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不同环境介质中微生物基本功能组分致炎效应研究进展

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摘要：微生物增殖及死亡过程释放病原相关分子模式(PAMPs),机体通过胃肠、呼吸和皮肤等途径长期暴露于 PAMPs 具有潜在致炎效应风险.空气、水和土壤等环境存在大量微生物,为 PAMPs 释放提供极为有利的天然条件.本研究归纳了 PAMPs 中重要物质内毒素、肽聚糖、磷壁酸、脂蛋白和 CpG DNA 特性;阐述不同环境介质如空气、水和土壤环境中 PAMPs 赋存特征与健康风险;介绍机体对 PAMPs 识别机制及其疾病诱发风险,并揭示 PAMPs 与环境污染物联合暴露后致炎能力呈现的协同增强效应;根据环境领域 PAMPs 研究现状,重点探讨现存不足之处,提出亟需加快 PAMPs 标准检测体系、暴露风险阈值和流行病学等方面研究,推动环境领域 PAMPs 研究进展,为全面理解和评估 PAMPs 健康风险提供参考依据.

关键词：微生物；病原相关分子模式；致炎效应物质；环境介质；健康风险
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Research progress on the inflammatory effects of the basic functional components of microorganisms in different environmental media. ZHANG Can[1], GUI Ping[2], ZHAO Qian-xiu[3], ZHANG Chuan-fu[3], TAN Chao-hong[4], CAO Xiao-mei[1], LI Ying[1], ZHANG Ming-lu[5*], BAI Miao[3,5*] (1.Chinese Academy of Quality and Inspection & Testing, Beijing 100176, China；2.China Academy of Urban Planning and Design, Beijing 100037, China；3.Center for Disease Control and Prevention of Chinese PLA, Beijing 100071, China；4.School of Environmental and Energy Engineering, Beijing University of Architecture and Technology, Beijing 102616, China；5.School of Light Industry Science and Engineering, Beijing Technology and Business University, Beijing 100048, China). *China Environmental Science*, 2026,46(1)：515~524

Abstract：The growth and death processes of microorganisms result in the release of pathogen-associated molecular patterns (PAMPs). Chronic exposure to PAMPs through the gastrointestinal, respiratory, and dermal routes poses a risk of inflammatory effects. The presence of large numbers of microorganisms in the air, water, and soil provides extremely favorable conditions for the release of PAMPs. This study summarizes the characteristics of endotoxins, peptidoglycan, teichoic acids, lipoproteins, and CpG DNA, which are pivotal substances in PAMPs. The occurrence and health risks of PAMPs in different environmental media, such as air, water, and soil, are introduced. The recognition mechanism of PAMPs and their ability to trigger disease are also discussed. The synergistic enhancement of inflammatory responses induced by combined exposure to PAMPs and environmental pollutants is analyzed. Based on current research of PAMPs in the environmental field, this study highlights the urgent need to accelerate research into standardized detection systems, exposure risk thresholds, and epidemiological studies of PAMPs, given the existing limitations. The aim of these efforts is to advance research progress on PAMPs in environmental science and to provide a reference for a comprehensive understanding and assessment of the health risks posed by PAMPs.

Key words：microorganism；pathogen-associated molecular patterns (PAMPs)；inflammatory substances；environmental media；health risks

微生物增殖或死亡解体释放多种具有免疫活性的功能组分,即病原相关分子模式(PAMPs),具有致炎风险.PAMPs 包括内毒素、肽聚糖、磷壁酸、脂蛋白、CpG DNA、β-葡聚糖、鞭毛蛋白和 RNA 等,进入机体被宿主细胞的模式识别受体(PRRs)识别,激活信号级联反应,引起一系列细胞因子表达升高,触发炎症反应[1-2].PAMPs 具有种类多,结构复杂,分子量不均一且分布范围宽等特点.空气、水、土壤等环境介质中广泛存在微生物,为 PAMPs 释放提供重要基础.机体通过胃肠、呼吸和皮肤等途径暴露于

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环境 PAMPs 后不会出现典型炎症反应,但是长期接触会促进慢性炎症甚至慢性疾病的发生.内毒素是 PAMPs 中代表性致炎效应物质,其潜在健康风险受到广泛关注[3-4].然而,除内毒素外的其它 PAMPs 目前在环境领域均未得到重视.本研究参考生物医学领域 PAMPs 的研究报道,概述 PAMPs 性质特征及其致炎效应,揭示不同环境介质中 PAMPs 赋存状况,探讨细胞 PRRs 对 PAMPs 识别机制,阐述不同种类 PAMPs 及其与环境污染物的协同毒性效应,并对未来环境领域 PAMPs 的研究进行展望.

1 材料与方法

1.1 文献检索

采用 PubMed、Elsevier、中国知网和万方数据进行文献检索.以“病原相关分子模式(PAMPs)”、“炎症(inflammation)”、“环境(environmental)”、“空气(air)”、“水(water)”、“土壤(soil)”和以下任一关键词“内毒素(endotoxins)”、“肽聚糖(peptidoglycan)”、“磷壁酸(teichoic acids)”、“脂蛋白(lipoproteins)”、“CpG DNA”作为检索主题词进行检索,文献发表时间为数据库建库至 2024 年 12 月,文献类型为“研究论文(research articles)”和“综述(review articles)”.

1.2 文献筛选

采用上述关键词共检索到相关文献 3444 篇.基于本研究的研究主题与相关学科背景,对检索获得的文献标题与摘要进行相关性筛选,并在此基础上对文献内容进一步开展评估,以确保文献内容与环境介质具有较强的关联性.依照上述筛选标准,排除无关以及重复文献后最终得到文献 298 篇.

2 PAMPs 与先天免疫

先天免疫是机体漫长进化过程中获得的普遍性防御机制,是机体抵抗微生物入侵的第一道防线.PAMPs 是微生物含有的一类具有恒定核心结构、进化高度保守的分子.PAMPs 在宿主细胞中并不存在,这使机体能够有效区分“自我”和“非我”,从而启动先天免疫反应[1].1989 年 Janeway 首次提出细菌、病毒、真菌等微生物的独特结构成分能被先天免疫细胞上的 PRRs 所识别[5].1996 年 Hoffmann 等发现果蝇对抗真菌感染过程中 Toll 发挥关键作用,确立其免疫学意义[6].1997 年 Medzhitov 和 Janeway 提出将微生物含有的不同于机体的特殊组分称为 PAMPs[7].微生物 PAMPs 来源于自身基本功能组分物质,主要包括内毒素、肽聚糖、磷壁酸、脂蛋白、CpG DNA、β-葡聚糖、鞭毛蛋白和 RNA 等.PAMPs 属于大分子物质,结构复杂,化学性质多样,即使同种物质也存在结构差异,导致免疫刺激能力显著不同.目前一些微生物自身组分虽然已被认定为 PAMPs,但是其生物学效应仍未明确,新种类 PAMPs 也在不断发现中.

3 PAMPs 主要种类

3.1 内毒素

内毒素,又称脂多糖(LPS),是革兰氏阴性菌和某些蓝藻的细胞壁组分.单个大肠杆菌约含有 1.2×10^5 个内毒素分子,约占其总表面积的 3/4[8];单个沙门氏菌约含有 10fg(10×10^{-15}g)的内毒素分子[9].内毒素分子由 O-特异性链、核心多糖、类脂 A 通过共价键连接而成(图 1).类脂 A 由氨基葡萄糖、脂肪酸链与磷酸基团组成,分子量为 2~4kDa,是内毒素的活性中心[10-11].不同种类细菌甚至同种细菌中类脂 A 的脂肪酸链数量、长度、饱和度与排列方式以及磷酸基团的修饰都存在差异,对内毒素生物活性产生影响[11].内毒素属于两亲性分子,具有疏水端和亲水端,在水中极易聚集成团.内毒素单体分子量 10~20kDa,粒径 0.002~0.02μm.当内毒素形成聚合体后分子量超过 1000kDa,粒径也增大至 0.1~1.0μm[3,10].

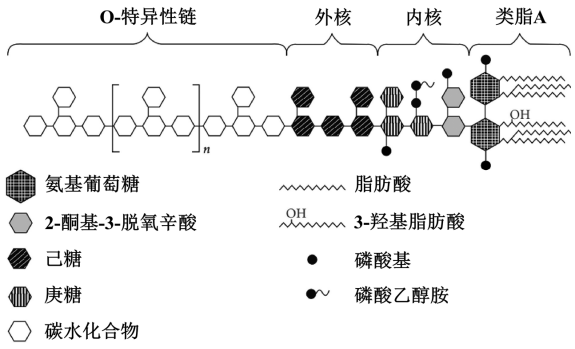


图 1 内毒素结构示意[19]

Fig.1 Schematic diagram of endotoxin structure

内毒素进入机体与脂多糖结合蛋白(LBP)结合,作用于 CD14 形成 LBP-LPS-CD14 复合体,激活 TLR4 受体,引发信号级联反应,启动机体免疫系统,诱导促炎细胞因子大量分泌[1,12].机体对内毒素极为

敏感,其在人体内超过 1ng/(kg·h)即可引起炎症反应[13].内毒素强免疫刺激能力与多种疾病密切相关,例如发热、哮喘、慢性炎症、低血压等,严重可能出现休克、多器官衰竭甚至死亡[14].内毒素具有极强的热稳定性,100℃高温处理 1h 仍难以破坏其生物活性,160℃条件下加热 2~4h 才能对其造成破坏[4].由于内毒素对机体具有强免疫刺激性,已成为医疗用品[15-16]与职业环境卫生[17-18]等领域的重要检查项目.

3.2　肽聚糖

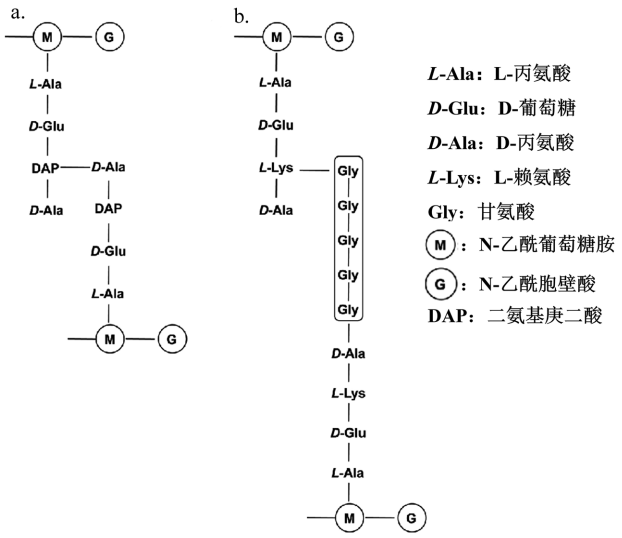


图 2　肽聚糖结构示意[29]

Fig.2　Schematic diagram of peptidoglycan structure

(a) 革兰氏阴性菌; (b) 革兰氏阳性菌

肽聚糖,又称粘肽、胞壁质或糖肽,是细菌细胞壁的重要组分.不同种类细菌的肽聚糖分布与含量存在差异.革兰氏阳性菌的肽聚糖位于菌体最外侧,占细胞干重的 30%~95%;革兰氏阴性菌的肽聚糖位于细胞质膜和外膜形成的周质空间内,占细胞干重的 5%~20%[20].革兰氏阳性菌的肽聚糖层较厚,例如枯草芽孢杆菌细胞壁肽聚糖层约 33.6nm,金黄色葡萄球菌的肽聚糖层约 33.8nm[21].肽聚糖是由若干单体聚合形成的网状大分子化合物,肽聚糖单体包括双糖与肽两部分(图 2).双糖单元由N-乙酰葡萄糖胺和 N-乙酰胞壁酸通过 β-1,4 糖苷键连接形成[22].不同种类细菌的肽聚糖在双糖单元数量上具有较大差异,例如枯草芽孢杆菌肽聚糖含有 50~250 个双糖单元,金黄色葡萄球菌肽聚糖的双糖单元数量通常为 18 个;革兰氏阴性菌肽聚糖含有 20~40 个双糖单元[23].肽聚糖的结构差异主要体现在肽链、多糖链长度等方面[24],其中肽聚糖分子量大小和二糖寡肽的保守重复结构是影响免疫活性的重要因素[25].

肽聚糖识别受体主要包括肽聚糖识别蛋白、核苷酸结合寡聚化结构域蛋白 1/2、TLR2 受体等[1,12].肽聚糖的免疫活性显著低于内毒素,诱导细胞因子的能力仅为内毒素的 1/10000;肽聚糖引起家兔体温升高的最小致热剂量为 7.3μg/kg,内毒素仅为 0.0027μg/kg[26].肽聚糖在自身免疫疾病中具有重要作用,系统性红斑狼疮和类风湿关节炎患者血清中肽聚糖片段 N-乙酰胞壁酰二肽的水平显著高于正常人[27].据报道,来源于链球菌的肽聚糖注射到大鼠体内可引发慢性关节炎[28].

3.3　磷壁酸

磷壁酸是革兰氏阳性菌细胞壁的特殊组分,由核糖醇或甘油残基通过磷酸二键相互连接而成,以磷酸多元醇分子的重复结构为主链的阴离子聚合物(图 3)[30].磷壁酸包括带负电荷的磷酸基团和带正电荷的 D-丙氨酸残基,因此大多数磷壁酸具有两性离子特性[31-32].根据磷壁酸在细胞表面不同的固定方式分为壁磷壁酸和脂磷壁酸,其中壁磷壁酸附着在细胞壁上,脂磷壁酸锚定在细胞膜上.由于壁磷壁酸缺少脂质部分,免疫活性显著低于脂磷壁酸.不同菌株脂磷壁酸结构差异,例如亲水主链长度、D-丙氨酸取代率以及疏水锚的脂肪酸成分等,这些均会影响其与细胞受体的相互作用,导致免疫活性发生改变[33].如果脂磷壁酸中 D-丙氨酸被 L-丙氨酸取代,免疫活性将降低 100 倍[34].

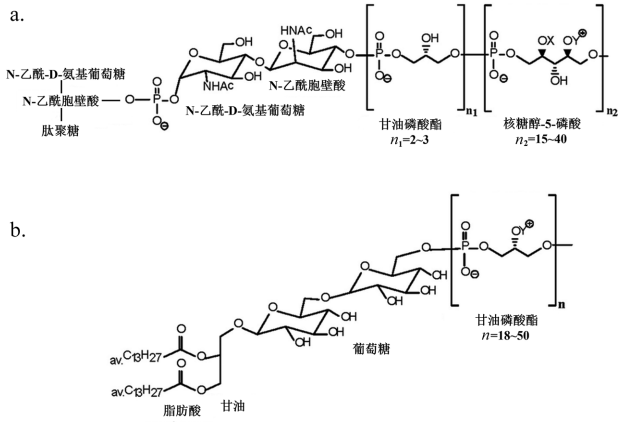


图 3　磷壁酸结构示意[39]

Fig.3　Schematic diagram of teichoic acid structure

(a) 壁磷壁酸; (b) 脂磷壁酸

TLR2 是脂磷壁酸的重要识别受体[1,12].磷壁酸的免疫活性显著低于内毒素,诱导细胞分泌促炎因子所需剂量是内毒素的 100~1000 倍;诱导巨噬细胞产生等量的一氧化氮,磷壁酸需要的剂量约为内毒素的 100000 倍[35-36].脂磷壁酸能诱导关节炎、肾炎、葡萄膜炎、脑脊髓炎和脑膜炎等,甚至引发败血性休克与多器官衰竭[37].据报道,将变形链球菌的脂磷壁酸注入大鼠牙龈,2 周后牙周组织出现明显的炎症反应和牙槽骨吸收现象[38].

3.4 脂蛋白

脂蛋白是细菌外膜的重要组成部分.每个细菌表面约有10^5个脂蛋白分子,每个脂蛋白分子的氨基酸数量约为 58 个[40].粪肠球菌脂蛋白含量约占其表面相关蛋白的25%[41].目前DOLOP数据库已列出278种细菌脂蛋白,其中大肠杆菌细胞膜约含有80种[42-43].不同脂蛋白的免疫活性具有差异, 其中脂化的 NH_2-末端氨基酸是影响脂蛋白免疫活性的重要因素[44].

TLR2 是脂蛋白的主要识别受体,TLR2 的下游信号传导需要与 TLR1 或 TLR6 相互作用形成异源二聚体[1,12].不同 TLR2 异源二聚体对脂蛋白的识别取决于脂蛋白酰化程度,例如三酰化脂蛋白被 TLR2/TLR1 识别,二酰化脂蛋白被 TLR2/TLR6 识别[1,12].脂蛋白的免疫活性与内毒素相近,甚至比内毒素更显著.例如大肠杆菌脂蛋白比内毒素能更有效的诱导小鼠腹腔巨噬细胞释放 TNF-α 和 IL-1[45].脂蛋白被认为是脓毒症的主要致病因素之一[46].伯氏疏螺旋体脂蛋白在莱姆病的发病机制中起重要作用[47].据报道,来源于金黄色葡萄球菌的脂蛋白能够刺激人肠上皮细胞,影响肠道炎症疾病的发展[48].

3.5 CpG DNA

未甲基化的胞嘧啶鸟嘌呤二核苷酸(CpG)的DNA 片段,简称 CpG DNA.CpG 基序的特征结构是以未甲基化的 CpG 二核苷酸为核心的回形序列,5’端的两碱基为嘌呤,3’端两碱基为嘧啶,即 5’-Pur PurCGPyr Pyr-3’[49].原核生物富含未甲基化的 CpG DNA,例如细菌基因组中 CpG DNA 的出现频率约为 1/16,其中仅 5%胞嘧啶被甲基化.哺乳动物 CpG DNA 的出现频率仅为 1/64,其中约 80%胞嘧啶被甲基化,导致 CpG DNA 表达频率仅有原核生物的 1/20 左右[50-51].这种差异使哺乳动物细胞将原核生物 CpG DNA 识别为“异物”,引发机体免疫反应.

TLR9 是机体识别 CpG DNA 的特异性受体.CpG DNA 与细胞膜结合被摄入细胞后与 TLR9 发生作用,触发 MyD88 依赖性途径,诱导细胞因子释放[1,12].不同细菌 DNA 的免疫活性具有显著差异.使用 15 种细菌 DNA 刺激 HEF293 细胞,检测 TLR9 表达水平,结果表明细菌基因组的 GC 含量越高,免疫活性越强[52].DNA 具有热稳定性,解链温度一般为 70~85℃,DNA 双链解开后会失去原有活性,但是变性的 DNA 在缓慢降低温度后活性仍可恢复.目前美国食品药品监督管理局对生物制品中残余 DNA 含量进行严格限制,建议将非致瘤性连续细胞的残留 DNA 控制在 10ng/剂以内,长度不超过 200bp[53].中国药典(2020 年版)规定冻干人用狂犬病疫苗(Vero 细胞)原液中残余 DNA 不高于 3ng/剂,大肠杆菌及酵母表达的治疗性基因工程重组产品不超过 10ng/剂,CHO 细胞为来源的重组乙型肝炎疫苗不超过 10pg/剂[15].CpG DNA 与自身免疫疾病密切关联,系统性红斑狼疮患者血清中富含低甲基化 CpG 的游离 DNA[54].据报道,每天注射 60mg 人工合成 CpG 的寡脱氧核苷酸,持续 3 周后小鼠淋巴器官的形态和功能显著改变,引发出血性腹膜炎和严重肝坏死[55].

4 不同环境介质 PAMPs 赋存特征与健康风险

4.1 空气环境

空气中生物气溶胶包含多种微生物及其释放的 PAMPs,它们通过呼吸系统进入人体后会对健康造成潜在威胁.Adhikari 等[56]发现家庭室内空气中小于 1μm 的颗粒物含有大量内毒素和 β-葡聚糖,最高占比分别达到 96.3%和 63.0%.挪威某垃圾处理厂工作环境的生物气溶胶中检测到大量微生物 DNA,细菌与真菌的平均 DNA 拷贝数分别为 0.61×10^5copies/m^3 和 2.45×10^5copies/m^3,并且 64%的样本能激活 TLR2,所有样本均能显著激活 TLR4,说明样本中含有多种 TLR2 和 TLR4 激动剂[57].Labohá 等[58]报道捷克地表水上方气溶胶中内毒素含量为 0.13~0.64EU/m^3,分离出的内毒素能诱导 BEAS-2B 细胞释放 IL-6 和 IL-8.海洋气溶胶样本能激活细胞 TLR2/6、NF-κB 和 IRF,但是与内毒素浓度没有相关性,说明 TLRs 受体与转录因子的激活是受到除内毒素外其它 PAMPs 等物质的联合作用[59].Boucher 等[60]研究发现生物气溶胶中常见物质内毒素、肽聚

糖和 β-葡聚糖均具有诱导骨髓来源树突状细胞活化的能力,仅凭内毒素不足以预测复杂生物气溶胶样本的免疫原性.为避免呼吸系统炎症,国际职业卫生委员会提出空气内毒素活性限值为 10ng/m^3[17];荷兰职业卫生标准针对个人可吸入粉尘暴露,建议内毒素活性应低于 50EU/m^3[18].然而,目前国内外均未对除内毒素以外的其它 PAMPs 物质制定限值标准.

4.2　水环境

内毒素作为水环境中重要的炎症诱导因子,近年来已经受到广泛关注.现有研究证实内毒素在地表水和地下水中普遍存在,但是浓度范围具有较大差异.北京地表水(南水北调中线来水、京密引水渠、密云水库)内毒素活性 21.0~68.2EU/mL[61-62];地下水内毒素活性 0.15~13.20EU/mL[63].日本地表水内毒素活性(100.8±39.8)~(164.0±92.8) EU/mL;地下水内毒素活性 0.02~0.36EU/mL[64].澳大利亚水库水内毒素活性(53±0.30)~(69±2.5) EU/mL,溪水内毒素活性(130±9.8) EU/mL[65].与水环境不同,血液接触用水中的内毒素早已得到重视,例如我国和欧洲药典均对注射用水中的内毒素含量作出明确规定,活性不能超过 0.25EU/mL[15-16].然而,对于水环境、生活用水等来说,目前国内外尚未建立相应的内毒素限值.水体中内毒素通过胃肠暴露引发的潜在风险虽然小于血液暴露与呼吸暴露,但是健康危害仍不容小觑.Broitman 等[66]报道小鼠通过饮水途径暴露于内毒素后导致胆碱缺乏动物出现肝损伤. Ravin 等[67]报道通过胃管给予兔子的内毒素剂量约有 1%能穿透肠屏障,进入血液循环系统后将造成更严重危害.目前除内毒素外的其它 PAMPs 在水环境和饮用水中鲜有报道,未来亟需开展相关研究.

4.3　土壤环境

土壤中微生物的种类与数量都极为丰富,每立方米土壤中细菌数量高达 10^{10} 个,细菌种类也多达 10^4 种[68],为 PAMPs 存在提供了重要基础条件.尤其是在土壤中广泛存在的 *Klebsiella*、*Pseudomonas* 和 *Enterobacter* 等革兰氏阴性菌,它们在生长、增殖以及裂解过程中均能释放内毒素[19].Zucker 等[69]报道柏林郊外土壤中内毒素含量高达 5900~1900000EU/g.Moniruzzaman 等[70]报道室内灰尘样本中内毒素浓度范围 138~942000EU/g.Kozajda 等[71]报道地板沉降灰尘中内毒素浓度为 409.38~150649.82ng/g,β-葡聚糖浓度为 5044.97~403915.88ng/g.对于土壤环境来说,除上述内毒素和 β-葡聚糖外,未见其它 PAMPs 相关研究报道.

5　PAMPs 识别与疾病诱发风险

5.1　PAMPs 识别机制

机体先天免疫系统通过细胞多种 PRRs 识别 PAMPs,包括 Toll 样受体(TLRs)、RIG-I 样受体、NOD 样受体、C 型凝集素样受体等,其中 TLRs 对于 PAMPs 的识别以及下游信号通路的激活至关重要.迄今为止,人体中已发现 10 种 TLRs(TLR1~TLR10)(表 1)[1].TLRs 信号转导途径如图 4 所示,主要包括 MyD88 依赖性途径与 MyD88 非依赖性途径,其中 MyD88 依赖性途径是 TLRs 主要信号通路.TLR3 使用 TRIF 作为适配器,属于 MyD88 非依赖性途径;TLR4 既可运用 MyD88 依赖性途径,又可运用 MyD88 非依赖性途径;其余 TLRs 介导的途径均属于 MyD88 依赖性途径.

表 1　TLRs 的细胞定位及其配体[1,12]

Table 1　Cellular localization of TLRs and their ligands

TLR	配体	TLR 定位	文献
TLR1	三酰化脂蛋白	细胞膜	[1]
TLR2	脂蛋白、肽聚糖、磷壁酸、酵母多糖	细胞膜	[12]
TLR3	病毒 dsRNA	内涵体	[12]
TLR4	内毒素(脂多糖)	细胞膜	[1]
TLR5	鞭毛蛋白	细胞膜	[1]
TLR6	二酰化脂蛋白、磷壁酸、酵母多糖	细胞膜	[12]
TLR7	病毒 ssRNA	内涵体	[12]
TLR8	病毒 ssRNA	内涵体	[12]
TLR9	CpG DNA	内涵体	[12]
TLR10	未知	细胞膜	[1]

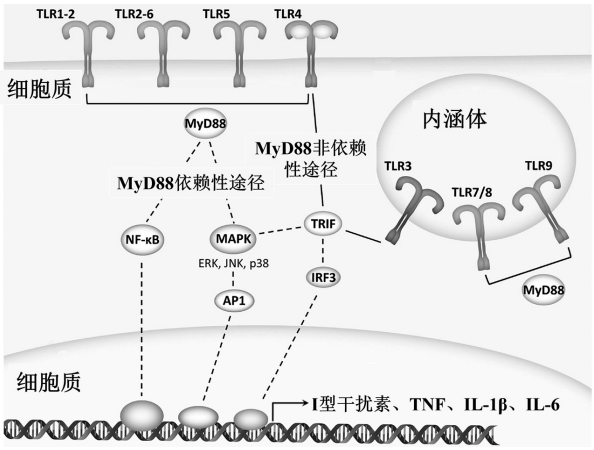


图 4　TLR 信号传导通路示意[72]

Fig.4　Schematic diagram of the TLR signaling pathway

PAMPs 激活细胞 PRRs 后触发炎症反应,释放多种细胞因子,包括促炎细胞因子和抗炎细胞因子,两类细胞因子的动态平衡变化决定炎症反应进程.当免疫系统持续激活,抗炎细胞因子与促炎细胞因子之间的平衡被打破,就会造成局部靶组织环境转向促炎状态.细胞因子的过量释放能引起免疫紊乱和炎症反应级联放大,甚至造成“细胞因子风暴”.

5.2 TLRs 和细胞因子高表达风险

PAMPs 激活先天免疫系统导致 TLRs 和促炎细胞因子高表达,这与多种疾病的发生发展过程密切相关.TLRs 被证实参与肿瘤的病理生理过程,多种肿瘤细胞均检测到 TLRs 高表达.TLR9 在乳腺癌细胞中高表达,参与乳腺癌细胞的侵袭与迁移[73];TLR4 和 TLR5 在肠化生和异型增生的胃上皮细胞和胃癌肿瘤细胞中高表达;TLR3、TLR4、TLR7 和 TLR9 在食管癌组织中高表达,并且与淋巴结转移有关; TLR4 通常在侵袭肿瘤的恶性免疫细胞中高表达[74]. TLRs 还与慢性疾病的发生密切相关.据报道,Ⅰ型糖尿病患者单核细胞 TLR2 和 TLR4 表达水平更高[75]; TLR2、TLR3 和 TLR4 在变应性鼻炎患者的鼻黏膜中表达上调[76];TLR4 和 TLR7 在非酒精性脂肪肝疾病中起重要作用[77-78];TLR2、TLR4 和 TLR9 参与慢性阻塞性肺疾病的发生,TLR4 被认为是维持慢性阻塞性肺疾病炎症反应的重要 TLRs[79];TLR2 在心肌细胞中高表达,激活 NF-κB 通路,介导心肌炎症、心肌纤维化、心肌细胞凋亡和心肌梗死等过程[80].

IL-6 和其它促炎细胞因子的高表达引起类风湿性关节炎患者的全身炎症,引发低白蛋白血症、贫血和骨质疏松症等[81].IL-6 高表达也与癌症具有密切联系,例如血清中较高水平的 IL-6 与男性罹患肝癌风险增加有关[82];过度活跃的 IL6/STAT-3 信号传导促进癌细胞增殖,导致肿瘤生长和侵袭性增加[83].阿尔茨海默病患者脑脊液和血浆中的 IL-6 水平均较高,表明 IL-6 与阿尔茨海默病的相关病理过程有关[84].TNF-α 是骨骼疾病发生的主要原因之一,过量 TNF-α 能引起全身性炎症反应,导致破骨细胞过度活化、骨形成受损,引发骨质疏松症[85].TNF-α 也是帕金森病中神经炎症的重要炎症介质之一,通过凋亡等机制导致多巴胺神经元的神经变性[86].

6 不同 PAMPs 及其与环境污染物的协同风险

微生物释放的 PAMPs 不是以单一组分存在,而是具有多组分混合暴露特征.据报道,不同种类 PAMPs 联合暴露会产生协同效应.小鼠联合静脉注射内毒素(5mg/kg)、脂蛋白(0.5mg/kg)和人工合成 CpG 的寡脱氧核苷酸(2mg/kg)引发的死亡率显著高于单独给药组[87].低剂量内毒素或细菌 DNA 单独注射 BALB/c 小鼠不会引起 TNF-α 显著升高,二者联合使用导致小鼠体内 TNF-α 显著增加[88].脂蛋白与内毒素的协同作用诱导 TNF-α 和 IL-6 大量释放,甚至引起小鼠致死性休克[46].单独注射肽聚糖或脂磷壁酸未对大鼠产生显著影响,但是二者同时注射引起大鼠多器官衰竭与休克[89].肽聚糖和脂磷壁酸的协同作用会导致猪发生呼吸衰竭和败血症[90].肽聚糖单体胞壁酰二肽不能有效诱导单核细胞 THP-1 释放 IL-8,但是与内毒素和脂磷壁酸联合使用时 IL-8 显著提升[91].

PAMPs 与环境污染物联合暴露也具有协同效应.例如内毒素和微囊藻毒素共存时,微囊藻毒素能协同内毒素抑制谷胱甘肽硫转移酶活性,引发细胞内活性氧和丙二醛水平显著升高,加速细胞凋亡[92].细胞单独暴露于细颗粒物时炎症介质 COX-2 表达水平未发生显著变化,但是预暴露 1h 后加入内毒素却显著提高与调控脂类炎症介质相关基因与蛋白的表达水平,证实颗粒物化学组分与内毒素之间存在协同致炎效应[93].Tsai 等[94]报道多环芳烃与内毒素存在协同效应.Bianchi 等[95]揭示纳米颗粒物与内毒素的协同致炎效应主要是由于纳米颗粒物促进磷酸化刺激 TLR4 受体相关炎症信号通路所导致.

7 环境领域 PAMPs 现有研究不足

从现有报道看,对于 PAMPs 物质的理解认知仍然有限,新种类 PAMPs 也在持续发现中,主要存在以下不足之处.

7.1 PAMPs 标准化检测体系尚未建立

PAMPs 属于微生物产生的天然代谢物质,即使来源于同一细菌的同种物质,其分子结构、组分含量、生物活性等也呈现多样且复杂的特征,这导致大多数 PAMPs 的标准物质在提取纯化、表征和定值方面具有较大难度.因此,目前很多种类 PAMPs 缺乏

相应的标准物质与标准样品,使标准检测方法难以建立.内毒素是 PAMPs 物质中的典型代表,目前国际上以鲎试验作为其现行标准检测方法,该方法被广泛应用于制药生产和医疗器械等领域.然而,除内毒素之外的其它 PAMPs 如肽聚糖、磷壁酸、脂蛋白和 CpG DNA 等,尚未建立标准测定方法.此外,针对环境介质的复杂性,在建立 PAMPs 标准化检测方法同时,还需要重点解决 PAMPs 特异性识别以及复杂基质干扰问题,开发适用于不同环境介质的 PAMPs 相关检测方法.

7.2　PAMPs 暴露安全阈值尚未确定

不同环境介质中微生物的存在为各种 PAMPs 赋存提供重要基础,通过呼吸、胃肠以及皮肤等暴露途径与机体长期接触,引发潜在的健康风险.目前,针对内毒素通过血液暴露的严重临床反应以及气溶胶引起的职业暴露风险,国内外药典以及职业卫生等权威机构已经对内毒素风险阈值作出明确规定[15-18].然而,除内毒素之外,很多种类 PAMPs 如肽聚糖、磷壁酸、脂蛋白和 CpG DNA 等暴露安全阈值均未确定.因此,还需要加强不同环境介质中 PAMPs 对机体潜在的毒理效应机制研究,推动各种暴露途径的安全阈值确定.

7.3　PAMPs 流行病数据尚不完善

目前报道已证实各种 PAMPs(如内毒素、肽聚糖、磷壁酸、脂蛋白和 CpG DNA)均具有较强的免疫活性,对机体的致炎风险不容忽视.然而,环境介质 PAMPs 诱导的炎症与普通炎症,在诊断时不易区分,临床上难以确诊.此外,PAMPs 在环境中污染水平极低,机体接触后不会出现明显的炎症反应症状,引起的“微炎症”反应极易被忽视.目前环境暴露 PAMPs 流行病学数据严重不足,亟需加强对环境领域 PAMPs 流行病学相关数据的积累.

8　结语

微生物在环境中广泛存在,在增殖或死亡解体过程释放多种 PAMPs,包括内毒素、肽聚糖、磷壁酸、脂蛋白、CpG DNA、β-葡聚糖、鞭毛蛋白和 RNA 等.PAMPs 通过胃肠、呼吸和皮肤等暴露方式进入机体后,被宿主细胞 PRRs 识别引起免疫应答,导致一系列细胞因子升高,引起炎症反应.PAMPs 诱发免疫反应过程中 TLRs 与细胞因子的高表达已被证实与多种慢性疾病的发生发展密切相关.目前,PAMPs 健康风险在环境领域尚未引起足够重视.基于当前 PAMPs 研究现状,建议将来研究工作应从 PAMPs 的标准检测体系建立、暴露风险阈值确定和流行病学数据积累等方面重点着手,推动 PAMPs 在环境领域的相关研究进展,为系统评估环境 PAMPs 的健康风险提供参考依据.

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