠道炎症[48]。虽然*IL-10*$^{-/-}$小鼠的微生物群多样性和丰富度随着时间的推移而下降, 但是仍会出现特定菌群丰度变化从而导致肠道炎症的产生。在常规饲养的*IL-10*$^{-/-}$小鼠中, *E. coli*和变形杆菌(*Proteobacteria*)的丰度随着时间的推移而增加, 这些小鼠结肠炎症很明显, 说明IL-10的缺失导致了*Proteobacteria*和*E. coli*丰度增加, 促进了肠道炎症的发生[49]。在*IL-10*$^{-/-}$小鼠的肠道中观察到*pks*阳性大肠杆菌(*pks*$^{+}$ *escherichia coli*, *pks*$^{+}$ *E. coli*)的数量

表1 IL-10对肠道菌群的影响

Table 1 Effect of IL-10 on gut microbiota

肠道菌群 Intestinal microbiota	变化 Change	结果 Consequence	参考文献 References
E. coli	Increase in abundance after IL-10 deficiency	Inflammation of the colon is obvious andeven leads to the development of IBD and CRC	[49-51,53,56]
Bacteroidetes	Increase in abundance after IL-10 deficiency	Increased *Bacteroides* abundance is associated with higher risk of IBD and CRC	[50,52-53,57]
Proteobacteria	Increase in abundance after IL-10 deficiency over time	It coincided with theactivation of spontaneous inflammation and the onset of colitis	[49,53]
Firmicutes	Decrease in abundance after IL-10 deficiency	Decreased abundance of *Firmicutes* leads to disruption of intestinal homeostasis	[49,57]
Verrucomicrobia	Decrease in abundance after IL-10 deficiency	The balance of microbiota is disrupted inthe intestinal	[49,56]
Lactococcus	Decrease in abundance after IL-10 deficiency	Intestinal mucosal damage and inflammation	[53]
Roseburia	Decrease in abundance after IL-10 deficiency	Intestinal mucosal damage and inflammation	[53]
L. johnsonii	The level of IL-10 expression was consistent with the abundance of *L. johnsonii*	Relief of DSS induced colitis	[55]
A. muciniphila	Decrease in abundance after IL-10 deficiency	Promote the development of IBD	[49,54]
Actinobacteria	Decrease in abundance after IL-10 deficiency	The balance of microbiota is disrupted in the intestinal	[49]

增加, *pks*$^+$ *E. coli*可导致CRC的发生[50-51]。在*IL-10*$^{-/-}$小鼠中, *pks*$^+$ *E. coli*和产肠毒素脆弱拟杆菌(*Enterotoxigenic Bacteroides fragilis*, ETBF)诱导了8-氧鸟嘌呤DNA损伤, 这与CRC的较高发病率相关[52]。因此, IL-10的缺失导致致病菌丰度增加, 促进肠道疾病的发生。IL-10的缺失还导致对黏膜健康有益的乳球菌(*Lactococcus*)、罗斯氏菌(*Roseburia*)以及嗜黏蛋白阿克曼氏菌(*Akkermansia muciniphila*, *A. muciniphila*)丰度下降, 进而导致黏膜损伤以及IBD的发生[49,53-54]。还有研究发现IL-10的表达水平与约氏乳杆菌(*Lactobacillus johnsonii*, *L. johnsonii*)的丰度呈正相关, 并且*L. johnsonii*激活巨噬细胞促进其分泌IL-10, 从而缓解小鼠结肠炎[55]。综上所述, IL-10通过维持黏液的功能以及肠道菌群的丰度从而维持肠道菌群的平衡状态。

5 IL-10在肠道中的抗炎作用

IL-10的抗炎作用表现在可以抑制许多促炎因子的分泌。IL-10与其受体的结合激活JAK1和TYK2, 随后导致STAT3的磷酸化, 反过来STAT3诱导多种抗炎分子比如IL-1RN、SOCS-3以及可溶性TNF受体等的产生, 这有利于抗炎环境的形成。SOCS-3可以抑制丝裂原活化蛋白激酶(mitogen-activated protein kinases, MAPK)的激活、NF-κB的入核以及随后诱导的促炎基因表达, 并且在肠道炎症中具有保护作用, IL-1RN则阻断由IL-1β与其受体结合而启动的促炎信号, 通过这些作用减少了TNF-α、IL-1β、IL-6等促炎因子的表达和分泌量, 从而达到抗炎作用。

IL-10在肠道中抑制促炎因子的产生, 在培养的人结肠组织中添加IL-10可抑制TNF-α和IL-1β的产生, 而人结肠黏膜外植体中IL-10的缺失导致IFN-γ、TNF-α和IL-17的上调[27,58]。这些结果表明, 在没有任何炎症刺激的情况下, IL-10可以抑制促炎因子的产生。在体内和体外的研究发现, IECs中IL-10R的缺失增加了肠上皮通透性, 并且小鼠结肠组织中IL-1β和IL-6等炎症因子表达水平升高[20]。此外, IECs是IL-10抗炎作用的效应细胞, 向培养的Caco-2细胞或新鲜分离的人IECs中添加IL-10(100 U/mL), 可以抑制单核细胞趋化蛋白-1(monocyte chemoattractant protein-1, MCP-1)的产生[59]。MCP-1在IBD患者中上调, 并且在肠道炎症期间黏膜免疫反应的启动和延

表2 *IL-10*$^{-/-}$小鼠与WT小鼠肠道菌群差异

Table 2 Difference of gut microbiota between *IL-10*$^{-/-}$ and WT mice

动物模型 Animal model	分析结果 Analysis result	参考文献 References
GF *IL-10*$^{-/-}$ and control WT mice were transferred to SPF conditions for twenty weeks	The levels of *Bacteroidetes*, *Proteobacteria* were increased in *IL-10*$^{-/-}$ mice	[50]
GF *IL-10*$^{-/-}$ and WT mice were colonized by SPF mic-robiota for two weeks	Compared with WT mice, the diversityand richness of *IL-10*$^{-/-}$ mice decreased over time, but the abundance of *Proteobacteria* and *E. coli* increased	[49]
GF *IL-10*$^{-/-}$ and WT colonized with SPF microbiota	*E. coli* abundance decreased over time in *IL-10*$^{-/-}$ and WT, but remaining higher in *IL-10*$^{-/-}$; in WT and IL-10 mice, the community structure changed over time from an early community dominated by *Firmicutes* with more *Proteobacteria* to one dominated by *Firmicutes*and *Bacteroides* with fewer *Proteobacteria*	[56]
IL-10$^{-/-}$ and WT mice	Bacteria in *IL-10*$^{-/-}$ mice can penetrate the mucous layer and come into direct-contact with the epithelium	[44]
IL-10$^{-/-}$ and WT mice were reared in SPF	The abundance of *E. coli* in mice reared in SPF was significantly higher	[49]
SPF *IL-10*$^{-/-}$ and WT mice	There were more immature particles in *IL-10*$^{-/-}$ mouse Paneth cells, more immature Paneth cells and less cryptidin-4 secretion	[23]
Nine weeks old *IL-10*$^{-/-}$ mice were treated with antibiotics	Without microbiota, Paneth cells were more mature, but with more amorphous granule	
IL-10$^{-/-}$ and WT mice were reared in SPF	The proportion of *Proteobacteria* and *Bacteroidetes* in *IL-10*$^{-/-}$ mice was relatively high, and the abundance of *Lactococcus* and *Roseburia* decreased	[53]

GF: 无菌; SPF: 无特定病原体。

GF: germfree; SPF: specific pathogen free.

续中发挥作用。还有研究发现, IL-10可以抑制IFN-γ诱导的IECs主要组织相容性复合体II(major histocompatibility complex II, MHC II)类分子的表达[29]。IL-10还影响IECs中的血清素转运体(serotonin transporter, SERT)的表达, SERT下调与溃疡性结肠炎(ulcerative colitis, UC)、IBS等各种功能性肠道疾病有关, 研究发现高浓度的IL-10(25 ng/mL)可诱导Caco-2细胞中SERT的上调[60]。综上所述, IL-10通过抑制肠道中促炎因子以及相关炎症介质的产生来发挥其抗炎作用, 从而来维持肠道的稳态。

6 IL-10与肠道疾病

6.1 IBD

IBD是一种慢性胃肠道炎症性疾病, 表现为克罗恩病(Crohn's disease, CD)和UC。IL-10是维持肠道内稳态和功能的关键介质, 这在IL-10缺陷小鼠会发展为自发性结肠炎中得到证实, 这些小鼠通常伴有溃疡、上皮增生、隐窝脓肿和黏蛋白耗竭等表现, 这与人类疾病的组织学特征相似[7]。IL-10与IBD高度相关, IL-10和IL-10R的突变与IBD的早期发病密切相关[61-62]。全基因组关联研究进一步揭示了IL-10轴在IBD发病机制中的重要作用[63]。此外, IECs中IL-10或IL-10R的缺失导致小鼠对结肠炎的易感性增加[20-21]。外源性提供的重组IL-10可以延缓这些IL-10缺陷小鼠结肠炎的发展。IL-10的保护功能已经在许多结肠炎模型(包括DSS诱导的结肠炎模型和CD45RB^{high} T细胞转移结肠炎模型)中得到证实[9]。基于IL-10的抗炎作用以及在小鼠结肠炎中的保护作用, IL-10有望治疗IBD。但是, 使用重组IL-10对IBD患者进行全身治疗的临床试验结果令人失望[64]。这可能是由于IL-10的血清半衰期短, 全身给药可能不足以将IL-10传递到黏膜炎症部位导致的。ZURITA等[65]通过构建乳酸乳球菌菌株携带治疗性IL-10质粒, 将其运送到肠道, 该策略不仅确保更有效和更直接地递送治疗质粒, 而且能够在损伤部位产生IL-10。该方法在DSS诱导炎症小鼠模型中成功展示了其抗炎和预防肠道炎症的作用, 在IBD治疗中具有创新和前景。一项临床前研究发现设计可以分泌IL-10的益生菌可以从宏观上减少肠道损伤, 并且这种转基因益生菌在CD患者临床研究中取得了良好的效果, 说明通过设计益生菌分泌IL-10来治疗IBD是可行的策略[66]。由此可见, IL-10虽然是抗炎因子, 但是能否成为治疗IBD的有效治疗靶点还需要进一步的研究以及临床试验。

6.2 CRC

慢性炎症通过诱导多种促炎因子如TNF-α和IL-6的产生促进癌变。在肠道炎症的情况下, 黏膜免疫反应导致CRC的发生, 如IBD患者结肠炎相关结肠癌的发病率增加。结直肠组织中缺乏IL-10R可能会导致严重的自发性结肠炎, 从而增加CRC发生的风险[67]。*IL-10*$^{-/-}$小鼠会出现慢性结肠炎和结肠腺癌, BERG等[68]研究发现30%~60%的*IL-10*$^{-/-}$小鼠在3~6个月内会出现CRC。在*IL-10*$^{-/-}$小鼠中, 致病性微生物丰度增加破坏了肠道稳态, 促进了CRC的发生。利用表达IL-10的转基因乳酸菌处理CRC小鼠模型, 结果发现IL-10抑制了肿瘤的生长[69], 并且健康小鼠长时间服用这些转基因乳酸菌不会产生副作用, 因此给IL-10治疗CRC提供了新的方法。聚乙二醇化的IL-10已用于多种实体肿瘤(包括肾细胞癌、非小细胞肺癌、结直肠癌等)的临床试验, 并且在肾细胞癌的治疗中取得了良好的效果[70]。此外, 结直肠癌术后7天患者IL-10表达水平较术前降低, 术后复发结直肠癌患者IL-10表达水平明显升高, 提示IL-10可能作为结直肠癌预后的生物标志物[71]。因此, 以IL-10为靶点治疗CRC还需要进一步研究和临床试验。

6.3 坏死性小肠结肠炎

坏死性小肠结肠炎是早产儿常见的肠道疾病, 其发病率、死亡率和晚期致残率较高。新生儿的肠道暴露在高浓度的细胞因子中, 可能是导致新生儿坏死性小肠结肠炎(neonatal necrotizing enterocolitis, NEC)发生的原因[72]。NEC对肠道微生物表现出过度的炎症反应, 并可能导致败血症的出现[73]。IL-10与小肠结肠炎相关, IL-10和IL-10R缺陷导致人类严重的早期发病以及新生儿严重的小肠结肠炎[6-7]。此外, IL-10还可能通过减轻肠道炎症程度, 延缓NEC进展, 避免手术治疗, 从而对NEC的病程起到控制作用[72]。因此, IL-10有望作为NEC发展的生物标志物在NEC的治疗中发挥作用。

7 总结与展望

自IL-10被发现以来的30年里, 由于这种细胞因子对先天和适应性免疫系统的有效调节作用, 肠道免疫学取得了巨大的进步。在肠道中, IL-10通过维持IECs的稳态、肠屏障完整性、肠道菌群的平衡状态以及在肠道中发挥抗炎作用来维持肠道稳态(图2)。因此, IL-10可能成为治疗肠道疾病的新靶点, 一些临床试验正在探索IL-10在自身免疫疾病和肠道疾病中的治疗潜力。分泌IL-10的转基因益生菌在CD患者临床研究中观察到患者疾病活动性降低, 并且这种转基因益生菌在患者体内是安全的, 这为IL-10治疗IBD提供了新的方法。在肿瘤治疗中, 聚乙二醇化的IL-10在肿瘤早期临床试验中取得了有希望的结果, 但是需要进一步临床试验探索其在CRC治疗中的潜力。此外, IL-10还能够调节细胞因子的活性和功能, 减轻免疫反应, 未来IL-10也可能会尝试用于移植排斥反应的治疗。总之, IL-10在维持肠道稳态中发挥重要作用, 但以IL-10为靶点来治疗肠道疾病还需要进一步研究和发掘。

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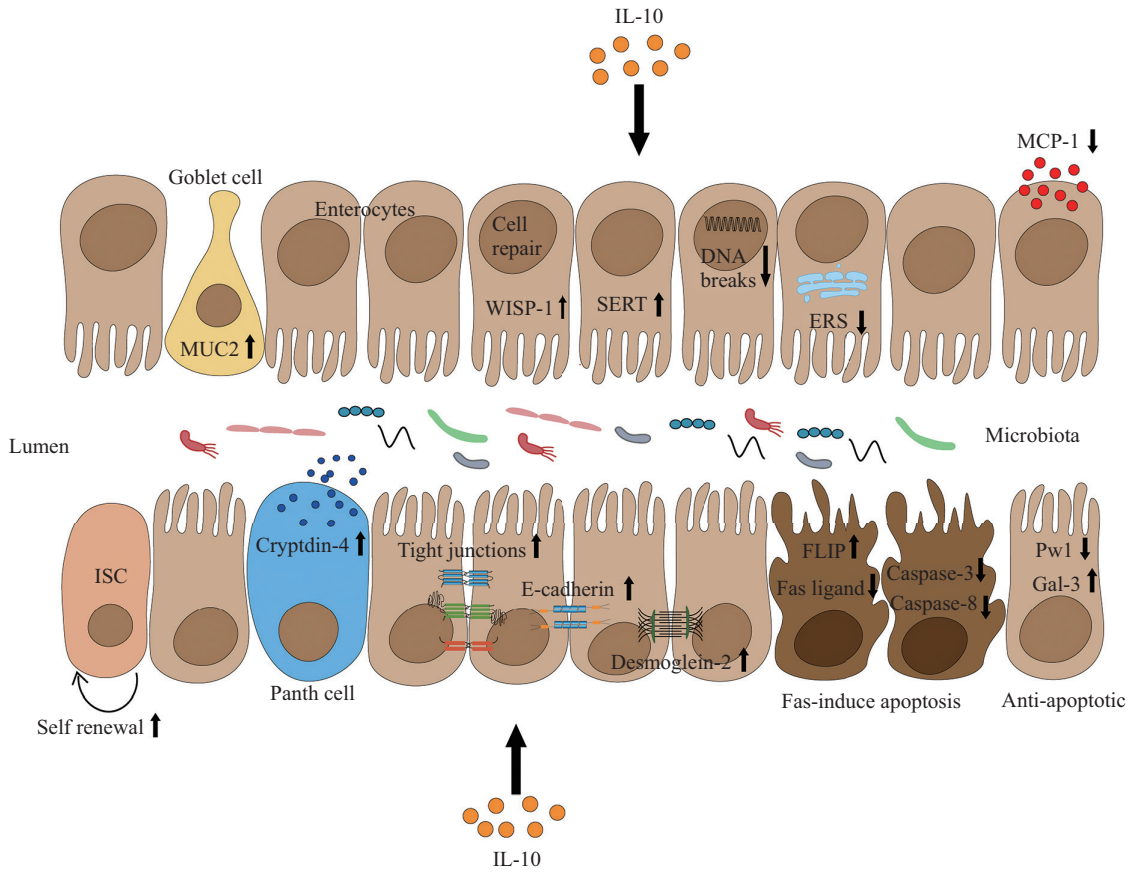

图2 IL-10在维持肠道稳态中的作用示意图

Fig.2 Schematic diagram of the role of IL-10 in maintaining intestinal homeostasis

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