

Toll 样受体 4 与炎性肠病和结肠癌

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摘要:Toll 样受体(TLR)是天然免疫中重要的模式识别受体,主要在免疫细胞上表达,能特异性地识别病原相关分子模式,并在启动和调节天然免疫及获得性免疫中起到重要作用。研究表明 TLR4 在炎性肠病和结肠癌中表达增高。文章主要综述 TLR4 在结肠癌及炎性肠病癌变过程中的作用。

关键词:Toll 样受体 4;炎性肠病;结肠肿瘤

中图分类号:R735.3⁺5 **文献标识码:**A **文章编号:**1671-170X(2013)09-0735-04
doi:10.11735/j.issn.1671-170X.2013.09.B016

Toll-like Receptor 4 in Inflammatory Bowel Disease and Colon Cancer

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Abstract:Toll-like receptors (TLRs) are the important pattern recognition receptors (PRR) in innate immunity, located on the cell surface, and can identify the pathogen associated molecular patterns (PAMPs) specificity. TLRs play an important role in the initiation and regulation of innate immunity and acquired immunity. Studies suggest that TLR4 expression increase in inflammatory bowel disease (IBD) and colorectal cancer. The role of TLR4 in colon cancer and carcinogenesis of IBD are reviewed.

Subject words:Toll-like receptor 4; inflammatory bowel disease; colorectal neoplasms

慢性炎症是某些癌症发生的一个主要的危险因素^[1],如胃幽门螺旋杆菌的感染与胃癌、人乳头状瘤病毒感染与宫颈癌、华支睾吸虫感染与胆管癌、溃疡性结肠炎与结肠癌等等。研究表明,炎症相关肿瘤大概占有肿瘤发生的 15%^[2]。正常人的胃肠道内寄生着众多的微生物,称之为肠道菌群,正常分布于肠道内的细菌对维持肠上皮内环境的稳定至关重要。当肠上皮内环境的稳定性被打破时,细菌所产生的代谢物以及菌体本身暴露于肠细胞,可能会引起机体的反应^[3]。Toll 样受体(Toll-like receptors, TLRs)家族中的 TLR4,能识别革兰氏阴性菌的内毒素(lipopolysaccharide, LPS)。研究表明 TLR4 在炎性肠病(inflammatory bowel disease, IBD)和结肠癌中表达

增高^[4-8]。本文将阐述 TLR4 与 IBD 和结肠癌的关系。

1 TLR4 分子结构与信号传导通路

1997 年,第 1 个 TLR 被发现^[9],并确定是 LPS 的受体,随后改名为 TLR4^[10,11]。TLR4 是 I 型跨膜蛋白,主要表达在内皮细胞、巨噬细胞、中性粒细胞以及树突状细胞,在正常的肠上皮细胞上 TLR4s 极少表达^[12-14]。TLR4 介导的信号转导途径,分为 MyD88 依赖性(髓样分化因子 88, MyD88)和 MyD88 非依赖性两条途径。

1.1 MyD88 依赖性途径

MyD88 依赖性途径是细胞通过表面 CD14 与 LPS-LBP 复合物(LPS-LPS 结合蛋白)结合后,可使胞外 TLR4 活化,并使 TLR4 形成同源二聚体,并在髓样分化蛋白-2(MD-2)协同下,与 MyD88 分子结合。

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收稿日期:2013-04-07;**修回日期:**2013-06-09

MyD88 分子为接头分子,有C端的TIR结构域和N端的死亡结构域DD。活化的TLR4通过胞浆区TIR(Toll interleukin-1 region, Toll/IL-1受体同源区)与胞浆内接头蛋白MyD88的C端TIR结合,并通过MyD88的N端死亡结构域募集结合IRAK(IL-1受体相关的激酶),活化IRAK后与TRAF6(TNF受体相关因子6)结合相互作用后,能诱导两个不同的途径:一种是TLR-MyD88/IRAK-丝裂原活化蛋白激酶(MAPK)途径;另一种是TLR-MyD88/IRAK-NF- κ B诱导激酶/NF- κ B途径。启动相关靶基因转录,表达炎症细胞因子(如TNF- α 、IL-6、IL-12等^[15]),来介导炎症反应。

1.2 MyD88 非依赖性途径

MyD88非依赖性途径是由TRIF(TIR-domain containing adaptor inducing IFN- β)和TRAM(TRIF-related adaptor molecule)参与NF- κ B的迟发激活通路和IRF-3(干扰素调节因子3)通路,它们使转录因子和IRF-3活化,同样也能促进IFN- β 的产生和树突状细胞的成熟、活化。TRIF能够通过MyD88相似的作用,从而引起NF- κ B晚期低水平的活化,但其主要的生物活性依赖于转录因子IRF-3。

2 TLR4 与正常的肠上皮

肠上皮虽然长期暴露于高浓度的细菌及细菌产物,但细菌和黏膜之间存在保护屏障,如食入细菌很难在胃酸环境下生存。而肠道黏膜的免疫系统防御功能可使有害微生物及其产物不能与肠上皮直接接触从而诱导肠上皮细胞上的TLR4信号^[3,13]。正常人的肠上皮细胞对LPS的反应性较低,主要是由于TLR4基因的低转录^[16],TLR4蛋白表达较少。同样,TLR4的协同蛋白MD-2的表达也是极少的,只有TLR4表达,却没有MD-2的协同,则TLR4信号通路是不会被LPS激活^[12-14]。

因此降低TLRs和其协同蛋白如MD-2在肠上皮的表达,可以作为控制肠上皮低反应性的一种方法^[17]。当炎症发生的时候,TLR4在修复损伤肠上皮过程中起到一定促进作用^[18],一些研究表明,当TLR4和MYD88缺失时,小鼠肠上皮的增生减少^[18,19],并且在无菌条件生长下的小鼠肠上皮增生要低于正常小鼠^[20]。这也间接提示我们,TLR4有促进肠上皮增生

的作用。

3 TLR4 与炎症肠病

动物研究表明寄生于肠道的菌群失调对炎症肠病的形成有一定的促进作用^[21],当肠上皮损伤时,就增加了细菌菌体和其代谢产物与肠固有层炎细胞接触的机会。在急性炎症时,TLR4阳性的巨噬细胞会迁移到黏膜,这些炎症细胞同时高表达TLR4的复合受体CD14,提高IBD的肠黏膜对LPS的反应性^[22],同时在炎症肠病患者身上可观察到TLRs(包括TLR4)的表达增高^[4,5]。在白细胞中,TLR4信号与NF- κ B的激活和促炎因子的释放有关系^[11],另外肠上皮在TLR4激活后,释放促炎因子^[23],有研究推测,肠上皮的TLR信号可能与白细胞的TLR信号对炎症肠病的发生有一个协同的作用^[24],从而加剧炎症反应程度。IBD患者的肠上皮损伤较严重^[25],可能是炎症肠病患者肠上皮对细菌的免疫反应过于强烈,致使肠上皮出现损伤、溃疡,甚至患者发生腹泻。

Frolova等^[26]用免疫组化的方法检测IBD患者的肠道活检标本中TLR4、CD14的表达情况。TLR4、CD14在活动期或静止期的溃疡性结肠炎(ulcerative colitis, UC)和克罗恩病(Crohn's disease, CD)的回肠末端、直肠的表达明显高于健康人。他们认为TLR4、CD14在肠黏膜的不同部位的表达失常也许就是IBD发病机制的关键所在^[26]。也有研究表明,在IBD的活动期,TLR4在肠上皮的表达是升高的。

4 TLR4 与结肠癌

结肠癌是IBD患者死亡率增加的主要原因^[27]。炎症的严重性与IBD患者发生结直肠癌变的危险程度有关^[28,29]。UC患者发生结直肠癌的概率高出正常人的5~8倍^[8]。TLRs不仅在免疫细胞表达^[30,31],其他肿瘤细胞上也有表达^[15]。UC并发结肠癌的患者TLR4表达增高,其周围正常组织TLR4无表达或低表达^[32]。

TLR4的mRNA在急性、慢性IBD中有所增高,但在AOM-DSS(dextran sodium sulfate-azoxymethane)诱导的肿瘤模型中,TLR4的表达是最高的,而且TLR4-/-小鼠有明显的抵抗肿瘤的形成^[7]。这种现象的原因可能是通过TLR4-COX-2-PGE2信号途径实

现的。环氧化酶 2(COX-2)的异常高表达,可能与结直肠癌的发展有关^[33]。在肠上皮细胞损伤时,TLR4 是 COX2 的表达必要条件^[34]。研究证实,TLR4-/-小鼠的结肠黏膜的表皮生长因子(EGFR)磷酸化水平明显低于野生型小鼠^[7]。前列腺素 2(PGE2)通过 EGFR 信号来刺激结肠肿瘤的发生^[35,36]。此外,口服 PGE2 能促进 TLR4-/-小鼠的结肠癌的发展^[7]。这意味着在结直肠癌发展过程中,PGE2 是 TLR4 下游的分子,也是一个潜在的能更有效预防结直肠癌的对象^[37]。当小鼠在 IBD 恢复时期给予外源性 PEG2,会增加小鼠炎症相关结肠癌的发生。TLR4 缺失时,黏膜将缺少 PGE2,COX-2 和双向调节蛋白(AR)产物表达,使 TLR4 缺失小鼠受到保护而不发展成为结肠肿瘤^[37],也可以间接说明 TLR4 可能参与了结肠炎相关肿瘤的形成。当用 TLR4/MD-2 拮抗剂抗体来抑制 AOM-DSS 诱导的野生型小鼠的 TLR4 信号通路,这种治疗很大程度地减少了结肠肿瘤发生的概率。用 AOM-DSS 处理野生型小鼠后,相对于周围组织,肿瘤成分的上皮上 TLR4 的免疫组化有较强的着色,这也意味着黏膜损伤时,上皮 TLR4 信号可能参与结肠的癌变过程^[18,38]。

5 TLR4 与结直肠癌的预后与治疗

结直肠癌是常见恶性肿瘤之一,在癌症引起的死亡中目前居第 4 位,而死亡的主要原因是由于肿瘤的转移^[39]。一些学者证实,TLR4 表达降低与结直肠癌转移潜能增加有关,当 TLR4 表达缺失时就会出现转移增加的现象^[40,41]。但在 Wang 等^[42]人认为,TLR4 在结肠癌中的高表达与肝转移有较大的关系,同时高表达者有较短的生存期。Hagstrom^[43]在他的研究中发现,在滤泡癌中 TLR4 表达的过高或过低与肿瘤的转移和侵袭性有较高的相关性。这就出现了一个非常有趣的现象。

有学者认为摄入高脂肪食物,尤其是高饱和脂肪酸和高碳水化合物饮食会影响肠内微生物群落以至于引起炎症、氧化应激和内源性的 TLRs 的表达^[44-46]。Wei 等认为柚苷可以抑制 TLR4 的表达,从而抑制结肠炎的发生^[47]。Sun 等^[48]认为雷帕霉素能抑制 TLR4 及 IL-6、PGE2 的表达,从而降低结肠癌的侵袭性。Liu 等^[49]证实用苹果果胶中提取的半乳糖醛

酸能抑制 DSS 诱导小鼠的结肠癌模型的形成。

肿瘤现在已经成为危害人类健康的一大危险因素,越来越多的学者认为结肠炎与结肠癌的发生发展有关。TLRs 信号使免疫细胞激活、成熟,有效的免疫反应抵抗病原微生物和恶性肿瘤是必要的。TLR4 配体有望改善结肠癌的治疗和预后,有待进一步研究。

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