流感病毒感染后固有免疫病理损伤机制的探讨

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摘要 流感病毒感染后可以造成广泛的免疫病理损伤,病毒的持续复制和宿主产生的过度的免疫应答是介导病理损伤的主要原因。文章主要针对病毒感染初始阶段,固有免疫应答中关键因子在抗病毒免疫和介导肺损伤中的利弊加以综述,为深入了解流感病毒防御机制及寻找出合理有效的治疗策略提供参考。

关键词 流感病毒;免疫病理损伤;天然免疫

Mechanism of Innate Immune Pathological Damage after Influenza Virus Infection

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Abstract Influenza virus infection can result in a wide range of immune pathological damage, and the continuous replication of the virus and the excessive immune response of the hosts are the main reasons for the injury. Based on the key factors in the initial stage of virus infection, this paper summarized the advantages and disadvantages of immune response in anti-virus and mediating lung injury, which provide a reference for in-depth understanding of the mechanism of influenza virus defense and a reasonable and effective treatment strategy.

Key Words Influenza virus; Immune pathological injury; Natural immunity

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流行性感冒,简称流感,是由流感病毒通过呼吸道感染引起的重要传染病。流感病毒属于正粘病毒科的分节段、单股、负链 RNA 病毒,其分节段的基因组导致其容易发生基因重组,并且在病毒传代中易发生抗原漂移,形成新的病毒株。根据其表面糖蛋白 HA 与 NA 的不同分别有 16 个与 9 个亚型。目前发现的可以感染人的亚型有 H1N1、H3N2、H2N2、pdm2009H1N1、H5N1、H9N2、H7N7、H7N2、H7N3 等,其中 H5N1、H7N9 对人有高致病性。流感病毒是典型的引起局部感染的病毒,呼吸道上皮细胞是流感病毒侵犯的主要部位。流感病毒感染过程中,机体的免疫应答对病毒的有效清除十分重要,但是过度的免疫应答又是介导免疫病理损伤的主要因素。为探讨流感病毒感染防御机制,寻找流感靶向治疗策略,我们主要对人及实验动物感染流感病毒初始阶段天然免疫病理损伤机制进行综述。

1 流感病毒的持续复制引起的病理损伤

流感病毒感染介导的小鼠肺损伤过程是一个多因素参与的复杂过程,其中病毒持续复制是造成损伤的主要因素之一。流感病毒通过其表面的 HA 蛋白特异性地与宿主细胞表面的唾液酸相结合,感染呼吸道上皮细胞,导致上皮细胞坏死性死亡、脱落。毒力较强的毒株感染后,病毒在感染部位持续复制,而高病毒载量和持续的病毒复制导致了炎性反应的持续存在,并最终导致了进行性的组织损伤[1-2]。病毒的高效的复制能力除了与病毒自身的多种成分如 HA(与肺上皮细胞特异性结合)、NA(子代病毒的释放)、PB2(病毒复制)[3]、NS1(抵抗宿主免疫应答力)[4]相关外,还与流感病毒感染后成功激活宿主细胞内的多条信号通路如 Ras/Raf/MERK/ERK 信号通路[5]、NF-κB 信号通路[6]、PKS 和 PI3K/AKT 信号通路[7]等以帮助其顺利完成复制、组装有关。

2 流感病毒感染继发的免疫损伤

流感病毒感染后病理损伤虽与病毒的持续复制相关,但并非必然关联。早前,Dawson TC 等通过基因敲除小鼠研究,发现一有趣现象:CCR5-/-小鼠染

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毒后虽病毒滴度相对正常,但肺部呈现出广泛的炎症应答反应和肺病理损伤,病死率高;而 CCR2-/-小鼠肺部病毒载量明显升高,但肺部浸润及肺损伤程度低,病死率反减低[8]。2009H1N1 流感大流行高死亡率主要发生在健康的大龄儿童和年轻成人,且在疾病早期,体内 IL-1、IL-12、IFN-γ、IL-6、TNF-α、IL-5、IL-10、IL-17 等细胞因子血清浓度均明显上升[9-10],再次证实产生了宿主免疫应答过度介导的病理损伤。

2.1 天然免疫的激活 天然免疫系统通过相应的模式识别受体(Pattern Recognition Receptors,PRRs)识别病原微生物,激活机体的免疫应答,是机体抵御病原微生物入侵的第一道防线,在病毒感染后率先发挥非特异性防护作用。天然免疫的激活主要通过 3 种 PRRs 途径:RIG-1(Retinoic Acid Inducible Gene I)样受体(RLR)途径、Toll 样受体(TLR)途径、NOD 样受体(NLR)途径。宿主细胞识别流感病毒核酸的 TLRs 主要为 TLR3 和 TLR7/8[11]。其中 TLR3 主要识别病毒 RNA,活化转录因子 IRF3(IFN Regulatory Factor 3,IRF3)、AP1(Activator Protein 1,AP1)和 NF-κB 的 p50/p65,激活干扰素介导的天然免疫应答[12]。TLR7 识别流感病毒的 ssRNA,激活 MyD88(myeloiddifferentiation factor88)依赖的信号通路,活化 IRF7,诱导产生 I 型干扰素和炎性因子,介导中性粒细胞的激活,同时也激活转录因子 NF-κB 信号通路,诱导干扰素等多种炎性因子的表达[13]。流感病毒 RNA 同时可以会被 RIG-I 识别,继而激活转录因子 IRF3、IRF7 和 NF-κB,进而诱导干扰素和细胞因子的表达,抵抗病毒的感染[14]。此外,NLR 可以识别流感病毒 RNA,活化 DCs(dendritic cells)和巨噬细胞中的 NLRP3 炎性复合体,通过 caspase-1 促进 IL-1β 和 IL-18 的活化,放大炎性反应,参与机体抗病毒免疫[15]。

2.2 细胞因子风暴介导的免疫损伤 流感病毒感染初期,病毒诱导天然免疫系统产生大量促炎性反应细胞因子参与机体免疫应答。无论是 1918 年的流感大流行还是 H5N1、H7N9 禽流感病毒均可引起以炎性反应细胞因子过度表达及功能失调为特点的“细胞因子风暴”的出现[16-17]。早前 Julkunen I 等的研究即发现甲型流感病毒感染后可以在呼吸道上皮细胞和白细胞中复制,在转录翻译水平上调控宿主细胞内 NF-κB,AP-1,STAT 和 IRF 信号通路,激活 caspase-1 酶,下调细胞凋亡通路,最终导致 RANTES、MIP-1α、MCP-1、MCP-3、IP-10、IL-1β、IL-6、IL-18、TNF-α、IFN-α/β 等的过度表达[18],且 IFN-α、TNF-α、IL-1α/β、IL-6、IL-8 等于疾病的严重程度相关[19]。这些细胞因子会加重病情,引发严重的呼吸道功能失调及致死性的肺部病理损伤。

I 型干扰素信号通路在病毒控制和病理损伤中有着双刃剑的作用。既往多项研究表明,I 型干扰素在抑制流感病毒的复制、播散中发挥重要作用[20],IFNAR1-/-小鼠感染流感病毒后肺部中性粒细胞浸润增加,病死率升高[21]。同时,多促炎因子和趋化因子亦可通过 I 型干扰素信号通路放大,诱导肺病理性损伤[21]。II 型干扰素,即 IFN-γ,在流感病毒感染的整个过程中均产生。感染早期 IFN-γ(感染 3 d 内)主要有巨噬细胞和自然杀伤细胞产生,感染后期(感染 5 ~ 10 d)主要由肺和次级淋巴结中的抗病毒 CD4 和 CD8 T 细胞产生。保护性记忆 CD4 T 细胞应答与病毒感染后肺部分泌 IFN-γ 的 CD4 T 细胞的水平直接相关[22]。IFN-γ 参与控制病毒感染和免疫调节。在流感早期给予 IFN-γ 干扰素可以增强机体的抗病毒能力,有保护性作用[23]。然该细胞因子对于病毒的有效清除及免疫应答的有效激发并非必需[24]。IFN-γ,即 III 型干扰素,是 2003 年新发现的一种类似于 I 型干扰素的信号通路,流感病毒感染后的体外培养的呼吸道上皮细胞和鼠肺中均检测到[25]。与 IFN-γ 不同,IFN-γ 并不依赖与 I 型干扰素信号的诱导,在 I 型干扰素信号缺失的情况下,流感病毒感染小鼠仍表现出有效的保护作用[26]。

众多研究表明流感中症患者中 TNF-α、IL-1、IL-6 水平明显升高,且有强有力的证据表明 TNF-α、IL-1 升高的程度与病情严重程度相关。然由 IL-1R、TNF-α、IL-6 介导的信号通路并非百害无利,更准确的说是有着介导宿主保护作用和免疫损伤中双重作用。IL-1R-/-小鼠肺部中性粒的募集减少,炎性病理损伤减轻,但是抗病毒 IgM 抗体水平同时降低,病毒清除延迟,病死率增加[27]。TNF-α 水平增高与高致病性流感病毒的发病和病死率相关。但有意思的是,接受抗 TNF-α 中和抗体治疗的小鼠炎性反应细胞募集、T 细胞因子产量降低,病死率降低[28];而在 TNFR-/-小鼠中病死率并无统计学意义[29]。TNFR 和 IL-1R 基因双阴性的小鼠的病死率显著降低,肺中细胞因子/趋化因子水平明显、中性粒细胞和巨噬细胞明显减少[30]。IL-6 水平与流感病理损伤呈现出强相关性,但是 IL-6 基因敲除后并未改变小鼠病死率[30]。相反,IL-6 信号缺如后,小鼠肺病理损伤加重、病毒滴度升高,肺部中性粒减少[31]。同时,IL-

6R 介导的信号通路为 CD4Th 细胞的产生、B 细胞和中和抗体应答所必须,这种免疫刺激抗病毒特性也许能解释为什么 IL-6 缺陷小鼠较高的肺病毒滴度和病死率。

除了细胞因子外,流感病毒感染还可诱导产生多种趋化因子,如 MCP-1(CCL2)、IL-10(CXCL10)、RANTES(CCL5)、IL-8 等,其升高水平在高致病力的毒株中更明显[32]。这些趋化因子与致死型流感病毒感染和病理损伤之间有一定联系,但这种联系目前尚未得到充分证实。

此外宿主免疫系统还产生多种抑炎因子来避免过度有害的免疫病理损伤。TGF-β 是一个被广泛研究的调节因子。TGF-β 在流感病毒感染小鼠中升高。早期有研究表明流感病毒 NA 蛋白可以将 TGF-β 有非活化形式转化为活化形式。但是高致病性 H5N1 流感病毒却无法活化 TGF-β,用腺病毒载体外源性转入活化的 TGF-β 后,H5N1 感染小鼠的病毒载量和死亡率降低,而中和 TGF-β 后,小鼠死亡率增加[33],可见 TGF-β 是一个保护性因子。此外,外周血 TGF-β 水平还是区别 A(H1N1)pdm09 与其他感染的一个很好的指标[34]。IL-10 通过调控 JAK-STAT 信号轴调节病原体感染后促炎免疫应答与抑炎免疫应答的平衡[35]。流感重症患者 IL-10 水平明显升高,这种上调可能是机体试图防止高细胞因子血症导致的炎性反应的一种保护性应答[36]。

2.3 固有免疫细胞介导的免疫损伤 流感病毒感染后引起单核/巨噬细胞、中性粒细胞向肺部的募集[37]。尽管募集的单核细胞/巨噬细胞在早期相当于为流感病毒的复制提供了一个储存器[38],但这一复制过程并不能有效进行,亦少有感染性病毒颗粒释放。大量研究表明,巨噬细胞、中性粒细胞在控制病毒复制和加剧细胞因子风暴中均发挥主要作用。用中和抗体清除巨噬细胞或中性粒细胞的小鼠感染 1918H1N1 流感病毒后体内细胞因子和趋化因子明显降低,但病毒感染失控,病死率增加;而在感染后 3 ~ 5 d 时清除巨噬细胞或中性粒细胞则对预后无明显影响[40]。此外,肺部定居的肺泡巨噬细胞(AMs)亦对病毒的控制有着重要作用[39]。肺泡巨噬细胞缺失小鼠的气道病毒复制增加,肺损伤加重[40]。BrandesM 等的研究表明通过减少而非完全消除中性粒应答的方法可以改善存活率[41]。

DCs 对流感病病毒易感,是专职抗原递呈细胞,在调节宿主固有免疫和适应性免疫起着关键作用。DCs 分泌 I 型 IFN 参与固有免疫应答,同时向 T 细胞呈递抗原,激活适应性免疫应答。不同 DCs 亚群诱导 T 细胞的能力不同,不同的流感病毒株激活的 DCs 呈递反应也存在差异[42]。在高致病性流感病毒株感染模型中检测到 TipDCs(TNF-α and Nitric Oxide Producing DCs)亚群[43],该亚群在病毒特异性 CD8T 细胞应答中至关重要,TipDCs 清除后会导致病毒复制失控。另一研究则显示[8],CCR2 + 单核细胞源性 DCs 在肺部聚集会加重肺损伤、小鼠染毒后发病和病死率增加;CCR2-/-小鼠肺部 CCR2 + 单核细胞源性 DCs 减少,小鼠发病率和病死率均降低。

3 结语

综上所述,流感病毒感染后宿主的免疫应答反应是多靶点、多条信号通路共同激活的、错综复杂的反应。虽然天然免疫在病毒感染早期可以做出一系列有利于机体及时有效的控制病毒感染的保护反应,然又同时具有双面性,任何一种应答因素多强都会导致严重的免疫病例损伤。现今的以调节宿主免疫应答的为靶点的研究多是试图通过抑制过度炎性反应,帮助机体抵御炎症损伤,却往往影响病毒的有效控制。我们期待的最理想的结果是能找到一种既能有效控制病毒复制、播散,又不诱导过度的炎症应答的药物,使免疫应答回归至稳态。

参考文献

[1] To KK, Hung F, Li IW, et al. Delayed clearance of viral load and marked cytokine activation in severe cases of pandemic H1 N1 2009 influenza virus infection[J]. Clin Infect Dis, 2010, 50(6): 850-859.

[2] de Jong M D, Simmons C P, Thanh T T, et al. Fatal outcome ofhuman influenza A(H5N1) is associated with high viral load andhypercytokinemia[J]. Nat Med, 2006, 12(10): 1203-1207.

[3] Neumann G, Kawaoka Y. Host range restriction and pathogenicity in the context of influenza pandemic[J]. Emerg Infect Dis, 2006, 12(6): 881-886.

[4] Lipatov A S, Andreansky S, Webby R J, et al. Pathogenesis ofHong Kong H5N1 influenza virus NS gene reassortants in mice: therole of cytokines and B-and T-cell responses[J]. J Gen Virol, 2005, 86(Pt 4): 1121-1130.

[5] Dai X, Zhang L, Hong T. Host cellular signaling inducedby influenza virus[J]. Sci China Life Sci, 2011, 54: 68-74.

[6] Hayden MS, Ghosh S. NF-kappaB, the first quarter-century: remarkable progress and outstanding questions[J]. GenesDev, 2012, 26: 203-234.

[7] Jackson D, Killip MJ, Galloway CS, et al. Loss of function ofthe influenza A virus NS1 protein promotes apoptosis but this is not due to a failure to activate phosphatidylinositol 3-kinase(PI3K)[J]. Virology, 2010, 396: 94-105.

[8] Dawson TC, Beck MA, Kuziel WA, et al. Contrasting effects of CCR5and CCR2 deficiency in the pulmonary inflammatory response to influenza A virus[J]. Am JPathol,2010,156:1951-1959.

[9] Rothberg MB, Haessler SD. Complications of seasonal and pandemic influenza[J]. Crit Care Med,2010,38(4Suppl):e91-e97.

[10] Lee, N., Chan, P. K., Wong, C. K., et al. Viral clearance andinflammatory response patterns in adults hospitalized for pandemic 2009influenza A(H1N1) virus pneumonia[J]. AntivirTher,2011,16(2):237-247.

[11] Sandra N. Lester and Kui Li. Toll-like receptors in antiviral innate immunity[J]. J Mol Biol,2014,426(6):1246-1264.

[12] Kawai T, Akira S. Antiviral signaling through pattern recognition receptors[J]. J Biochem,2007,141(2):137-145.

[13] Wan Q, Wang H, Han X, et al. Baicalin inhibits TLR7/MYD88 signaling pathway activation to suppress lung inflammation in mice infected with influenza A virus[J]. Biomed Rep, 2014, 2(3):437-441.

[14] Koyama S, Ishii KJ, Kumar H, et al. Differential role of TLR-and RLR-signaling in the immune responses to influenza A virus infection and vaccination[J]. J Immunol,2007,179(7):4711-4720.

[15] Pang IK, Iwasaki A. Inflammasomes as mediators ofimmunity against influenza virus[J]. Trends Immunol,2011,32:34-41.

[16] Cheung CY, Poon LL, Lau AS, et al. IInduction of proinflammatory cytokines in human macrophages by influenza A(H5N1) viruses: a mechanism for the unusual severity of human disease? [J] Lancet, 2002,360(9348):1831-1837.

[17] Wang Z, Zhang A, Wan Y, et al. Early hypercytokinemia is associated with interferon-induced transmembrane protein-3 dysfunction and predictive of fatal H7N9 infection[J]. ProcNatlAcadSci U S A., 2014,111(2):769-774.

[18] Julkunen I, Sareneva T, Pirhonen J, et al. Molecular pathogenesis of influenza A virus infection and virus-induced regulation of cytokine gene expression[J]. Cytokine Growth Factor Rev, 2001, 12(2-3): 171-180.

[19] Kristien, Van Reeth. Cytokines in the pathogenesis of influenza[J]. Veterinary Microbiology,2000:109-116.

[20] Arimori Y, Nakamura R, Yamada H, et al. Type I interferon plays opposing roles in cytotoxicity and interferon-γ production by natural killer and CD8 T cells after influenza A virus infection in mice[J]. J Innate Immun,2014,6(4):456-466.

[21] Seo SU, Kwon HJ, Ko HJ, et al. Type Iinterferon signaling regulates Ly6C(hi) monocytes and neutrophils during acute viralpneumonia in mice[J]. PLoS Pathog,2011,7:e1001304.

[22] McKinstry KK, Strutt TM, Kuang Y, et al. Memory CD4$^+$ T cells protect against influenza through multiple synergizing mechanisms[J]. J Clin Invest,2012,122(8):2847-2856.

[23] Weiss ID, Wald O, Wald H, et al. IFN-gamma treatment at early stages of influenza virus infection protects mice from death in a NK cell-dependent manner[J]. J Interferon Cytokine Res,2010,30(6):439-449.

[24] Nguyen HH, van Ginkel FW, Vu HL, et al. Gammainterferon is not required for mucosal cytotoxic T-lymphocyte responses or heterosubtypicimmunity to influenza A virus infection in mice[J]. J Virol, 2000,74(12):5495-5501.

[25] StefaniaCrotta, Sophia Davidson, TanelMahlakoiv, et al. Type I and type III interferons drive redundant amplification loops to induce a transcriptional signature in influenza-infected airway epithelia[J]. PLoSPathog,2013,9(11):e1003773.

[26] Jewell NA, Cline T, Mertz SE, etal. Lambda interferon is the predominant interferon induced byinfluenza A virus infection in vivo[J]. J Virol,2010,84(21):11515-11522.

[27] Schmitz N, Kurrer M, Bachmann MF, Kopf M. Interleukin-1 is responsible for acute lung immunopathology but increases survival of respiratory influenza virus infection[J]. J Virol, 2005, 79(10): 6441-6448.

[28] Hussell T, Pennycook A, Openshaw PJ. Inhibition of tumor necrosis factor reduces the severity of virus-specific lung immunopathology [J]. Eur J Immunol,2001,31(9):2566-2573.

[29] Salomon R, Hoffmann E, Webster RG. Inhibition of the cytokine response does not protect against lethal H5N1 influenza infection[J]. Proc Nat AcadSci U. S. A., 2007, 104(30):12479-12481.

[30] Perrone LA, Szretter KJ, Katz JM, et al. Mice lacking both TNF and IL-1 receptors exhibit reduced lung inflammation and delay in onset of death following infection with a highly virulent H5N1 virus[J]. J Infect Dis,2010,202(8):1161-1170.

[31] Dienz O, Rud JG, Eaton SM, et al. Essential role of IL-6 in protection against H1N1 influenza virus by promoting neutrophil survival in the lung[J]. Mucosal Immunol,2012,5(3):258-266.

[32] de Jong MD, Simmons CP, Thanh TT, et al. Fatal outcome of human influenza A(H5N1) is associatedwith high viral load and hypercytokinemia[J]. Nat Med,2006,12(10):1203-1207.

[33] Carlson CM, Turpin EA, Moser LA, et al. Transforming growth factor-beta: activation by neuraminidase and role in highly pathogenic H5N1 influenza pathogenesis[J]. PLoS Pathog,2010,6:e1001136.

[34] Rendón-Ramirez Erick J., Ortiz-Stern Alejandro, Martinez-Mejia Corazon, et al. TGF-β Blood Levels Distinguish Between Influenza A (H1N1) pdm09 Virus Sepsis and Sepsis due to Other Forms of Community-Acquired Pneumonia[J]. Viral Immunology, 2015, 28(5): 248-254.

[35] Carey AJ, Tan CK, Ulett GC. Infection-induced IL-10 and JAK-STAT: A review of the molecular circuitry controlling immune hyperactivity in response to pathogenic microbes[J]. JAKSTAT, 2012, 1(3):159-167.

(下接第 1482 页)

role in disease, and therapeutics[J]. Nat Med, 2015, 21(7): 677-687.

[5] Watanabe H, Gehrke S, Contassot E, et al. Danger signaling through the inflammasome acts as a master switch between tolerance and sensitization[J]. J Immunol, 2008, 180(9): 5826-5832.

[6] I-Yin Chen, Takeshi Ichinohe. Response of host inflammasomes to viral infection[J]. Trends mcrobiol, 2015, 23(1): 55-63.

[7] Broderick L, de Nardo D, Franklin BS, et al. The inflammasome and autoinflammatorysyndromes[J]. Annu Rev Pathol, 2015, 10: 395-424.

[8] Wu Y, Ren J, Zhou B, et al. Gene silencing of non-obese diabetic receptor family (NLRP3) protects against the sepsis-induced hyper-bile acidaemia in a rat model[J]. Clin ExpImmunol, 2015, 179(2): 277-293.

[9] 李青, 汪昌宁, 宋亚玲. NALP3 炎性体与相关疾病的研究进展[J]. 牙体牙髓牙周病学杂志, 2011, 21(6): 355-359.

[10] Negash AA, Ramos HJ, Crochet N, et al. IL-1beta production through the NLRP3 inflammasome by hepatic macrophages links hepatitis C virus infection with liver inflammation and disease[J]. PLoSPathog, 2013, 9: e1003330.

[11] Kanneganti TD, Body-Malapel M, Amer A, et al. Critical role for cryopyrin/Nalp3 in activation of caspase-1 in response to viral infection and double-stranded RNA[J]. J. Biol. Chem, 2006, 281(48): 36560-36568.

[12] Ichinohe T, Lee HK, Ogura Y, et al. Inflammasome recognition of influenza virus is essential for adaptive immune responses[J]. J. Exp. Med, 2009, 206(1): 79-87.

[13] Thomas PG, Dash P, Aldridge JR Jr, et al. The intracellular sensor NLRP3 mediates key innate and healing responses to influenza A virus via the regulation of caspase-1[J]. Immunity, 2009, 30(4): 566-575.

[14] Allen IC, Scull MA, Moore CB, et al. The NLRP3 inflammasome mediates in vivo innate immunity to influenza A virus through recognition of viral RNA[J]. Immunity, 2009, 30(4): 556-565.

[15] McAuley JL, Tate MD, MacKenzie-Kludas CJ, et al. Activation of the NLRP3 inflammasome by IAV virulence protein PB1-F2 contributes to severe pathophysiology and disease[J]. PLoSPathog, 2013, 9(5): e1003392.

[16] Stout-Delgado HW, Vaughan SE, ShiraliAC, etal. Impaired NLRP3 inflammasome function in elderly mice during influenza infection is rescued by treatment with nigericin[J]. J Immunol, 2012, 188(6): 2815-2824.

[17] Kato H, Takeuchi O, Sato S, et al. Differential roles of MDA5 and RIG-I helicases in the recognition of RNA viruses[J]. Nature, 2006, 441(7089): 101-105.

[18] Rintahaka J, Wiik D, Kovanen PE, et al. Cytosolic antiviral RNA recognition pathway activates caspases 1 and 3[J]. J. Immunol, 2008, 180: 1749-1757.

[19] Pothlichet J, Meunier I, Davis BK, et al. Type I IFN triggers RIG-I/TLR3/NLRP3-dependent inflammasome activation in influenza A virus infected cells[J]. PLoS Pathog, 2013, 9(4): e1003256.

[20] 牛俊领, 陈明宽, 吴淑娴, 等. NLRP3 炎症小体在流感病毒感染中的作用[J]. 中国细胞生物学学报, 2015, 37(4): 547-552.

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(上接第 1479 页)

[36] Teijaro JR. The Role of Cytokine Responses DuringInfluenza Virus Pathogenesisand Potential Therapeutic Options[J]. Current Topics in Microbiology and Immunology, 2015, 386: 3-22.

[37] Perrone LA, Plowden JK, García-Sastre A, et al. H5N1 and 1918 pandemic influenza virus infection results in early and excessive infiltration of macrophages and neutrophils in the lungs of mice[J]. PLoS Pathog, 2008, 4(8): e1000115.

[38] Pang IK, Pillai PS, Iwasaki A. Efficient influenza A virus replication in the respiratory tract requires signals from TLR7 and RIG-I[J]. Proc Nat AcadSci U. S. A., 2013, 110(34): 13910-13915.

[39] Tumpey TM, Garcia-Sastre A, Taubenberger JK, et al. Pathogenicity ofinfluenza viruses with genes from the 1918 pandemic virus: functional roles of alveolarmacrophages and neutrophils in limiting virus replication and mortality in mice[J]. J Virol, 2005, 79(23): 14933-14944.

[40] Tate MD, Pickett DL, van Rooijen N, et al. Critical role of airway-macrophages in modulating disease severity during influenza virus infection of mice[J]. J Virol, 2010, 84(15): 7569-7580.

[41] Brandes M, Klauschen F, Kuchen, et al. A systems analysis identifies a feedforward inflammatory circuit leading to lethal influenza infection[J]. Cell, 2013, 154(1): 197-212.

[42] Hartmann BM, Thakar J, Albrecht RA, et al. Human Dendritic Cell Response Signatures Distinguish 1918, Pandemic, and Seasonal H1N1 Influenza Viruses[J]. J Virol, 2015, 89(20): 190-205.

[43] Aldridge JR Jr, Moseley CE, Boltz DA, et al. TNF/iNOS-producing dendritic cells are the necessary evil of lethal influenza virus infection[J]. Proc Nat AcadSci U. S. A., 2009, 106(13): 5306-5311.

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