

针对丝裂原活化蛋白激酶信号通路的胃癌靶向治疗研究进展

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【摘要】 胃癌在全世界范围内都具有较高的发病率和死亡率,是威胁人类健康的一大难题。靶向治疗药物的出现,使中晚期胃癌治疗得到突破,延长了无数胃癌患者的生存期,但耐药和毒性作用等问题仍然存在,因此需要寻找更加安全可靠的靶向药物。近年来,丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路被发现与胃癌的发生发展密切相关,能够影响胃癌细胞的增殖、侵袭、凋亡等,也有许多影响MAPK信号通路的药物被相继发现。本文通过查阅相关文献,对针对MAPK信号通路的胃癌靶向治疗药物的研究作一综述,以期对胃癌的靶向治疗提供新的思路。

【关键词】 胃癌; 丝裂原活化蛋白激酶信号通路; 靶向治疗; 综述

Research progress on targeted therapy for gastric cancer with mitogen-activated protein kinase signaling pathway

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【Abstract】 Gastric cancer has a high morbidity and mortality rate all over the world and is a major problem threatening human health. The emergence of targeted therapeutic drugs has made a breakthrough in the treatment of middle and advanced gastric cancer and extended the survival time of countless gastric cancer patients. However, drug resistance and toxic effects still exist, so it is necessary to find safer and more reliable targeted drugs. In recent years, mitogen-activated protein kinase (MAPK) signaling pathway has been found to be closely related to the occurrence and development of gastric cancer, which can affect the proliferation, invasion and apoptosis of gastric cancer cells. Moreover, many drugs affecting MAPK signaling pathway have been discovered in succession. By referring to relevant documents, this article reviews the researches of targeted therapeutic drugs for gastric cancer targeting MAPK signaling pathway, hoping to provide a new idea for the research of targeted therapy for gastric cancer.

【Key words】 Gastric cancer; Mitogen-activated protein kinase signaling pathway; Targeted therapy; Review

胃癌作为一种常见的消化道肿瘤,每年新发病例超过100万,是全球第五大恶性肿瘤^[1]。2020年,因胃癌死亡的人数占全球癌症死亡病例的7.7%,成为第四大癌症死亡相关原因^[2]。对于早期胃癌,内镜下治疗和手术切除能够达到较好的根

治效果,而中晚期转移性胃癌仍缺乏有效的治疗手段^[3]。目前针对进展期胃癌最常用的治疗方式是在围手术期进行ECF(表柔比星+顺铂+氟尿嘧啶)方案或FLOT(多西他赛+奥沙利铂+亚叶酸钙+5-氟尿嘧啶)方案的辅助化疗,尽管能取得一些效果,但治愈率仍然很低。目前,越来越多的分子靶向药物正被发现,可以用于治疗胃癌,如针对表皮生长因子受体(epithelial growth factor receptor, EGFR)、人表皮生长因子受体2(human epidermal growth factor receptor 2, HER2)、血管内皮生长因子(vascular

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endothelial growth factor, VEGF)、间质表皮转化因子(cellular-mesenchymal to epithelial transition factor, c-MET)等靶点的药物^[4]。近些年,丝裂原活化蛋白激酶(mitogen-activated protein kinase, MAPK)信号通路在胃癌中的研究取得了丰硕的成果,为中晚期胃癌的治疗提供了新的选择。

1 丝裂原活化蛋白激酶信号通路

MAPK 是一组能被不同的细胞外刺激因子激活的丝氨酸-苏氨酸蛋白激酶。MAPK 信号通路至少由 3 种激酶组成:丝裂原活化蛋白激酶激酶激酶(mitogen-activated protein kinase kinase kinase, MAP3K)、丝裂原活化蛋白激酶激酶(mitogen-activated protein kinase kinase, MAP2K)、MAPK^[5]。哺乳动物细胞中表达 14 种 MAPK,经典的 MAPK 有细胞外调节蛋白激酶(extracellular regulated protein kinases, ERK)1/2、p38 家族(p38 α 、p38 β 、p38 γ 和 p38 δ)、c-Jun 氨基末端激酶(c-Jun N-terminal kinase, JNK)家族(JNK1、JNK2 和 JNK3),其余 MAPK 如 ERK5、ERK7、nemo 样激酶(nemo-like kinase, NLK)还未被充分研究^[5]。MAPK 可以通过多种细胞机制调节多种生物过程,如增殖、凋亡、信号转导、转移,MAPK 家族在免疫的发生和肿瘤的形成中也发挥了重要的作用^[5-8]。

ERK/MAPK 信号通路可以被细胞因子、病毒、癌基因等多种刺激因子激活,发挥调控作用^[9]。该通路的主要结构包括:接收细胞外信号的小 G 蛋白 Ras、蛋白激酶 Raf、胞外信号调节激酶的激酶(MARK/ERK kinase, MEK)、ERK 以及下游的效应蛋白。当信号通路不活跃时,ERK 蛋白通常定植于细胞质中,一旦信号刺激使 ERK 磷酸化和二聚化,被激活的 ERK 就会被转运至细胞核中,调节下游蛋白的活性,从而参与细胞增殖、细胞分化、细胞周期调节、细胞凋亡和组织形成,并进一步促进肿瘤形成^[10]。

p38/MAPK 和 JNK/MAPK 信号通路相类似,都可以被生长因子、炎症细胞因子以及各种环境刺激因素激活^[11-12]。激活 p38 家族的 MAP2K 主要为 MKK3、MKK6,MAP3K 则有许多种,包括凋亡信号调节激酶 1 (apoptosis signal regulating kinase-1, ASK1)、转化生长因子- β 激活激酶 1(transforming growth factor- β -activated kinase 1, TAK1)^[13]。此外,p38 的另一种激活方式并不依赖于 MAP2Ks,而是

通过转化生长因子激活激酶结合蛋白(TAK1-binding protein 1, TAB1)和 T 细胞表面的抗体受体(T cell receptor, TCR)直接与 p38 结合,导致 p38 自磷酸化从而被激活^[14]。p38/MAPK 的底物多种多样,可以是细胞质中的蛋白,也可以是细胞核中的转录因子,因此其发挥的生物效应也非常丰富,如促进炎症的发生,参与细胞的生长、分化、衰老和凋亡^[12]。激活 JNK 的 MAP3K 与 p38 相似,主要为 TAK1^[15],主要靶点是激活蛋白-1(activator protein-1, AP-1)上的早期反应转录因子 c-Jun,参与细胞的凋亡、存活与衰老^[16-18]。

2 丝裂原活化蛋白激酶信号通路与胃癌的关系

许多学者发现胃癌的发生发展与 MAPK 信号通路的激活有着密不可分的关系。早在 2005 年,Liang 等^[19]通过实验发现 MAPKs 在大多数胃癌中都过表达,其中,ERKs 的过表达可能与肿瘤的 TNM 分期、浆膜侵袭和淋巴结受累有关,p38 的过表达很可能在胃癌的某些亚型中有着显著作用。

Pandian 等^[20]通过收集 ERK/MAPK 基因组发现,与正常胃组织相比,所有的 ERK/MAPK 基因组在胃肿瘤样本中被发现高度激活。另外,与弥漫型肿瘤相比,肠型胃肿瘤中 ERK/MAPK 基因组的活化程度更高。同时,ERK/MAPK 信号通路与胃癌细胞中的 E2F 转录因子、Myc 癌基因、转化生长因子- β (transforming growth factor- β , TGF- β)等致癌通路也呈正相关。

p38 和 JNK/MAPK 信号通路共同被称为应激激活蛋白激酶通路,它们对癌的发生发展起着复杂的双向作用^[21]。一方面,p38 通过促进细胞周期阻滞、分化、凋亡以及强迫细胞衰老,产生抑制肿瘤的作用;另一方面,p38 通过增强肿瘤细胞的存活和迁移,或加强肿瘤细胞对化疗药物的抵抗,来促进癌症^[22]。与 p38 相似,JNK 也是通过参与细胞凋亡、分化和衰老来抑制肿瘤细胞^[23];通过增强癌细胞的存活、调控细胞自噬以及抑制 p53 抑癌基因来促进肿瘤的进展^[16,20]。

另外,MAPK 信号通路还在一些促进胃癌发生发展的途径中发挥重要作用。如花生四烯酸脂氧合酶 5、同源结构域基因 10、钙释放激活钙调节剂 2、p21 活化蛋白激酶等都是通过激活 MAPK 中的一种或多种家族,来促进胃癌的发生、增殖或转

移^[24-27]。幽门螺杆菌释放的一些毒力因子也会激活 MAPK 信号通路,并由此增加细胞内肝素酶的表达,从而有助于进展期胃癌的转移,增强其耐药性,并促进胃癌的复发^[28-29]。而一些微小RNA 则可能通过抑制 MAPK 信号通路,来抑制胃癌细胞的增殖与侵袭,如微小 RNA-433^[30]。

3 靶向丝裂原活化蛋白激酶信号通路治疗胃癌

3.1 ERK/MAPK 信号通路

Pandian 等^[20]在后续的实验中发现,ERK/MAPK 抑制剂 PD98059 能够有效杀伤胃癌细胞。这不难令人想到,一些能够抑制 ERK/MAPK 信号通路的药物,可以在人体内起到治疗胃癌的效果。例如普萘洛尔,作为非选择性 β_1 与 β_2 -肾上腺素受体阻断剂,一般用于心律失常以及高血压的治疗,近年来越来越多的证据表明阻断 β -肾上腺素能信号可以抑制肿瘤的生长。Koh 等^[31]通过多种实验以及异种移植小鼠模型发现普萘洛尔能够非剂量依赖性显著抑制胃癌细胞的增殖。其中主要的一个机制,就是普萘洛尔能够降低 MEK-ERK/MAPK 信号通路的活性从而抑制肿瘤细胞增殖和免疫逃逸、诱导肿瘤细胞凋亡,其主要方式是普萘洛尔可以减少环磷酸腺苷(cyclic adenosine monophosphate, cAMP)的产生,而被 cAMP 直接激活的环磷酸腺苷调节鸟嘌呤核苷酸交换因子(cyclic adenosine monophosphate regulation of guanine nucleotide exchange factor, EPAC)具有诱导 MEK-ERK 信号通路磷酸化的功能。钙通道阻滞剂乐卡地平同样可以通过抑制 ERK/MAPK 信号通路起到抑制胃癌细胞增殖的作用。Panneerandian 等^[32]发现乐卡地平与多柔比星联合使用能够增强胃癌细胞对多柔比星的敏感性,这一特性是由于乐卡地平能够反向调控被多柔比星激活的 ERK/MAPK 信号通路。

许多从植物中提取的天然化合物也被发现可以通过抑制 ERK/MAPK 信号通路产生抑制胃癌细胞生长的作用。血根碱是一种能从血根、罂粟等植物中提取的生物碱,具有多种生物活性如诱导细胞凋亡、扰乱微管,并具有抗菌作用^[33]。研究表明,血根碱可以通过抑制错误激活的信号转导途径、诱导细胞凋亡和抑制肿瘤细胞增殖等方式发挥其抗癌作用^[34]。Zhang 等^[35]在胃癌细胞中加入血根碱后发现血根碱对胃癌细胞的生长和侵袭都

有一定的抑制作用。随后他们又进行了 CCK-8 增殖实验,发现血根碱通过增加双特异性磷酸酶 4 (dual specificity protein phosphatase 4, DUSP4) 的表达,以剂量依赖的方式下调 ERK 的活化及其下游信号分子的表达,从而发挥抗肿瘤作用。肉豆蔻素是一种广泛存在于肉豆蔻、肉桂、欧芹等香料中的天然物质,具有抗炎、抗菌、抗增殖活性等药理活性,过度食用还会产生潜在的细胞毒性^[36-37]。肉豆蔻素也具有一定的抗肿瘤作用,与其他化疗药物联合使用时会增强化疗效果起到抗耐药的作用^[38]。Song 等^[39]将胃癌细胞暴露于不同浓度的肉豆蔻素中以探讨肉豆蔻素对胃癌的作用及其机制。他们发现肉豆蔻素正是通过抑制 EGFR/ERK 信号通路抑制胃癌细胞的增殖,其不仅能减少 EGFR 的蛋白水平,还能抑制 ERK 的活化。

3.2 p38/MAPK 和 JNK/MAPK 信号通路

大多数的药物都是通过促进 p38 和 JNK/MAPK 信号通路,来抑制胃癌的发生发展。近些年,许多天然化合物被研究是否通过上调 p38 和 JNK 的活性而发挥抗癌效应。木兰花碱是从一些常用的中草药(如青藤、黄连)中分离出的一种重要的生物碱,具有重要的生物活性如免疫激活、抗炎、抗菌、降血糖,可以用来治疗多种疾病,如糖尿病、过敏、感染、骨质疏松等^[40-41]。在癌症治疗方面,木兰花碱对肺癌、乳腺癌、胶质瘤和横纹肌肉瘤的癌细胞都有一定的抑制潜力^[42]。Sun 等^[43]探索了木兰花碱对胃癌的抗癌活性,研究用不同浓度的木兰花碱处理了胃癌细胞,发现木兰花碱可以呈时间依赖性产生细胞毒性,并通过异种移植小鼠实验证实了木兰花碱在体内的抗肿瘤作用。随后,研究者通过分子分析了解到,木兰花碱正是通过激活 JNK 从而诱导胃癌细胞的凋亡和细胞周期的阻滞来发挥作用的。五味子是一种传统的中草药,其提取物已被用于缓解多种疾病,如治疗血管损伤、诱导白血病细胞损伤、缓解糖尿病并发症、预防神经退行性疾病、抗肿瘤^[44-46]。Kim 等^[46]通过实验证实五味子提取物对胃癌细胞存在杀伤作用,并证明五味子通过激活 p38/MAPK 和 JNK/MAPK 信号通路提高凋亡相关因子且降低 B 淋巴细胞瘤-2 基因的表达水平,从而促进了 AGS 胃癌细胞的凋亡。从桔梗根中提取的桔梗皂苷 D、一种从藻类提取出的多糖、土木香内酯等天然化合物,也都可以通过对 p38 或 JNK 信号通路的激活促进胃癌细胞的

凋亡^[47-49]。

一些常见的药物也出乎意料地被证实通过该通路发挥治疗胃癌的作用。如褪黑素是一种由松果体产生的激素,用来使哺乳动物适应季节的变化,调节人体昼夜节律,如今作为一种非处方药被人们广泛地用于治疗失眠^[50-51]。近些年流行病学研究表明褪黑素对多种肿瘤细胞具有明显的凋亡、抗血管生成、抑癌和抗增殖作用^[52]。Li等^[53]研究褪黑素抗胃癌细胞的分子机制,发现褪黑素通过p38和JNK途径抑制了核因子 κ B的活化,促进了胃癌细胞的凋亡。青蒿素由中国中医药科学院研究小组从青蒿中提取而出,在东南亚地区广泛应用于疟疾的治疗,它的衍生物双氢青蒿素(dihydroartemisinin, DHA)也被证明具有抗菌和抗病毒活性^[54-55]。近年来DHA被认为具有潜在的抗癌活性^[56], Zhang等^[57]发现DHA也是通过激活p38和JNK/MAPK信号通路来诱导胃癌细胞的凋亡。

某些人们熟悉的抗癌药物也是通过p38和/或JNK/MAPK信号通路来发挥抑制胃癌的作用。伊立替康为晚期结直肠癌的一线用药,近年的研究发现,伊立替康能够呈时间和剂量依赖性地抑制胃癌细胞,其机制正是通过刺激p38和JNK/MAPK信号通路,诱导自噬,从而抑制肿瘤生长^[58]。复方斑蝥素胶囊是一种常用于治疗原发性肝癌、肺癌等恶性肿瘤的中成药。Sun等^[59]研究发现复方斑蝥素胶囊可以通过激活p38和JNK/MAPK信号通路,抑制人胃癌细胞增殖,促进其凋亡。莪术颗粒在临床上主要用于慢性萎缩性胃炎伴肠化生的治疗,通过上调p38和JNK蛋白的表达而发挥作用^[60]。山柰酚是一种具有抗癌作用的天然化合物,能够通过激活IRE1-JNK-CHOP通路,激活胃癌细胞的自噬^[61]。

有一小部分的药物则是通过抑制p38和JNK/MAPK信号通路来发挥治疗胃癌的作用。如胡椒碱可以通过抑制p38/MAPK信号通路来降低白介素6的表达从而抑制胃癌的转移和恶变^[62]。根皮素能够显著减少p38和JNK的磷酸化,降低通路的活性,从而使胃癌细胞停留在细胞周期的G2/M期,抑制其迁移能力^[63]。

4 总结与展望

虽然治疗胃癌仍然是一个令人棘手的难题,但近年来胃癌的发病率和死亡率在全球范围内都

有所下降,2018年全球范围内因胃癌死亡的人数占有癌症死亡人数的8.2%,而2020年已经下降为7.7%,人数也减少了将近2万^[64]。这是因为近年来新出现的化疗药物和化疗方案,大大提高了中晚期胃癌患者的生存率。传统化疗虽能延长患者的生存期,但疗效有限且会严重降低患者的生活质量,故仍需靶向药物投入临床使用,而MAPK信号转导通路就是一个可以利用的靶点。

其中ERK家族主要参与细胞的增殖和细胞周期调控,这可能与胃癌的生成、发展和突变有关。目前已经发现许多药物可以通过抑制ERK及其通路的活性来发挥抗胃癌的作用,但是一些研究还只局限于体外水平或者只适用于动物实验,其在人体内的效果还需进行一些相关的临床试验来分析。

p38和JNK家族主要参与细胞的生长存活和凋亡,因此其与胃癌的关系具有双重性。靶向p38和JNK的药物可以通过抑制或促进相应的信号通路,来发挥抗癌作用。其复杂的双向调节机制以及相互影响的关系仍需要更进一步的研究和探索,以更好地开发可应用于临床的药物。

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