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Toll 样受体在慢性疾病中的研究进展

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[摘要] Toll 样受体(Toll-like receptor, TLRs)是免疫系统参与活化炎症反应的初始应答者之一,TLRs 主要参与的是非特异性免疫和炎症反应。有研究表明,TLRs 是多种慢性疾病(癌症、非酒精性脂肪肝、慢性阻塞性肺疾病、心血管疾病以及神经退行性疾病等)相关发展的激活因子,并在其疾病的发展中起着十分重要的作用。本文主要对 TLRs 在上述这些主要的慢性疾病中的作用进行综述。

[关键词] Toll 样受体;炎症;慢性疾病;天然产物
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Research progress of Toll-like receptors in chronic diseases

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[**Abstract**] Toll-like receptors (TLRs) are one of the initial responders of immune system involved in the activation of inflammatory responses. TLRs are mainly involved in non-specific immune and inflammatory responses. Studies have shown that TLRs act as activating factors in the development of a variety of chronic diseases (cancer, nonalcoholic fatty liver disease, chronic obstructive pulmonary disease, cardiovascular disease and neurodegenerative diseases), and play a very important role in the development of the diseases. This article reviews the role of TLRs in these major chronic diseases.

[**Key words**] Toll-like receptor; inflammation; chronic disease; natural products

1　Toll 样受体(Toll-like receptors,TLRs)简介

TLRs 是固有免疫中关键的模式识别受体(pattern recognition receptor,PRRs),其不仅可以识别病原体相关模式分子(pathogen associated molecular pattern,PAMPs),也可以识别内源性损伤相关模式分子(damage associated molecular pattern, DAMPs)[1]。目前已有 11 种不同类型的 TLRs 在不同类型的细胞中被识别,且每种类型都有不同的配体,如脂类、脂蛋白、核酸和蛋白质。TLRs 是参与非特异性免疫的一类重要蛋白质分子,也是连接非特异性免疫和特异性免疫的桥梁。所有 TLRs 同源分子都是Ⅰ型跨膜蛋白,主要分为胞膜外区、胞浆区和跨膜区 3 部分,其中胞浆区是 TLRs 的核心区域,可引起下游信号级联反应,进而激发相关信号通路的产生[2]。TLRs 介导的疾病中多伴随着炎症反应的发生。

2　Toll 受体与慢性疾病的关系

TLRs 的主要功能是通过识别各种微生物的 PAMPs 来对其进行非特异性免疫防御[3]。TLRs 被激活后,识别 PAMPs 并快速激活包括接头蛋白、信号复合体和转录因子复合体负责的细胞内信号级联反应,最终导致机体产生各种炎性细胞因子,从而加速病原体的清除。有研究发现,体内许多分子如蛋白 B1、热休克蛋白、IL-1α 都可以作为内源性 PAMPs,由炎症反应或受损细胞产生并进一步介导免疫反应。当 TLRs 被长时间激活时,特别是在没

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有外源性 PAMPs 的情况下,机体会错误识别内源性 PAMPs,并对机体细胞产生作用,其中 TLRs 最常见的致病作用为慢性炎症损伤[4],导致各种慢性炎症疾病的发生,如癌症、心血管疾病和神经系统疾病等。下面我们将进一步讨论 TLRs 在不同慢性疾病中的作用。

2.1 TLRs 与癌症 TLRs 除了在哺乳动物宿主防御微生物感染方面发挥作用外,还参与组织稳态的各个方面,包括组织修复和再生[5-6]。肿瘤的发生与微生物感染、损伤、炎症和组织修复密切相关,许多信号通路及其相互作用都参与了这些过程,其中 TLRs 通路是最主要的,表现在:① TLRs 与炎症级联反应密切有关,而感染及损伤所引起的炎症反应还可进一步促进肿瘤的形成。② TLRs 参与了多种人类肿瘤的病理生理过程[7],它从细胞增殖、细胞分裂、耐药性、侵袭和转移开始,就参与肿瘤的不同发展过程[7-8]。这些因素都为肿瘤细胞提供了生长优势。

在多种肿瘤细胞及实体瘤中均可检测到 TLRs 的表达。Tongtawee 等[9]和 Chen 等[10]研究表明 TLR-2/4 的基因多态性尤其是 TLR-4 Asp299Gly 和 Thr399Ile 多态性与胃癌的发生紧密相关。此外,有 Meta 分析显示,TLR-4 多态性、Asp299Gly 和 Thr399Ile 对结肠癌也具有较高的发病风险[11]。同样,TLR-9 多态性与宫颈癌发病率也密切相关[12]。在前列腺癌细胞中,除了 TLR-3, TLR-4 和环氧化酶系统被证明可以增加前列腺癌细胞的增殖、迁移和侵袭性外[13],雄激素依赖的长非编码 RNA-PART-1 诱导 TLR-3 的表达也可促进前列腺癌细胞的增殖[14]。脂多糖(lipopolysaccharide,LPS)介导的 TLR-4 上调也已被证明可以增加肝癌[15]和食管鳞癌细胞[16]的存活和增殖。Meseure 等[17]发现 TLR-9 高表达激活下游信号通路,促进上皮间充质细胞转化进程,参与乳腺肿瘤细胞的侵袭与转移。TLR-9 的表达也与口腔鳞状细胞癌的增殖能力密切相关[18]。在咽喉癌中,刺激 TLR-3 上调可增加 MAP 激酶途径介导的肿瘤细胞[19]。TLR-5 基因多态性与乳腺癌发病率增加有关[20]。胰腺癌细胞增殖与 TLR-7 依赖的 MAPK-ERK1/2 信号通路相关[21]。总之,TLRs 与多种恶性肿瘤的发生、发展密切相关,且在不同的肿瘤细胞中有不同的表达途径。有关 TLRs 在致癌过程中所起作用的详情见表 1[22]。合成的 TLRs 抑制剂也可用治疗疾病,如 IMO-8400。IMO-8400 是 TLR-7,8 和 9 的抑制剂,可通过抑制 *MYD88 L265P* 突变驱动的信号传导和细胞存活治疗 *MYD88 L265P* 突变的 B 细胞淋巴瘤[23]。

表 1 不同的 TLRs 与各种癌症的关系

受体	癌症	作用
TLR-2	结肠癌	PI3K/Akt/NF-kB 途径
	胃癌	TLR-2/超氧化物歧化酶轴及 TLR-2 的多态性
	口腔癌	TLR-2 基因多态性
TLR-3	咽喉癌	MAP 激酶途径
	结肠癌	TLR-3 过表达
TLR-4	胃癌	TLR-4 过表达
	甲状腺癌	TLR-4 过表达
	前列腺癌	TLR-4 与前列腺癌的发生、发展密切相关
	乳腺癌	TLR-4 促进乳腺癌的发生、发展
		RNAi 沉默 TLR-4 可抑制乳腺癌细胞增殖,诱导细胞凋亡
	宫颈癌	TLR-4 多态性增加
	胰腺癌	PI3K/Akt 信号通路
	结肠癌	TLR-4 的过表达和多态性
TLR-5	乳腺癌	TLR-5 基因多态性
TLR-7	胰腺癌	MAPK-ERK1/2 信号通路
TLR-9	乳腺癌、结肠癌	TLR-9 过表达

2.2 TLRs 与非酒精性脂肪肝 非酒精性脂肪肝(nonalcoholic fatty liver disease, NAFLD)是影响肝组织常见的代谢性疾病,它经过一系列单纯性肝脂肪变性,逐渐发展为脂肪性肝炎、纤维化和肝硬化[24]。肝脂肪变性是肝细胞内三酰甘油/脂质积聚的一种状态;伴随着炎症因子的分泌而形成脂肪性肝炎;通过肝星状细胞活化和慢性炎症进一步发展为纤维化和肝硬化[24-25]。已有很多证据表明,TLRs 中 TLR-4[26]和 TLR-7[27]在 NAFLD 的发生和发展过程中起着重要作用。TLR-4 与肝脏脂肪生成和 β-氧化有关,TLR-4 下调可引起脂肪生成减少和 β-氧化增加,从而增加脂质清除率和降低脂毒性[28]。诱导 TLR-7 可增加肝癌细胞的自噬,从而对 NAFLD 具有保护作用[29]。此外,TLR-5 也可以通过调节肠道微生物群抵抗高脂饮食诱导的肝脂肪变性[30]。

2.3 TLRs 与动脉粥样硬化(atherosclerosis, AS) AS 是一个复杂的发病过程,伴随了多种病理现象的发展:① 脂质化巨噬细胞的产生。AS 导致内皮发

生损伤,进而使内膜或纤维层中的脂质积聚或渗出,为了处理过量的脂质,机体通过损伤激活的内皮细胞将巨噬细胞募集到这些部位,如果脂质负荷过高,巨噬细胞会积聚并转化为含脂质的泡沫细胞[31]。② 炎症反应过程中病理现象。AS 导致内膜过度纤维化、脂肪斑块形成、平滑肌细胞增殖和单核细胞、T 细胞及血小板等细胞迁移,这些细胞都是在炎症反应中形成的。所以,在 AS 的发生和发展过程中,慢性炎症分子及其相关信号分子传导起着至关重要的作用[32]。在这些促炎症信号中,TLRs 发挥了主要的调节作用[33]:① TLRs 可促进动脉粥样硬化的形成。TLR-4 是血管内皮组织中的主要受体,在血管内皮组织中有促进动脉粥样硬化进展的作用[34];TLR-5 也显示出通过募集活化巨噬细胞而具有促动脉粥样硬化作用[35];TLR-7 增加了由自噬和炎性细胞因子分泌介导的巨噬细胞中动脉粥样硬化斑块的累积[36];TLR-2 是血管内皮组织中另一种重要的受体,其活性低下可降低动脉粥样硬化和血脂异常的发生率,显示 TLR-2 与动脉粥样硬化的发生呈正相关[37]。② TLRs 对动脉粥样硬化有抑制作用。TLR-7 通过抑制巨噬细胞的炎症激活来减轻动脉粥样硬化[38];Koulis 等[38]研究表明,当 TLR-9 完全缺乏时会加重动脉粥样硬化,在 TLR-9 敲除鼠中上调 TLR-9 可改善动脉粥样硬化病变现象。

2.4 TLRs 与慢性阻塞性肺疾病(chronic obstructive pulmonary disease, COPD) COPD 是一种以持续气流受限为主要特征的可以预防和治疗的慢性呼吸系统疾病。COPD 是多种不同疾病状态的集合,而非特指单一的疾病,通常是指慢性支气管炎和肺气肿。其中肺血管的慢性炎症及其所引起的肺血管重塑被认为是 COPD 的基本病理特征之一,但其机制未明。近年来有研究表明 PRRs 在 COPD 慢性炎症的启动和维持过程中扮演着重要角色,其中,尤以 TLRs 与 COPD 发病关系最为密切[40]。吸烟、有害气体、微生物及 DAMPs 等与 TLRs 相互作用并完成跨膜信号转导,然后再通过依赖于 MYD98 的 NF-κB 通路调控炎症基因的转录、翻译和表达,产生并释放 IL-6,IL-8,COX-2,PGE2 等炎性因子。产生的炎性产物不仅可以直接损伤细胞、破坏细胞外基质,还可作为内源性配体与中性粒细胞、NK 细胞等表面的相应受体结合[40,42],进一步合成并释放大量炎症介质然后募集炎症细胞,形成一个正反馈循环,导致肺部炎症反应级联被放大并持续存在。TLR-2,TLR-4,TLR-9 都参与了 COPD 的发病过程,其中 TLR-4 被认为是维持 COPD 炎症反应的主要 TLRs[43]。研究发现,肺部炎症损伤的大鼠中 TLR-4 表达明显增加[44];在 COPD 患者的肺血管中 TLR-4 表达水平也有所增加[43]。因此,TLR-4 在肺部炎性反应及 COPD 的发展过程中起着重要的作用。

2.5 TLRs 与神经退行性疾病 炎症反应是阿尔茨海默病(Alzheimer's disease, AD)[45]、帕金森病(Parkinson's disease, PD)[46]等多种神经退行性疾病发生和发展的主要因素。TLRs 介导的小胶质细胞活化在神经退行性疾病中也扮演着重要的角色[47]。对于 AD,TLR-4 通过诱发神经炎症,从而增加 β-淀粉样蛋白(amyloid β-protein, Aβ)的积累,进而促进 AD 的发展[48]。随着进一步的研究表明,急性激活 TLR-4 会减轻 Aβ 的积累,而慢性激活可诱导 Aβ 沉积[50]。TLR-2 的激活也与 AD 有关,抑制 TLR-2 的表达可降低 Aβ 的积累和神经胶质细胞的激活[51]。TLR-5 过表达可抑制 Aβ 的积累从而具有治疗 AD 的作用[52]。TLR-9 激活可降低 Aβ 的积累[53]。PD 是另一种神经退行性疾病,研究表明,*TLR-9 rs352140* 基因多态性可增加 PD 的风险,导致多巴神经元变性[54]。Dzamko 等[55]研究发现,TLR-2 在 PD 发病脑区的表达升高与病理性 α-突触核蛋白水平相关,TLR-2 上调可累积 α-突触核蛋白而导致 PD 发展。

3 天然产物与 TLRs 相关的慢性疾病研究

天然产物因其化学多样性而成为药物的重要来源。早期的研究表明,植物提取物具有调节 TLRs 的潜力,在 Chahal 等[56]的研究结果表明,多种植物提取物及其生物活性成分在调节 TLRs 方面都具有重要作用。早期有报道称姜黄是抗癌和抗氧化化合物的重要来源[57],从姜黄中提取的姜黄素和姜黄水提取物 *C. Longa* 也均具有有效的抗炎作用进而起到抗癌作用[58]。Rana 等[59]在其研究中又进一步表明,一种新型化学修饰的富含非羰基化合物的 *C. Longa* 提取物 CMCE 也可以通过抑制 TLR-4 信号并下调 IKK-MAPK 在白血病细胞中的信号转导来发挥抗癌作用。与癌症相似,TLRs 也参与 NAFLD 的发展,研究表明,姜黄素可通过有效下调 TLR-2/4/9 信号通路,进而抑制四氯化碳诱导的肝纤维化[60-61]。茶多酚是另一种兼具抗氧化活性的抗肿瘤物质,Chen 等[62]的研究表明,茶多酚可以通过下调 TLR-4 表达从而抑制黑色素瘤细胞的增殖、侵袭和迁移。

绿茶提取物也显示可通过下调 NF-kB 中 TLR-4 介导的促炎因子的表达来降低小鼠 NAFLD 的发病率[63]。天然产物已被证明是重要的 TLRs 抑制剂，且可不同程度干扰疾病的发展。上述研究表明，天然产物与 TLRs 抑制剂的功效类似，具有良好的临床研究前景，是相关领域的研究热点，可进行深入的探讨与研究。

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