How much do vertebrates depend on the innate immune system to fight infection?

病原体感染的天然免疫防御效应

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摘要 机体的天然免疫系统是古老的、保守的和重要的抗感染防御体系。脊椎动物、无脊椎动物甚至植物受到病原微生物攻击时, 均可以活化并产生不同的天然免疫防御应答。天然免疫系统如何防御病原体微生物感染, 一直是免疫学甚至生命科学领域的重要课题。因此, 哺乳动物(小鼠(*Mus musculus*)和人)的天然免疫防御效应和机制研究成为目前免疫学领域的研究热点和重点。研究主要集中在病原体的免疫识别、免疫细胞集聚和病原体免疫清除等不同阶段的天然免疫防御效应和机制。本文主要从以上3个方面简要评述了近年来在天然免疫细胞防御病原微生物感染的效应及机制方面的研究进展。针对某一热点研究主题, 也引用了较为详尽的文献综述。这将有助于研究者从整体上认识天然免疫系统、天然免疫细胞和分子对病原体感染的防御效应。

关键词 病原体感染, 感染免疫, 天然免疫, 免疫防御, 巨噬细胞, 中性粒细胞

机体的天然免疫系统是古老的、保守的和重要的抗感染防御体系^[1,2]。从植物到动物, 从无脊椎动物到脊椎动物, 天然免疫防御系统在抗击外来病原微生物感染中发挥了重要调节作用。而天然免疫系统如何防御病原微生物感染也一直是免疫学领域甚至生命科学领域的重要课题^[2]。近年来, 随着细胞免疫学、分子免疫学及感染免疫学等相关学科的发展, 国内外免疫学研究者天然免疫防御效应和机制研究中获得了一些重要的研究成果^[3~5], 本文主要针对在病原体的免疫识别、免疫细胞集聚和病原体免疫清除等不同阶段的天然免疫防御效应和机制研究进展作简要评述。

1 病原体的免疫识别

多种免疫细胞类型定居在病原体入侵感染机体局部, 免疫细胞可以表达模式识别受体(pattern recognition receptors, PRRs)识别病原微生物^[5,6]。通

常, 广泛受影响的免疫细胞是组织定居巨噬细胞(tissue residential macrophages)和树突状细胞(dendritic cells)^[7~9]。肥大细胞(mast cells)可能在炎症感染的早期阶段释放细胞因子和介质(如组织胺、前列腺素等)^[10]。巨噬细胞和树突状细胞通过细胞表面、内质网或溶酶体、细胞浆等内的PRR可以识别并吞噬致病微生物。结果可以导致定居吞噬细胞和肥大细胞活化、促炎因子释放。释放的促炎因子可以介导炎症级联反应, 并明显改变病原体感染局部组织微环境(图1)^[8,11]。

1989年, Janeway^[12]提出天然免疫系统通过模式识别受体PRRs识别病原微生物理论。在1997年, Medzhitov和Janeway^[13,14]系统提出了PRRs和模式识别(pattern recognition)作用的概念, 证实了PRR的模式识别作用赋予天然免疫系统识别“自己”和“非己”的能力, 揭示了天然免疫的重要生物学意义。PRRs的配体可以存在一种或多种病原体上, 是病原微生物

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图1 (网络版彩色)天然免疫细胞通过PRR模式识别病原微生物

Figure 1 (Color online) Pathogenic microorganisms recognized by innate immune cells by PRR pattern

生存的必要和保守成分,称为病原体相关分子模式(pathogen-associated molecule pattern, PAMPs)^[15,16].具有抗原提呈能力的天然免疫细胞通过其PRR模式识别作用,吞噬处理并将其加工成主要组织相容性复合体MHC(major histocompatibility complex)-肽复合物,递呈给辅助T细胞(T helper cells, T_H cells).同时,只有将其某一物质识别为有害物质后,才表达B7分子,提供共刺激信号^[14,17,18].这样,PRR模式识别可以有效区分“自己”和“非己”,体现了免疫系统免疫识别的作用PRR模式识别本质.

PRR模式识别受体主要包括Toll样受体(toll-like receptors, TLRs), NOD样受体(NOD-like receptor, NLRs), RIG-I样受体(RIG-like receptors, RLRs)和细胞表面的c型凝集素受体(c-type lectin receptors, CLRs)^[19,20]. Toll样受体是进化中比较保守的一种受体家族,至少包括13个成员. TLR能特异识别PAMP,在抗细菌感染(TLR2或TLR4)、抗病毒感染(TLR7/8, TLR3或TLR4)和抗真菌(TLR4或9)感染中发挥调控作用.除了TLRs, NLR, RLR和CLR在病原体免疫识别中也发挥重要调控作用^[21]. NLR属于进化上最古老的PRR家族. NLR信号通路中涉及炎症小体激活方面的研究较为深入.炎症小体由半胱氨酸蛋白酶1(caspase 1)、衔

接蛋白ASC (apoptosis-associated speck-like protein containing CARD)组成,可由NLR家族成员核苷酸结合寡聚化结构域样受体蛋白1(nucleotide binding domain like receptor protein 1, NLRP1), NLRP3和NLRC4激活^[22].炎症小体的激活导致促炎因子IL-1 β 和IL-18分泌增多,从而促进炎症反应和细胞坏死^[23].另外,RLR和CLR在天然免疫识别病原体中也发挥重要调控作用^[24,25]. PRR信号可以活化相似的下游胞内信号,包括核转录因子 κ B(nuclear factor kappa B, NF- κ B)途径和有丝分裂原激活的蛋白激酶(mitogen-activated protein kinase, MAPK)或者干扰素调节因子(interferon regulatory factor, IRF)等,从而调节炎症免疫应答(图1)^[26~28].

天然免疫识别的重要性在同种异体移植排斥反应中也存在一些相似的现象.器官移植后受体内供受者细胞混合嵌合率常成为诱导器官移植耐受的有效指标.同种异体小鼠(*Mus musculus*)骨髓移植后嵌合体小鼠中受者巨噬细胞出现特异性的对供者和受者抗原免疫应答反应能力(非调理素吞噬能力和T细胞刺激增殖能力)降低,而对无关第三者却显示正常的免疫应答能力^[29~31].这表明,小鼠骨髓嵌合体巨噬细胞具有特异性的天然免疫识别能力.然而,在移植免疫中介

导天然免疫特异性识别, 是否存在与PRR相似的模式识别受体, 仍需大量深入细致研究工作。

2 免疫细胞集聚到炎症位点

2.1 天然免疫细胞迅速集聚到炎症位点

局部定居免疫细胞释放的细胞因子和炎症介质可以改变局部血管上皮细胞并促进感染的组织转变为炎症的状态。尤其是肿瘤坏死因子 α (tumor necrosis factor α , TNF α)、IL-1及脂类等可以引起一系列形态学和分子变化最终导致血管扩张、血流变快、淋巴细胞浸润到病原体感染的炎症局部。在多数情况下, 中性粒细胞是最早集聚到炎症周围的免疫细胞。它具有多种颗粒可以降解吞噬的物质、产生活性氧基团(reactive oxygen species, ROS), 从而降解蛋白质、脂类并损伤DNA^[32]。近来, 许多研究集中在寻找促进中性粒细胞集聚和功能活性的重要信号分子。证实, AKT1/PKB1(protein kinase B1)^[33]、AKT2^[34]、磷酸酶Wip1 (wild-type p53 induced phosphatase 1)^[35,36]、癌胚抗原相关抗原黏附分子1(carcinoembryonic antigen associated cell adhesion molecule 1, CEACAM1)^[37]、白细胞三烯B4 (leukotrienes B4, LTB4)^[38]、趋化因子受体2 (chemokine receptor 2, CXCR2)^[39]和CXCR4^[40]等在促进中性粒细胞集聚和功能活性中发挥重要调控效应^[4]。在中性粒细胞进入到炎症位点后, 可以直接吞噬活的病原微生物或者促进它们的颗粒成分与病原微生物形成吞噬小体。如果中性粒细胞进入到炎症位点, 没有直接遇到病原微生物, 那它们可以释放颗粒而调节局部细胞因子环境抗击病原微生物。这些颗粒成分不仅对病原微生物是有毒的, 同时也将损伤局部组织和细胞。例如, 弹性蛋白酶、组织蛋白酶等都可以导致宿主组织细胞损伤。在早期感染中, 缺失这些颗粒成分的小鼠, 常对细菌感染敏感性增强。中性粒细胞最终将凋亡并被巨噬细胞清除^[41]。

几乎与中性粒细胞的集聚信号相似, 单核细胞也可以迅速集聚到感染局部位点^[42~44]。血液中炎性单核细胞可以直接集聚到感染的组织, 接着进入其引流淋巴通道(局部引流淋巴管和淋巴结)。感染局部促炎信号(包括促炎细胞因子和病原微生物分子)可以诱导发育成熟的单核细胞从骨髓迁出。而局部感染组织上皮细胞黏附分子表达上调则可以招募血循环中炎性单核细胞(CD115⁺Ly6C^{high})。单核细胞在感

染局部有直接的抗病原微生物感染作用, 尤其在肺和皮肤感染中^[43~45]。也可以携带微生物抗原到局部淋巴结, 传递抗原给经典树突状细胞(classical dendritic cells, cDC), 从而诱发CD4⁺T细胞和CD8⁺T细胞获得性免疫应答, 促进病原体的最终清除或者引发慢性感染性炎症反应^[44~46]。

2.2 中性粒细胞和巨噬细胞协调促进免疫防御调节

中性粒细胞和巨噬细胞都是由共同的骨髓前体细胞分化而来。在病原体入侵感染局部, 中性粒细胞和巨噬细胞抗感染存在明显协同调节机制。病原体感染入侵机体, 巨噬细胞前体(单核细胞)和成熟的中性粒细胞通过血流集聚到感染局部。而且, 集聚的单核细胞可以分化为炎性巨噬细胞(CD11b⁺Ly6c⁺)或者经典树突状细胞参与抗微生物感染防御。感染组织局部的定居巨噬细胞通过模式识别和产生细胞因子或者趋化因子调节集聚的中性粒细胞转化为炎症的表型^[32,45]。因此, 巨噬细胞和中性粒细胞是以合作的形式招募其他部位的巨噬细胞和中性粒细胞到感染局部。另外, 中性粒细胞和巨噬细胞也存在负反馈调节机制。正常中性粒细胞可以不断从骨髓发育成熟并释放和迁移到外周血或组织。在病原微生物感染时, 血中中性粒细胞迅速集聚到炎症位点、吞噬病原微生物。吞噬病原微生物的中性粒细胞出现凋亡, 而后被巨噬细胞清除。巨噬细胞吞噬凋亡的中性粒细胞后, 将降低IL-23分泌, 抑制T_H17细胞分化和IL-17产生, 减少粒细胞集落刺激因子(granulocyte colony-stimulating factor, G-CSF)产生细胞G-CSF分泌, 最终负性调节骨髓中性粒细胞生成和释放入血(图2)^[4,47]。

在效应阶段, 集聚的中性粒细胞和巨噬细胞从以下几个方面协作调节。巨噬细胞吞噬凋亡和没有凋亡的中性粒细胞, 可将中性粒细胞病原微生物分子传给巨噬细胞并提高巨噬细胞抗病原微生物能力^[48]。除吞噬完整的中性粒细胞外, 巨噬细胞也能获得释放的中性粒颗粒和颗粒酶。另外, 巨噬细胞和中性粒细胞相互作用也体现在炎症感染消退阶段。当巨噬细胞由于吞噬大量凋亡的中性粒细胞后功能出现抑制时, 正常的中性粒细胞也可以作为吞噬病原体的替代者, 发挥吞噬病原体的效应^[3]。而当感染过程被控制后, 中性粒细胞集聚会减少, 而炎症巨噬细胞会凋亡并被健康的巨噬细胞清除, 使感染部位

图2 (网络版彩色)巨噬细胞通过IL-23/IL-17-G-CSF轴调控中性粒细胞生成和释放

Figure 2 (Color online) Macrophages regulate the production and release of neutrophils through the IL-23/IL-17-G-CSF axis

恢复健康状态. 另外, 中性粒细胞还可以指导巨噬细胞分化. 在鼠疫菌感染早期, 中性粒细胞通过分泌IL-17可以有效促进巨噬细胞表型分化而促进其抗鼠疫菌感染能力^[49,50].

2.3 感染局部环境调节浸润的天然免疫细胞分化

组织定居巨噬细胞或者集聚在炎症局部的外周血单核细胞在局部的特异感染环境中也可以分化为组织巨噬细胞不同的功能亚型, 从而在感染调节中发挥作用. 巨噬细胞通常可以分化为两种亚型^[3,43,45]. 在1型细胞因子环境中(促炎因子环境), 促炎细胞因子或微生物成分(细菌脂多糖LPS(Lipopolysaccharides))可活化经典激活巨噬细胞(classically activated macrophages, type 1 macrophages, M1), 通过其表达的TLRs等识别病原微生物, 并分泌促炎细胞因子(TNF α , IL-12, IL-1 β , IL-23和IL-6等)、趋化因子(CXCL10(chemokine(C-X-C motif) ligand 10)或CCL5(chemokine(C-C motif) ligand 5)等)及诱导性一氧化氮合酶发挥抗病原微生物感染效应. 相反, 在2型细胞因子环境中(抑炎因子环境), IL-4, IL-13, IL-10或

TGF β 等可活化替代激活巨噬细胞(alternatively activated macrophages, type 2 macrophages, M2), 通过分泌抗炎细胞因子(IL-10或TGF β)及促进精氨酸酶活性, 在缓解1型病原微生物感染和抗胞内微生物感染等2型炎症中发挥调节作用(图3). M2巨噬细胞根据其诱导刺激不同, 还可以分为M2a, M2b和M2c亚型, 在平衡1型炎症反应和诱导获得性免疫应答清除病原微生物中起作用.

目前, 系列研究已经证实, 感染局部细胞因子环境可通过有效调节巨噬细胞分化而抗病原微生物感染(图4). 主要有几条信号传导途径在调节感染局部巨噬细胞分化中发挥重要调控作用^[3,43,51]. 经典途径, LPS可通过巨噬细胞表面TLR4受体, 刺激NF- κ B等诱导M1分化, 促进其抗病原体感染效应. 替代途径, IL-4可结合IL-4R α 并招募IL-2R γ 链或IL-13R α I链(取决于细胞类型). IL-13可以结合IL-13R α I链并招募IL-4R α . 然后, 两个细胞因子下游通过相似的信号途径, 主要是涉及磷酸化STAT6(signal transducer and activator of transcription 6), 使其核转位, 调节核中大量转录因子活性, 包括PPAR γ (peroxisome proliferator-activated

图3 (网络版彩色)病原体感染局部环境调节巨噬细胞集聚和分化及抗病原微生物免疫应答

Figure 3 (Color online) Local cytokine milieu of infections of pathogenic microorganisms regulate macrophage aggregation and differentiation and the immune responses of anti-pathogen infection

图4 (网络版彩色)病原体感染诱导巨噬细胞表型分化的机制

Figure 4 (Color online) Mechanism of differentiation of macrophages induced by pathogen infection

receptor γ)或IRF4等指导M2分化, 在抗病原微生物感染中发挥调节作用. 除STAT6依赖性途径外, 生长因

子、IL-4和IL-13也通过STAT6非依赖性途径活化三磷酸肌醇激酶(three inositol phosphate kinase, PI3K)-

AKT-缺氧诱导因子1 α (hypoxia inducible factor 1 α , HIF1 α)信号^[52,53], 调节M2分化. 目前, 靶向巨噬细胞表型转化关键调控分子研究已经成为促进天然免疫防御病原微生物感染的有效策略和手段. 在抗病原微生物感染免疫研究中, 除靶向巨噬细胞表型分化调节外, 靶向髓系抑制细胞(myeloid-derived suppressor cells, MDSCs)^[54~57]、中性粒细胞^[58]及树突细胞表型分化调控^[59~61]也成为重要的抗感染天然免疫防御研究重点.

3 病原体的免疫清除

虽然天然免疫防御可以有效清除病原体. 然而, 不同的病原体常活化获得性免疫应答才能被最终清除. 未分化的淋巴细胞, 如未分化T细胞(naïve T cells)接受其分化过程中天然信号刺激可以分化为不同类型的T细胞从而决定获得性免疫应答的类型(图3). 细胞因子IL-12和干扰素(interferon γ , IFN γ)可以促进未分化细胞分化为T_H1细胞(产生效应因子IFN γ 的CD4⁺T细胞)在抗细胞内病原微生物感染中发挥调节作用. 而细胞因子IL-4可以促进未分化细胞分化为T_H2细胞(产生效应因子IL-4的CD4⁺T细胞)在抗寄生虫和细胞内病原体感染中发挥调节作用. 细胞因子IL-6和转化生长因子 β 1 (transforming growth factor β 1, TGF β 1)等可以促进未分化细胞分化为T_H17细胞(产生效应因子IL-17的CD4⁺T细胞)在保护宿主黏膜细菌和真菌感染中发挥调节作用^[62,63]. 另外, 一些新的T细胞亚群发现(如T_H9细胞)和抗感染作用也在逐渐阐明^[64,65]. 因此, 靶向重要的抗原提呈细胞(巨噬细胞或树突状细胞), 通过调节其抗原提呈能力、共刺激分子表达及细胞因子分泌等可以有效指导T细胞不同亚型分化, 从而在最终免疫清除病原体中发挥作用. 虽然目前天然免疫细胞对获得性免疫调节作用研究仍处于初级阶段, 但近来本课题组及其他实验室的一些工作已经显示其重要调节作用(图5). 促分裂原活化的蛋白激酶(mitogen activated protein kinase, MAPK)途径在天然免疫细胞功能调节中发挥重要作用. 该途径包括细胞外信号调节的激酶(extracellular signal-regulated kinase, Erk), c-Jun的N-末端激酶(c-Jun N-terminal kinase, JNK)和p38途径. 研究显示, p38的亚单位p38 α 在DC缺失, 可以明显提高IL-6分泌, 而在其作用的T细胞信号转导和转录激活因子3 (signal transducer and activator of transcription 3, STAT3)活化增强并表现为有利于T_H17细胞分

图5 (网络版彩色)病原体感染诱导树突状细胞依赖性T细胞分化调节机制

Figure 5 (Color online) Regulatory mechanisms of DC-dependent T cell differentiation induced by pathogenic infections

化^[66]. 进一步研究证实, p38上游的负性调控分子有丝分裂原激活蛋白激酶磷酸酶1 (mitogen-activated protein kinase phosphatase 1, MKP1)在树突细胞依赖性T细胞抗真菌感染中发挥调控作用. 树突细胞MKP1通过调节IL-12和IL-23分泌可以指导T细胞分化为T_H1和T_H17细胞^[67]. 机制研究显示, MKP1下调p38MAPK途径, 促进IL-6分泌并抑制IL-12产生, 最终促进T_H17细胞分化, 而抑制T_H1细胞分化, 在抗白色念珠菌感染中发挥调控作用. 近年来, 本课题组^[68]研究发现, 沉默信息调节因子1 (sirtuin 1或silent mating type information regulation 2 homolog 1, SIRT1)在树突细胞缺失, 不能明显改变其表面共刺激分子表达和T细胞的刺激增殖能力, 但是却明显促进IL-12分泌增多, 而TGF β 1表达降低. 在其作用的T细胞, 表现为IL-12R β 2和TGF β R2表达改变及其下游的STAT1及SMAD3 (TGF β 细胞因子超家族的细胞内信号转导分子)等表达出现相应改变, 最终诱导T_H1细胞分化增多, 而抑制调节性T细胞(regulatory T cells, T_{reg} cells)分化, 在抗革兰氏阳性球菌李斯特菌感染中发挥调节作用. 重要的是, 树突细胞SIRT1依赖性细胞因子分泌变化是通过代谢调控子HIF1 α , 并且非依赖哺乳动物雷帕霉素靶向基因(mammalian

target of rapamycin, *mTOR*)信号途径(图5). 这提示, 代谢调控子SIRT1可能通过HIF1 α 依赖性代谢调控途径, 改变细胞因子分泌, 并指导T细胞依赖性分化及抗感染免疫应答. 同时, 这也显示, 靶向树突细胞关键信号分子, 可以针对性调节T细胞依赖性革兰氏阳

性球菌或者白色念珠菌等不同病原微生物感染免疫应答, 有助于提高免疫防御能力, 控制炎症消退. 也为靶向特异性的天然免疫细胞, 并着眼于病原体感染免疫防御的3个阶段, 从而全面彻底清除病原微生物感染的免疫防治策略和方案研究提供了新依据.

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Innate immune defense effects of pathogenic microorganism infection

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The innate immune system is old, conservative and important anti-infection defense system. How does the innate immune system defend against an array of invading microbial pathogens including bacteria, viruses, parasites and fungi, which becomes an important research topic in the immunological fields. This article just summarized the different stages of immune defense against pathogenic microorganism, including the innate immune recognition, the recruitment of innate immune cells, and the pathogen immune clearance.

The innate immune system comprises various immune cells including DCs, macrophages and neutrophils that sense and respond rapidly to aid in the elimination of microbial pathogens, thereby providing the first line of host defense against infection. This early innate microbial sensing is achieved via the recognition of distinct molecular motifs, termed pathogen-associated molecular patterns (PAMPs), of microbial components, such as proteins, lipids, nucleic acids and carbohydrates, by evolutionarily conserved host germline encoded pattern recognition receptors (PRRs). The interactions between the various PRRs and their cognate PAMPs trigger a complex cascade of intracellular signaling pathways leading to the production of cytokines and chemokines that mediate the induction of antimicrobial and inflammatory responses. There are several distinct families of PRRs including Toll-like receptors (TLRs), nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) and the retinoic acid-inducible gene-I (RIG-I)-like receptors (RLRs) are involved during this course. Macrophages and DCs engulf microbes by detecting PRRs. The result of pathogen recognition is activation of resident phagocytes and mast cells and the release of proinflammatory cytokines.

Proinflammatory cytokines induce changes in local blood vessel endothelial cells that promote the conversion of the infected tissue to an inflamed state. In particular, TNF- α and IL-1 cause a series of morphological and molecular changes that collectively lead to increased migration of leukocytes and flow of plasma to the infected site. In most cases, neutrophils arrive within hours followed by a later influx of monocytes. After entering the site of inflammation, neutrophils phagocytose any available microbes and direct the contents of their granules toward these phagosomes. If neutrophils detect TNF- α , but do not directly encounter any microbial particles after entering the tissues, they release their granules into the extracellular space in an effort to create an inhospitable environment for nearby pathogens. All options for neutrophils, however, result in the same eventual fate: their death by apoptosis and clearance by macrophages. Macrophages enter the site of inflammation after neutrophils, called by many of the same signals. In addition to the clearance of apoptotic neutrophils, macrophages also contribute to the killing of microbial organisms. They engulf and degrade microbes using proteases, antimicrobial peptides. Depending on the inflammatory microenvironment, macrophages can also be programmed to various distinct subsets and the heterogeneity of circulating monocytes may predefine their polarization fate once they arrive at tissues.

The innate immune system is also responsible for initiating an adaptive immune response specifically tailored to the invading microbe. DCs play a critical role in translating the appropriate signals from the innate to adaptive immune system to mediate the regulation of adaptive immunity. The adaptive immune system consists of B and T cells that express highly diverse repertoires of B- and T-cell receptors, respectively, and generates specificity in antibody and cellular responses and long-term memory. Our previously studies have demonstrated that sirtuin 1 (SIRT1), a histone deacetylase, plays an essential role in mediating proinflammatory signaling in DCs, consequentially modulating the balance of proinflammatory T helper type 1 (T_H1) cells and anti-inflammatory Foxp3⁺ regulatory T cells (T_{reg} cells). And, it implicates a DC-based SIRT1-HIF1 α metabolic checkpoint controls T cell specification in anti-infection immunity. Recently, SIRT1 also plays important effects in controlling differentiation of myeloid-derived suppressor cells (MDSCs) and Th9 cell differentiation in infectious inflammation.

pathogenic infection, infectious immunity, innate immunity, immune defense, macrophages, neutrophils

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