

NF- κ B 信号通路在儿童川崎病心脏损伤中的研究进展

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[摘要] 川崎病, 又称为皮肤黏膜淋巴结综合征, 是一种全身急性血管炎性病变, 属于自身免疫性疾病。目前, 该疾病发病具体机制尚不明确, 可能涉及核因子 κ B (nuclear factor-kappa B, NF- κ B) 信号通路参与的免疫反应、炎症反应、血管内皮损伤等诸多因素。尤其是川崎病合并心脏损伤患儿预后不佳, 研究人员希望通过探索川崎病心脏损伤的具体发病机制, 为临床诊断和治疗提供新的选择, 并降低其发病率。该文就NF- κ B信号通路在儿童川崎病心脏损伤中的机制进展做一综述, 为后续研究提供理论指导。

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[关键词] 核因子- κ B; 信号通路; 川崎病; 儿童

Recent research on the nuclear factor-kappa B signaling pathway in cardiac injury in children with Kawasaki disease

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Abstract: Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is a systemic acute vasculitis belonging to autoimmune disease. Up to now, the specific pathogenesis of this disease remains unclear, and it may involve various factors such as immune response, inflammatory response, and vascular endothelial injury caused by the activation of the nuclear factor-kappa B (NF- κ B) signaling pathway. In particular, children with KD and cardiac injury tend to have a poor prognosis, and researchers hope to explore the specific pathogenesis of cardiac injury in KD to provide new options for clinical diagnosis and treatment and reduce the incidence rate of this disorder. This article reviews the recent research on the role of the NF- κ B signaling pathway in cardiac injury in children with KD, so as to provide a basis for future studies.

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Key words: Nuclear factor- κ B; Signaling pathway; Kawasaki disease; Child

1 NF- κ B 信号通路介绍

核因子 κ B (nuclear factor-kappa B, NF- κ B) 是一种转录因子, 与细胞凋亡、肿瘤发生、炎症反应及各种自身免疫性疾病有关。通常, NF- κ B 的激活被认为是应激反应的一部分, 它可被多种因素激活, 包括细菌和病毒感染、促炎细胞因子及抗原受体的参与^[1-3]。众所周知, NF- κ B 家族成员与癌蛋白 ν -Rel 有结构同源性, 因此将他们归类为 NF- κ B/Rel 蛋白。在哺乳动物中该家族有5种蛋白, 分别为: RelA (p65), RelB, c-Rel, NF- κ B1

(p50) 和 NF- κ B2 (p52), 通过结合其他分泌型蛋白质或者 DNA, 从而发挥生物学作用。NF- κ B 信号通路主要包括典型激活途径和非典型激活途径。典型激活途径能够被包括炎症因子、免疫因子及细胞分裂、增殖等相关信号所激活, 从而引起级联放大反应, 进一步影响组织或者机体的炎症反应进程, 乃至疾病的发生和发展。非典型激活途径通常由转录激活因子人类 p100 蛋白和 RelB 蛋白介导, 通过调节细胞因子的产生和释放^[4-5], 进一步参与组织或机体的炎症损伤从而影响疾病的发生和进展。

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2 NF- κ B 信号通路在川崎病心脏损伤中的作用

川崎病发病机制复杂,导致临床早期不能明确诊断而延误治疗。NF- κ B 信号通路在川崎病合并心脏损伤中可能的作用机制主要包括以下几个方面。

2.1 参与免疫激活

一般情况下,幼稚CD4⁺T细胞分化为辅助性T (T helper, Th) 1和Th2效应细胞。Th1细胞通过产生干扰素- γ (interferon- γ , IFN- γ) 来引导对细胞内病原体的防御, Th2细胞则可以直接抵抗细胞外病原微生物的入侵,并参与过敏反应。它们的共同特点是产生一系列炎性细胞因子,包括白细胞介素 (interleukin, IL) -4、IL-5、IL-6、IL-9、IL-13、IL-25等。研究发现,当NF- κ B活化减少时, Th1细胞的反应性将会降低,从而降低对病原体的杀伤作用,增加了对机体的有害刺激作用^[6-7]。此外, NF- κ B已被证实附着于IL-4位点上,并且与核因子活化的T细胞的两个增强子位点相结合,进而诱导免疫应答^[8]。通常, Th2细胞的发育由IL-4刺激后启动, IL-4刺激后触发转录激活因子6的激活,同时激活NF- κ B信号通路,形成正反馈调控。调节性T (regulatory T, Treg) 细胞功能的发挥也由NF- κ B介导,同时控制T细胞的内在活动、小鼠胸腺上皮细胞 (mouse thymic epithelial cell, mTEC) 的发育及树突状细胞的发育^[9]。NF- κ B信号通路是树突状细胞募集、稳定和促进对宿主组织的免疫耐受所必需^[10]。另外, NF- κ B亚单位RelA和cRel均被NF- κ B经典信号通路激活,通过直接调节RelB的转录共同参与mTEC的分化。研究发现,在川崎病急性期,外周血中性粒细胞、单核细胞和活化的 $\gamma\delta$ T细胞数量明显增加,表明先天性免疫反应的过度激活,同时外周血中Th17细胞增多, Treg细胞减少^[10],以上一系列因素的变化加速了川崎病的发生和发展,与NF- κ B的激活密切相关。

2.2 参与炎症反应及调控炎症因子释放

研究表明, IL-1是川崎病急性炎症期的核心,而NF- κ B信号通路参与了炎症反应的激活^[5]。在炎症反应过程中, IL-1可以直接激活冠状动脉内皮细胞,导致细胞间黏附分子表达水平上调,同时产生IL-6和IL-8^[11],在炎症因子的诱导下导致细胞死亡。NF- κ B信号通路被激活后,肿瘤坏死因

子- α (tumor necrosis factor- α , TNF- α) 和基质金属蛋白酶 (matrix metalloproteinase, MMP) 释放增多,通过激活Toll样受体4进一步促进其他相关因子的表达^[12-13]。大部分MMP转录受NF- κ B的特异性调控, NF- κ B不仅能特异性上调MMP1、MMP3、MMP9的表达,还能扩大炎症反应,进而加速病情的发展。TNF- α 、IL-1和MMP等细胞因子彼此协同在心血管系统炎症损伤过程中发挥着重要作用^[14]。其中, TNF- α 参与急性心肌炎的发病过程, IL-1可加速冠状动脉血管炎症的发生,进一步促进了川崎病心脏病变的发生和进展^[15-16]。

2.3 诱导血管内皮损伤

内皮功能障碍通常是心血管系统并发症的早期改变。内皮素,也称为内皮细胞特异性分子-1,是一种主要由内皮细胞分泌的可溶性糖蛋白,当NF- κ B信号通路被激活时,诱导产生和释放炎症因子IL-1、IL-6、IL-1 β 和TNF- α ,上述炎症因子可上调内皮素的表达,进而影响细胞间黏附分子-1 (intercellular cell adhesion molecule-1, ICAM-1) 和血管细胞黏附分子-1 (vascular cell adhesion molecule-1, VCAM-1) 的表达。ICAM-1和VCAM-1是内皮细胞上表达的黏附分子,可通过上调促炎细胞因子的表达,参与白细胞的黏附和迁移。ICAM-1增强炎症细胞和内皮细胞之间的黏附,促进内皮细胞的活化,使炎症因子更容易穿透内皮。VCAM-1是炎症过程中微血管内皮激活和动脉粥样硬化过程中动脉内皮细胞功能障碍之间的关键联系。VCAM-1可以选择性地黏附于单核白细胞和淋巴细胞,介导循环中单核细胞的招募及其黏附和迁移至血管壁,在动脉粥样硬化的发生中起重要作用,这些分子进一步促进白细胞迁移和炎症反应放大,从而导致心血管系统的损伤,进而加速了川崎病心脏病的发病过程^[17-18]。

3 展望

目前,尽管关于NF- κ B信号通路在川崎病合并心脏损伤中的研究有限, NF- κ B信号通路在川崎病合并心脏损伤中的具体致病机制将被逐渐揭示。需要广大学者做更加深入的研究,相信在不久的将来, NF- κ B因子会成为川崎病合并心脏损伤在早期诊断、预防及治疗方面的新靶点,给临床患者的治疗带来新希望。

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