

doi: 10.13241/j.cnki.pmb.2017.05.045

MAPKs 信号通路在动脉粥样硬化发生发展中的调控作用*

张云¹ 旦菊花² 孙鑫¹ 许浩博¹ 陈海波¹ 姚建挺¹ 田野^{1,2Δ}

(1 哈尔滨医科大学附属第一医院 黑龙江 哈尔滨 150001; 2 哈尔滨医科大学病理生理室 黑龙江 哈尔滨 150081)

摘要: 丝裂原激活蛋白激酶(mitogen-activated protein kinases, MAPKs)信号通路是生物体内重要的信号传导通路,其主要参与调控细胞的增殖、生长、分化、凋亡和炎症反应等多种生理病理过程。MAPKs 信号通路在多种心血管疾病的病理过程中起着重要调控作用。动脉粥样硬化(athrosclerosis, AS)所致的各种急重症严重危害人类的健康,发病率呈逐年上升的趋势,但是动脉粥样硬化发生发展的分子机制尚不完全清楚。近年来,MAPKs 信号通路在动脉粥样硬化(athrosclerosis, AS)的发生发展中的作用已成为是研究的热点。

关键词: 丝裂原激活蛋白激酶; MAPKs 信号通路; 动脉粥样硬化; 炎症反应

中图分类号: R543.5 **文献标识码:** A **文章编号:** 1673-6273(2017)05-968-03

MAPKs Signal Transduction Pathways in the Development of Athrosclerosis*

ZHANG Yun¹, DAN Ju-hua², SUN Xin¹, XU Hao-bo¹, CHEN Hai-bo¹, YAO Jian-ting¹, TIAN Ye^{1,2Δ}

(1 the First Affiliated Hospital of Harbin Medical University, Heilongjiang, Harbin, 150001, China;

2 Division of Pathophysiology, Harbin Medical University, Heilongjiang, Harbin, 150081, China)

ABSTRACT: Mitogen-activated protein kinase (MAPK) signal transduction pathways are ubiquitous and highly evolutionarily conserved mechanisms of eukaryotic cell regulation, controlling essential processes in all eukaryotic cells, including cell proliferation, development, differentiation, apoptosis and inflammation reaction. MAPK signaling cascades likely play an important role in the pathogenesis of cardiac and vascular disease. Atherosclerosis is a chronic disease of the arterial wall, and a leading cause of death and loss of productive life years worldwide, while its molecular mechanism of development is unclear. Recently, more attention is paid to its functions in the atherosclerotic development.

Key words: Mitogen-activated protein kinases(MAPKs); MAPKs signal transduction pathways; Atherosclerosis; Inflammation

Chinese Library Classification(CLC): R543.5 **Document code:** A

Article ID: 1673-6273(2017)05-698-03

动脉粥样硬化(Atherosclerosis, AS)发病机制的研究一直是当前的热点,近年来多项研究表明血管内皮细胞、巨噬细胞/泡沫细胞、血管平滑肌细胞等共同参与了 AS 的发生发展过程,但其相关分子机制仍待进一步研究^[1]。丝裂原激活蛋白激酶(mitogen-activated protein kinases, MAPKs)信号通路作为生物体内重要的细胞内信号传导通路,调节着细胞的生长发育、增殖、分化及凋亡等基本生命活动^[2]。MAPKs 信号通路转导级联反应对动脉粥样硬化、心肌肥厚、再狭窄等多种心血管疾病的发病过程具有重要的调控作用^[3]。本篇综述将从 MAPKs 信号通路对动脉粥样硬化斑块中的内皮细胞,巨噬细胞/泡沫细胞和平滑肌细胞的调控来阐述其在动脉粥样硬化发生发展过程中的作用。

1 MAPKs 信号通路

MAPKs 信号通路普遍存在于哺乳动物细胞中,主要有 MAPKKK、MAPKK 和 MAPK 三类保守的蛋白激酶组成,细胞外信号与细胞膜上相应的受体结合后,激活 MAPKs 信号通路

的三级酶联反应 MAPKKK/MAPKK/MAPK,通过活化不同类型的 MAPKs 并激活其相应的下游应答分子,调控各种细胞应答^[4]。MAPKs 是一组丝/苏氨酸蛋白激酶,其家族成员主要分为传统型和非传统型,传统型 MAPKs 由细胞外信号调节蛋白激酶(ERK1/2)、c-JUN 氨基酸末端蛋白激酶(JNK)、p38 和 ERK5 组成,而非传统型 MAPKs 则包括 ERK3/4、ERK7 和尼莫样蛋白激酶(NLK)组成^[5]。目前,研究最多的 MAPKs 通路有 MAPKKK/MAPKK/ERK1/2、MAPKKK/MAPKK/p38 和 MAPKKK/MAPKK/JNK,ERK1/2 主要参与调节细胞的增殖和分化,而 p38 和 JNK 则与细胞的炎症反应及凋亡的调节密切相关^[6]。在生理情况下,激素、生长因子、细胞因子等不同的细胞外刺激可激活不同的 MAPKs 家族成员,通路间通过相互“对话”而共同调节其下游的相关蛋白激酶和转录因子,最终精确完成细胞的各种生理活动,包括基因转录,蛋白的生物合成、细胞周期的调控、凋亡和分化等细胞活动过程^[7-10]。MAPKs 信号通路在正常的生理活动和许多炎症性疾病中发挥中至关重要的调控作用。在动脉粥样硬化的病理过程中,MAPKs 信号通路的异常

* 基金项目:国家自然科学基金项目(81371709)

作者简介:张云(1988-),女,硕士研究生,研究方向:动脉粥样硬化, E-mail: kbxbd126@126.com

Δ 通讯作者:田野, E-mail: yetian@ems.hrbmu.edu.cn

(收稿日期:2016-04-01 接受日期:2016-04-24)

激活与斑块内的炎症反应、表型转换、病理性增殖和凋亡等病理反应密切相关^[11,12]。

2 MAPKs 信号通路参与血管内皮细胞的损伤

血管内皮损伤是动脉粥样硬化的重要环节之一,损伤学说认为:高血压、氧化低密度脂蛋白和吸烟等危险因素导致动脉内膜内皮损伤,触发动脉粥样硬化的发生^[13]。在体和离体实验均表明,湍流可触发内皮细胞炎症反应和表型转换等^[14,15]。Berk BC 等^[16]研究表明,层流可以激活内皮细胞的 ERK5 通路从而减少内皮细胞炎症及凋亡,同时抑制 JNK 激活而减少 TNF 等炎症因子介导的细胞凋亡与炎症反应,进而起到了保护内皮细胞的作用,此外,血流时间梯度变化可以通过激活 ERK1/2 及其下游应答分子而使内皮细胞增殖。

Schieven GL 和 Wang W-Y 等研究表明,血管内皮细胞在低密度脂蛋白及 TNF α 等炎症介质的作用下,可通过激活 p38 而促进炎症因子的释放和趋化炎症细胞,加重炎症反应^[17,18],且 JNK 的激活与低密度脂蛋白诱导的内皮细胞的炎症与凋亡反应密切相关^[19]。此外,尼古丁可通过激活内皮细胞的 P38 及其相关下游信号通路,增加 ICAM-1 和 VCAM-1 等细胞粘附因子的表达水平,进而趋化炎症细胞聚集,促进动脉粥样硬化斑块的发生发展^[20,21]。因此,MAPKs 信号通路参与了多种外界刺激因素引起血管内皮细胞的炎症损伤,整合并调控着内皮细胞的各种生物学反应。

3 MAPKs 信号通路的调控巨噬细胞向泡沫细胞的转化

在动脉粥样硬化发生早期阶段,泡沫细胞的形成是其重要步骤之一。MAPKs 信号通路在泡沫细胞形成过程中的作用近来有不少相关的文献报道。动物实验研究表明,泡沫细胞的形成依赖于 JNK2 的激活,此外 p38 α 的激活也可能是其中重要的影响因素之一^[3,22,23]。同时细胞实验表明,氧化低密度脂蛋白孵育的巨噬细胞 JNK, p38 α 和 ERK 都迅速被激活,且孵以 JNK 抑制剂或 p38 α 抑制剂之后,同样以氧化低密度脂蛋白孵育,巨噬细胞未被成功诱导形成泡沫细胞^[23,24]。另外,Mei S 等^[25]研究表明, p38 的激活通过抑制细胞的自噬作用进而促进胆固醇酯化和泡沫细胞的形成。目前还不清楚氧化低密度脂蛋白介导激活的 JNK2 是否是通过内吞作用直接调控巨噬细胞对氧化低密度脂蛋白的摄入,可能激活的 JNK2 可以促进结合于细胞表面受体的氧化低密度脂蛋白内吞作用的相关蛋白的表达和活化水平。

4 MAPKs 信号通路调控血管平滑肌细胞的表型转换和炎症反应

血管平滑肌细胞的表型转换、增殖迁移和炎症应激等在动脉粥样硬化的过程中起着重要的作用^[26-28]。细胞研究表明,不饱和脂蛋白刺激信号可通过 PI3K / PKB(Atk)和 p38/MAPK 两个途径转导,共同调控血管平滑肌细胞的表型转换参与动脉粥样硬化的进展^[29]。生长因子可以激活 ERK1/2 和 p38,并分别抑制血管平滑肌细胞收缩表型基因(SM α -actin, SM-MHC 和 SM22 α)的表达和促进合成表型基因的表达,使动脉粥样硬化过程中

血管平滑肌细胞完成表型转换。动物实验表明,球囊拉伤大鼠颈动脉后,发现 ERK1/2, JNK1/2 和 p38 α 的激活均可促进内膜增生和血管平滑肌细胞的增殖,并通过基因敲除鼠进一步证实 ERK1/2, JNK1/2 和 p38 α 活性的降低与动脉粥样硬化斑块的形成减少密切相关^[30]。

同时,也有研究表明, Ras / Raf / MAPK(ERK/p38)信号转导通路的激活是多种炎症介质、细胞因子等促血管平滑肌细胞增殖作用的共同途径之一,其机制主要与 AP-1、Elk-1、SRF 等多种转录因子的激活和相关细胞周期蛋白的合成增加有关^[30-33]。此外,血管的扩张和收缩可以使血管平滑肌细胞维持一定的细胞表型,而血管伸缩程度的异常增加或减弱均可通过依赖于 ERK/MAPK 和 p38/MAPK 的信号通路影响血管平滑肌细胞 MCP-1、NF- κ B 等炎症基因的表达水平^[34,35]。

5 小结与展望

综上所述,动脉粥样硬化斑块引发的急性心脑血管事件严重危害人类健康,而 MAPKs 信号通路在动脉粥样硬化斑块发生进展过程中的多种细胞病理反应起着重要的调控作用,不同的细胞外刺激可以通过 MAPKs 信号通路的多条并行通路和 MAPKs 通路间的 " 对话 " 共同调节 AS 斑块内各个细胞炎症反应及死亡过程。但对于 AS 斑块形成及进展所涉及的不同细胞而言,同一刺激可引起 MAPKs 信号通路不同组员和不同程度的激活或抑制,出现不同的细胞应答反应。因此,对这一领域广泛而深入的研究将有助于对动脉粥样硬化性疾病的认识,并为该疾病的防治开辟新药物靶点。

参考文献(References)

- [1] Gerszten RE, Tager AM. The monocyte in atherosclerosis-should i stay or should i go now?[J]. New England Journal of Medicine, 2012, 366: 1734-1736
- [2] Johnson GL, Lapadat R. Mitogen-activated protein kinase pathways mediated by erk, jnk, and p38 protein kinases [J]. Science, 2002, 298: 1911-1912
- [3] Muslin A. Mapk signalling in cardiovascular health and disease: Molecular mechanisms and therapeutic targets [J]. Clinical Science, 2008, 115: 203-218
- [4] Cargnello M, Roux PP. Activation and function of the mapks and their substrates, the mapk-activated protein kinases [J]. Microbiology and Molecular Biology Reviews, 2011, 75: 50-83
- [5] Keshet Y, Seger R. The map kinase signaling cascades: A system of hundreds of components regulates a diverse array of physiological functions[J]. Map kinase signaling protocols. Springer, 2010, 3-38
- [6] Kyriakis JM, Avruch J. Mammalian mapk signal transduction pathways activated by stress and inflammation: A 10-year update[J]. Physiological reviews, 2012, 92: 689-737
- [7] Chang L, Karin M. Mammalian map kinase signalling cascades[J]. Nature, 2001, 410: 37-40
- [8] Keshet Y, Seger R. The map kinase signaling cascades: A system of hundreds of components regulates a diverse array of physiological functions[J]. Methods Mol Biol, 2010, 661: 3-38
- [9] Rincon M, Davis RJ. Regulation of the immune response by stress-activated protein kinases[J]. Immunological reviews, 2009, 228: 212-224

- [10] Rose BA, Force T, Wang Y. Mitogen-activated protein kinase signaling in the heart: Angels versus demons in a heart-breaking tale [J]. *Physiological reviews*, 2010, 90: 1507-1546
- [11] Cargnello M, Roux PP. Activation and function of the mapks and their substrates, the mapk-activated protein kinases [J]. *Microbiology and molecular biology reviews: MMBR*, 2011, 75: 50-83
- [12] Kyriakis JM, Avruch J. Mammalian mapk signal transduction pathways activated by stress and inflammation: A 10-year update [J]. *Physiological reviews*, 2012, 92: 689-737
- [13] Karaflou M, Lambrinouaki I, Christodoulakos G. Apoptosis in atherosclerosis: A mini-review [J]. *Mini reviews in medicinal chemistry*, 2008, 8: 912-918
- [14] Dolan JM, Kolega J, Meng H. High wall shear stress and spatial gradients in vascular pathology: A review [J]. *Annals of biomedical engineering*, 2012, 1-17
- [15] Birukov KG, Bardy N, Lehoux S, et al. Intraluminal pressure is essential for the maintenance of smooth muscle caldesmon and filamin content in aortic organ culture [J]. *Arteriosclerosis, thrombosis, and vascular biology*, 1998, 18: 922-927
- [16] Berk BC. Atheroprotective signaling mechanisms activated by steady laminar flow in endothelial cells [J]. *Circulation*, 2008, 117: 1082-1089
- [17] Schieven GL. The biology of p38 kinase: A central role in inflammation [J]. *Current topics in medicinal chemistry*, 2005, 5: 921-928
- [18] Wang WY, Li J, Yang D, et al. Oxldl stimulates lipoprotein-associated phospholipase a2 expression in thp-1 monocytes via pi3k and p38 mapk pathways [J]. *Cardiovascular research*, 2010, 85: 845-852
- [19] Lin S J, Shyue S K, Liu P L, et al. Adenovirus-mediated overexpression of catalase attenuates oxldl-induced apoptosis in human aortic endothelial cells via ap-1 and c-jun n-terminal kinase/extracellular signal-regulated kinase mitogen-activated protein kinase pathways [J]. *Journal of molecular and cellular cardiology*, 2004, 36: 129-139
- [20] Ueno H, Pradhan S, Schlessel D, et al. Nicotine enhances human vascular endothelial cell expression of icam-1 and vcam-1 via protein kinase c, p38 mitogen-activated protein kinase, nf kb, and ap-1 [J]. *Cardiovascular toxicology*, 2006, 6: 39-50
- [21] Wang Y, Wang Z, Zhou Y, et al. Nicotine stimulates adhesion molecular expression via calcium influx and mitogen-activated protein kinases in human endothelial cells [J]. *The international journal of biochemistry & cell biology*, 2006, 38: 170-182
- [22] Silverstein RL, Febbraio M. Cd36 and atherosclerosis [J]. *Current opinion in lipidology*, 2000, 11: 483-491
- [23] Rahaman SO, Lennon DJ, Febbraio M, et al. A cd36-dependent signaling cascade is necessary for macrophage foam cell formation [J]. *Cell metabolism*, 2006, 4: 211-221
- [24] Zhao M, Liu Y, Wang X, et al. Activation of the p38 map kinase pathway is required for foam cell formation from macrophages exposed to oxidized ldl [J]. *Apmis*, 2002, 110: 458-468
- [25] Mei S, Gu H, Ward A, et al. P38 mitogen-activated protein kinase (mapk) promotes cholesterol ester accumulation in macrophages through inhibition of macroautophagy [J]. *Journal of Biological Chemistry*, 2012, 287: 11761-11768
- [26] Lacolley P, Regnault V, Nicoletti A, et al. The vascular smooth muscle cell in arterial pathology: A cell that can take on multiple roles [J]. *Cardiovascular research*, 2012, 95: 194-204
- [27] Gomez D, Owens GK. Smooth muscle cell phenotypic switching in atherosclerosis [J]. *Cardiovascular research*, 2012, 95: 156-164
- [28] Mack CP. Signaling mechanisms that regulate smooth muscle cell differentiation [J]. *Arteriosclerosis, thrombosis, and vascular biology*, 2011, 31: 1495-1505
- [29] Muto A, Fitzgerald TN, Pimiento JM, et al. Smooth muscle cell signal transduction: Implications of vascular biology for vascular surgeons [J]. *Journal of vascular surgery*, 2007, 45: A15-A24
- [30] Deaton RA, Su C, Valencia TG, et al. Transforming growth factor-β1-induced expression of smooth muscle marker genes involves activation of pkn and p38 mapk [J]. *Journal of Biological Chemistry*, 2005, 280: 31172-31181
- [31] Zhou J, Hu G, Herring BP. Smooth muscle-specific genes are differentially sensitive to inhibition by elk-1. *Molecular and cellular biology*, 2005, 25: 9874-9885
- [32] Kavurma MM, Khachigian LM. Erk, jnk, and p38 map kinases differentially regulate proliferation and migration of phenotypically distinct smooth muscle cell subtypes [J]. *Journal of cellular biochemistry*, 2003, 89: 289-300
- [33] Orr AW, Hastings NE, Blackman BR, et al. Complex regulation and function of the inflammatory smooth muscle cell phenotype in atherosclerosis [J]. *Journal of vascular research*, 2009, 47: 168-180
- [34] Guest TM, Vlastos G, Alameddine FM, et al. Taylor WR. Mechanoregulation of monocyte chemoattractant protein-1 expression in rat vascular smooth muscle cells [J]. *Antioxidants & redox signaling*, 2006, 8: 1461-1471