

综述

丝裂原活化蛋白激酶信号通路 在寻常型银屑病发病机制中的研究进展

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摘要: 寻常型银屑病的主要组织病理学特征为表皮增殖、真皮炎症细胞浸润、新生血管生成和 Munro's 微脓肿的形成, 其机制与相关信号通路有着密切关系。丝裂原活化蛋白激酶(MAPK)信号通路的上游信号分子如 miRNA、细胞因子等的异常表达导致下游信号分子的异常激活在银屑病的发病中有着重要作用, 且有望成为新的干预靶点。本研究就 MAPK 信号通路在寻常型银屑病发病机制中的研究进展进行综述, 为药物研发、精准治疗提供参考。

关键词: 寻常型银屑病; 丝裂原活化蛋白激酶; 信号通路; 细胞因子; 发病机制

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Research progress of mitogen activated protein kinase signaling pathway in pathogenesis of psoriasis vulgaris

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Abstract: Main histopathological features of psoriasis vulgaris are epidermal proliferation, dermal inflammatory cell infiltration, neovascularization and the formation of Munro's microabscesses, and its mechanism is closely related to the related signal pathways. Abnormal expression of upstream signal molecules such as miRNA and cytokines of mitogen activated protein kinase (MAPK) signal pathway leads to abnormal activation of downstream signal molecules, which plays an important role in the pathogenesis of psoriasis, and is expected to become a new intervention target. The article reviewed the research progress of MAPK signaling pathway in the pathogenesis of psoriasis vulgaris, so as to provide reference for drug development and precision treatment.

Key words: psoriasis vulgaris; mitogen activated protein kinase; signal pathway; cytokines; pathogenesis

银屑病是常见的慢性皮肤病^[1], 不仅会导致患者生活能力降低, 而且患者大多存在精神障碍、抑郁等心理问题^[2]。银屑病病因复杂, 主要包括遗传、环境和行为因素等, 其发病机制主要为免疫细胞功能紊乱、角质形成细胞(KC)增殖分化失调等。相应的组织病理学特征为表皮增生、真皮炎症细胞浸润、新生血管生成和角质层中性粒细胞聚集(Munro's 微脓肿)^[3]。目前关于银屑病的发病机制仍需要持续探索。

丝裂原活化蛋白激酶(MAPK)家族是将细胞外信号传递至细胞核内的一组丝氨酸-苏氨酸激酶, 主要参与细胞增殖、凋亡、分化和免疫应答^[4]。这一途径被不同细胞外信号激活, 如细胞因子、神经递质、细胞应激、miRNA 等^[5], 接下来通过依次磷酸化将上游信号传递至下游应答分子调节各种细胞活动。MAPK 信号通路由细胞外信号调节激酶(ERK)、c-Jun 氨基末端激酶(JNK)、P38 丝裂原活化蛋白激酶(P38MAPK)、ERK5 等

4条亚通路组成。MAPK信号通路相关蛋白(ERK、JNK、P38)在银屑病中高表达,且分布部位有所改变。磷酸化的ERK在银屑病皮损基底层和棘层细胞内高表达,且主要表达于胞核中;而银屑病非皮损区和正常人皮肤只表达于基底层细胞的胞浆内^[6]。银屑病皮损KC核中JNK的表达增加^[7]。FUNDING A T等^[8]研究发现,P38在银屑病皮损棘层及颗粒层的胞核内表达,在患者非皮损及正常人的表皮中仅在颗粒层胞浆中表达。MAPK信号通路在银屑病组织病理形成过程中有着举足轻重的作用,目前ERK5作用尚不明了,以下对ERK、JNK、P38等3条MAPK的分支通路在银屑病中的作用进行论述。

1 角质形成细胞的增殖、分化与凋亡

1.1 ERK信号通路

ERK信号通路与银屑病KC异常生物学行为有密切关系。首先,在寻常型银屑病的发展过程中,多种因素可以激活ERK通路。有研究^[9-10]表明皮损中低表达的miRNA与靶基因结合可以激活ERK通路,如miR-876-5p与血管生成素-1(Ang-1)靶向结合、miR-215-5p靶向调控DYRK1A。银屑病中高表达的LncRNA RP6-65G23.1和抗癌素M均可以激活ERK通路^[11-12],从而促进KC增殖且抑制凋亡。此外,ERK通路激活后,还可以促进KC分化。研究^[13-14]发现银屑病中过表达Lin28a可下调miR-let-7的表达水平,miR-let-7b通过靶向IL-6介导的ERK信号通路使分化标记物K10蛋白表达增加,从而使KC分化受损。

其他研究^[15-17]发现,银屑病中ERK通道激活后,皮损中ETS癌基因家族成员1(ELK-1)、FOS样蛋白抗原1、c-jun、AP-1、细胞周期蛋白D1(cyclin D1)的表达升高,促进KC的增殖。磷酸化ERK激活核内E26转化特异性转录因子(ETS),其结构域包含ELK1、ELK3和ELK4蛋白。一方面ETS蛋白作为一组进化相关的DNA结合转录因子,通过与特定的启动子和增强子结合促进基因表达^[18]。另一方面ETS磷酸化可诱导编码转录因子的JUN和FOS家族,两者不仅形成不同的AP-1二聚体识别基因上游的应答元件促进KC增殖;同时JUN和FOS家族又可促进cyclin D1表达,驱动KC从G₁期向S期过渡^[19]。此外,ERK通路激活后,凋亡标志物Bax、Livin表达降低,抗凋亡标志物Bcl2表达升高,促凋亡蛋白

和抗凋亡蛋白比例失衡,抑制KC的程序化凋亡^[20]。

1.2 JNK信号通路

银屑病中JNK通路被激活,进而诱导KC异常增殖与分化。WANG Y等^[21]研究表明在银屑病KC中miR-320b下调,靶向sox9、AKT3,正向调控SAPK/JNK信号通路,从而促进KC增殖。研究^[22]表明银屑病中IL-22通过激活JNK信号通路降低缝隙连接细胞间通讯和Cx43的表达,促进KC增殖。RIZALDY D等^[23]发现银屑病患者Th2细胞因子(IL-4、IL-13和IL-31)和Th17细胞因子(IL-17A和IL-22)可通过激活JNK信号通路刺激KC中纤毛生成和IFT88活性增加,损害KC分化。

1.3 其他

银屑病中的某些细胞外因子可同时激活多条通路而影响KC。JIANG M等^[24]研究发现血管内皮生长因子(VEGF)在银屑病患者中显著升高,激活ERK和P38通路,上调K6、K16和K17,从而促进KC增殖和迁移。ERK通路激活后,降低K1和K10使KC不完全分化。IL-22可以使JNK、ERK和P38的磷酸化水平增加,从而诱导KC增殖^[25]。

2 免疫炎症反应

2.1 ERK与JNK信号通路

在银屑病中,IL-17和IL-23的分泌是协调局部组织炎症的关键介质^[3]。CHEN H L等^[26]研究发现银屑病皮损中半乳糖凝集素-7(Galectin-7)降低。Galectin-7通过KC中的miR-146a/ERK通路减弱IL-17A和IL-17A诱导的IL-6和IL-8的产生。有研究^[27]表明在银屑病中,f富含半胱氨酸血管生成诱导因子61(CYR61/CCN1)表达增加,激活JNK/AP-1通路,诱导KC产生CCL20,CCL20作用于CCR6,IL-17表达增加。另外NOVOSZEL P等^[17]发现树突状细胞(DC)中c-Jun/AP-1是DC诱导toll样受体7(TLR7)免疫应答的核心驱动因子,TLR7可以激活c-Jun/AP-1,从而正向调控CCL2和IL-23的表达,促进银屑病皮肤炎症。

2.2 P38信号通路

在银屑病的发展过程中,P38 MAPK信号通路被炎症介质激活同时可以诱导炎症介质的表达。①皮肤中P38 MAPK的激活参与了IL-17依赖的银屑病发病机制。研究^[28-29]表明IL-17A通过激活P38 MAPK促进IL-19、IL-20、IL-36 γ 的产

生; IL-17A、IL-17F 通过激活 P38MAPK 信号通路, I κ B ζ (NFKBIZ 基因编码) 表达升高, 而 I κ B ζ 是银屑病相关基因 CCL20、 β -防御素 (DEFB4)、IL-8、壳多糖酶 3 样蛋白 1 (CHI3L1) 的关键调控因子^[30-31]。朗格汉斯细胞中 P38 激活后, 通过增加 IL-23 和 IL-6 特异性地促进 IL-17 的产生^[32]。

② TNF- α 也参与了 P38 MAPK 的激活。P38 蛋白酶的激活介导 TNF- α 诱导的 EGFR 磷酸化, p-EGFR 可以激活 ERK 通路, 从而诱导 TSLP 的产生^[33]。TNF- α 诱导蛋白 (TNFAIP) 家族是由 TNF- α 诱导产生的一组蛋白质, 主要参与免疫稳态的调节过程, 银屑病中 TNFAIP3 下调与 P38 活化相关^[34]。③ P38 通路的激活也与 KC 中其他因子有关。KC 外泌体激活 P38 通路促使中性粒细胞产生 IL-6、IL-8 和 TNF- α ^[35]。抗菌蛋白 S100A7 已被发现在银屑病皮损中高表达, 随后激活 P38 MAPK 通路, 诱导 KC 中成熟 IL-1 α 表达^[36]。CYR61/CCN1 通过激活 P38 信号通路促进银屑病 KC 中 IL-1 β 、CCL20 的产生^[27, 37]。

3 血管增生

新生血管增多作为银屑病的病理特征之一, 主要与银屑病血浆和皮损组织中增多的血管生成因子水平升高有关, 如 VEGF、碱性成纤维细胞生长因子 (bFGF)、Ang-1、Ang-2^[38]。XUE Y D 等^[39] 研究发现银屑病皮肤组织中 miR-205-5p 的表达水平降低, 在体内外的研究发现其靶向 Ang-2、VEGF, 激活 P38 和 ERK 信号通路, 促进表皮增生和血管生成。

4 Munro's 微脓肿形成

WU P 等^[40] 研究表明银屑病患者皮损中 IL-8 显著升高, IL-8 作为中性粒细胞的趋化剂, 可以趋化中性粒细胞进入角质层, 进而形成 Munro's 微脓肿^[41-42]。研究^[40] 发现银屑病中有多种途径可以促进 IL-8 的增加, 如 CYR61/CCN1 通过 JNK/NF- κ B 通路促进 KC 产生 IL-8; 半乳糖凝集素-3 (Galectin-3) 在银屑病皮损中表达降低, 通过 JNK 通路高表达 IL-8^[41]; IL-17E 刺激巨噬细胞后, 激活 P38 通路, 产生 IL-8^[42]。

综上所述, MAPK 信号通路与寻常型银屑病有着千丝万缕的联系。首先 miRNA、细胞因子、半乳糖凝集素等可以激活 MAPK 信号通路, 而 MAPK 信号通路的激活可诱导银屑病 KC 异常增殖分化、促进免疫应答、新生血管以及 Munro's 微

脓肿的形成。MAPK 信号通路作为银屑病发病机制的交叉点, 在治疗方面针对其靶点的抑制剂呼之欲出。目前大量试验证明抑制 MAPK 通路可以显著改善银屑病的症状。ERK 抑制剂 JS1287 能够降低咪喹莫特诱导的小鼠表皮厚度, 减轻其表皮充血水肿和炎症细胞浸润^[43]。P38 抑制剂 BIRB796 局部治疗可能会防止银屑病皮肤的进一步发展, P38 抑制剂 ATI-450 现在处于银屑病的临床前研究阶段^[44]。在现阶段基础上仍需大量的临床前期研究及临床研究, 以提高对 MAPK 通路抑制剂的认知, 完善 MAPK 信号通道在银屑病治疗中的作用, 为临床治疗提供新的思路。

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