翻译起始因子5A2与肿瘤的研究进展

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摘要 真核翻译起始因子5A2(eukaryotic translation initiation factor 5A2, eIF5A2)是一种在真核细胞蛋白质翻译起始和延伸过程中发挥作用的蛋白, 它是eIF5A的其中一个亚型, 在多种肿瘤细胞中的异常高表达往往与该肿瘤的发生和发展相关。eIF5A2所特有的羟腐赖氨酸, 可以成为肿瘤治疗的潜在靶点, 为临床带来新的思路。

关键词 真核翻译起始因子5A2; 表达; 肿瘤; 转移

Recent Advances of Research on Eukaryotic Translation Initiation Factor 5A2 in Tumors

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Abstract Eukaryotic translation initiation factor 5A2 is a protein which plays roles in translation initiation and elongation processes in eukaryotic cells. It is one isoform of eIF5A. The aberrant overexpression of eIF5A2 in many types of tumor cells is associated with tumorigenesis and progression. Hypusine, a unique amino acid residue component of eIF5A, may become a potential target for antitumor therapy and bring new ideas in the clinical treatment.

Keywords eukaryotic translation initiation factor 5A2; expression; tumor; metastasis

真核翻译起始因子5A2(eukaryotic translation initiation factor 5A2, eIF5A2)是一种在真核细胞蛋白质翻译起始和延伸过程中发挥作用的蛋白[1-2], 除此之外, 它还具有促进细胞凋亡、抑制病毒复制等功能[2-3]。近年来, 越来越多的研究报道表明, eIF5A2与肿瘤的发生发展密切相关, 在多种肿瘤转移侵袭过程中, 肿瘤细胞内eIF5A2的表达存在不同程度的升高, 更有文献将其列为致癌基因[4-6]。目前, 已有研究将eIF5A2作为判断肿瘤转移及预后的指标之一[7-11]。本文就近年来eIF5A2在肿瘤细胞中的异常表达、作用及机制的相关研究作一综述。

1 eIF5A2的结构与功能

1976年, 真核细胞翻译起始因子eIF5A在一次体外实验中被首次发现, 它能够促进聚苯丙氨酸的翻译合成[12], 在蛋白质翻译过程中发挥起始和延伸的作用[1]。eIF5A有eIF5A1和eIF5A2两种亚型, 它们受同样的翻译后修饰——羟腐赖氨酸化[13-14]。eIF5A1在生物体大部分组织与细胞中大量存在, 与之不同的是, eIF5A2在正常组织细胞中表达较低, 但在多种恶性肿瘤细胞中则明显升高, 因而引起了广泛的关注[2,15]。eIF5A2是一个较保守的蛋白, 其分子大小约17 kDa。目前已明确eIF5A2定位于人类染色体的3q26.2区域, 翻译后受到脱氧辅蛋白合酶(deoxyhypusine synthase, DHS)和脱氧辅蛋白羟化酶(deoxyhypusine hydroxylase, DOHH)的催化, 形成羟腐赖氨酸残基, 前者的作用是将亚精胺催化形成脱氧辅蛋白, 而后者是将产物催化为羟腐赖氨酸残基,

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该修饰对形成成熟和有活性的eIF5A2具有重要作用[16]。有研究称, *DHS*和*DOHH*基因敲除后将导致eIF5A失活, 这对包括小鼠在内的大多数真核生物都是致命的[17]。另外, 通过对eIF5A1与eIF5A2的3D结构比较, 发现两者氨基酸残基的差异都远离羟腐赖氨酸位点[18], 这对保持羟腐赖氨酸残基的稳定性具有重要意义。在人类中, eIF5A1和eIF5A2有94%氨基酸序列同源, 其中84%序列一致, 它们的主要区别在近羧基端区域, 这提示了两者功能上的差别主要在于此(图1)[5]。将酵母eIF5A1羧基端的氨基酸序列突变后, 酵母的蛋白质合成减少了30%[16], 而eIF5A2的羧基端功能则鲜有文献报道。

目前已知eIF5A2最主要的作用是促进蛋白质的合成, 但人们对这一过程的细节还知之甚少。有研究发现eIF5A2参与了部分与mRNA代谢相关的过程, 如转录[19]、mRNA合成–降解[20]、核质转运[21]等。在酵母菌的体内实验中发现, eIF5A2可在eIF5A1缺失环境下大量表达并代偿性地行使其功能[22]。利用eIF5A2过表达的小鼠研究发现, eIF5A2的大量表达加速了小鼠的衰老, 相较对照组小鼠出现了诸如生命周期缩短、体重不增加、骨质疏松等症状[23]。目前人们对于eIF5A2是否具有其他功能仍在不断探索中。

2 eIF5A2在肿瘤中的异常表达

正常生理情况下, eIF5A1在人体内大多数组织、细胞中呈高表达; 与此相反, eIF5A2只有在睾丸中表达, 脑组织中少量表达。研究者首次在卵巢癌细胞系中发现eIF5A2呈高表达, 在对卵巢癌标本的染色体进行扩增时, 发现了eIF5A2的转录情况[2,5,24]。另有研究表明, eIF5A2的表达与细胞增殖相关, 甚至促使细胞发生恶化, 转变为肿瘤细胞。eIF5A2的过表达引起了小鼠胚胎成纤维细胞(national institutes of health, NIH3T3)的恶性转化, 而沉默人卵巢癌细胞UACC-1598的*eIF5A2*基因后, 细胞增殖明显减缓[16], 提示了eIF5A2在正常细胞内过表达可导致细胞的恶化癌变。大量数据显示, eIF5A2在特定组织中表达升高往往预示着恶性肿瘤的发生, 有人已将其列为判断肿瘤发生、发展的指标, 甚至将其列为癌基因[4-5]。eIF5A2的高表达与膀胱癌[25]、鼻咽癌[7]、非小细胞肺癌[8]、胃癌[9]、肝癌[26]、结直肠癌[27]、胰腺癌[28]、宫颈癌[10]、食管鳞状细胞癌[29]、黑色素瘤[30]等肿瘤的发生相关, 在某些肿瘤如膀胱癌[25]、鼻咽癌[7]、结直肠癌[27]、胰腺癌[28]、胃癌[9]、黑色素瘤[30]中, 更是与侵袭转移、预后、患者生存率息息相关。在非小细胞肺癌[8]、宫颈癌[10]、胃癌[9]和结直肠癌[6]中, eIF5A2的表达与肿瘤的恶性程度呈正相关。另外, eIF5A2异常表达与低生存率的相关性也时有报道, 如胃癌[9]、鼻咽癌[7]、非小细胞肺癌[8]、宫颈癌[10]、神经胶质瘤[11]等(表1)。

大量证据表明, 与翻译相关的蛋白参与了细胞分裂分化的调控[16], eIF5A2原本只是在蛋白质翻译起始中发挥作用, 但如果异常表达, 就可能成为诱导细胞癌变、促进肿瘤细胞增殖的元凶[31]。有实

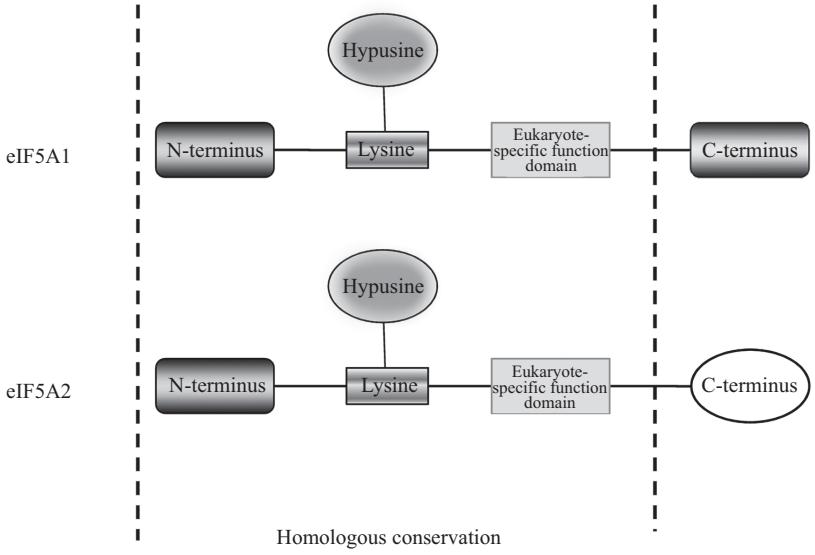


图1 eIF5A1和eIF5A2的结构图

Fig.1 The structures of eIF5A1 and eIF5A2

表1 eIF5A2异常升高与各种肿瘤行为特征

Table 1 Aberrant overexpression of eIF5A2 and behavior characteristics of various tumors

行为特征 Behavior characteristics	肿瘤类型 Tumor types	相关文献 References
Cell proliferation	Bladder cancer	[25]
	Colorectal carcinoma	[27]
	Pancreatic cancer	[28]
	Epidermoid cancer	[32]
Invasion Metastasis	Bladder cancer	[25]
	Nasopharyngeal carcinoma	[7]
	Gastric cancer	[9]
	Colorectal carcinoma	[27]
	Pancreatic cancer	[28]
	Melanoma	[30]
Tumor stage and grade	Non-small cell lung cancer	[8]
	Gastric cancer	[9]
	Cervical cancer	[10]
	Colorectal carcinoma	[6]
Survival rate	Nasopharyngeal carcinoma	[7]
	Non-small cell lung cancer	[8]
	Gastric cancer	[9]
	Cervical cancer	[10]
	Neuroblastoma	[11]

验室在抑制表皮样肿瘤细胞增殖过程中发现, 干扰素-α(interferon-α, IFN-α)减少了75%的羟腐赖氨酸合成, 而羟腐赖氨酸对于eIF5A2行使功能是极为重要的, IFN-α对抑制肿瘤细胞增殖起了一定作用[32]。这一研究说明, eIF5A2参与了细胞增殖, 甚至对于肿瘤细胞的分裂分化起到了推动作用。曾有人对结直肠癌患者的eIF5A2表达水平做过研究, 发现淋巴结和远距离转移与eIF5A2的高水平表达相关, 说明eIF5A2在肿瘤形成的早期对疾病的预后及患者的生存率有一定影响[16]。这些研究提示, eIF5A2在许多肿瘤中可作为一个判断预后及预估生存率的指标。

研究证实, eIF5A与真核细胞的持续性增殖密切相关[33]。如果在哺乳动物细胞或人类肿瘤细胞(例如非小细胞肺癌细胞)增殖过程中加入GC7(一种DHS酶的抑制剂), 能产生明显抑制增殖的作用[34-35]。也有文献报道, eIF5A2的过表达促进了结直肠癌细胞的增殖和侵袭[27], 而敲除*eIF5A2*基因则能诱导肿瘤血管的重塑, 提高肿瘤对化疗药物的敏感性[36]。曾有人报道了与肿瘤转移相关的17个基因, 其中之一是*DHS*, 它翻译后合成的酶是eIF5A2成熟过程中所必需的[37]。体内研究发现, eIF5A2的高表达促进了膀胱癌细胞的侵袭, 敲除*eIF5A2*基因后, 膀胱癌细胞的迁移能力受到抑制, 同时上皮间质转化(epithelial-mesenchymal transition, EMT)也被逆转, 如果使eIF5A2过表达则会出现相反的情况[25]。因此, 推测eIF5A2在肿瘤转移中具有一定的作用, 但其作用机制和通路还需要进一步研究。

3 eIF5A2异常表达对肿瘤细胞侵袭转移的作用及机制

与eIF5A2相关的肿瘤患者往往生存率较低, 其中一个重要原因是eIF5A2参与并促进肿瘤转移和淋巴结的侵袭。有人在胃癌中发现了3个与淋巴结转移相关的基因, *eIF5A2*是其中之一[38]。对肝癌病理组织染色分析显示, 肿瘤边缘eIF5A2的表达比肿瘤内部更高, 说明eIF5A2对肝癌细胞的侵袭具有重要推动作用。过表达的eIF5A2使肿瘤细胞的迁移能力显著提高, 而利用siRNA沉默*eIF5A2*基因后, 细胞的迁移能力明显受抑制[39]。在组织培养、基质胶侵袭等体外实验中, *eIF5A2*的基因被敲除后, 肿瘤细胞的迁移能力也随之减弱。同样的情况也发生在异种移植的食管鳞状细胞癌[19]、肝癌[40]和膀胱癌[25]等体内实验中, 表明eIF5A2的过表达能促进肿瘤细胞的侵袭和迁移, 而加入GC7则会抑制这种作用[2]。eIF5A2的抑制表达和过表达实验从不同角度表明其参与了肿瘤的侵袭迁移, 并在转移的特定阶段发

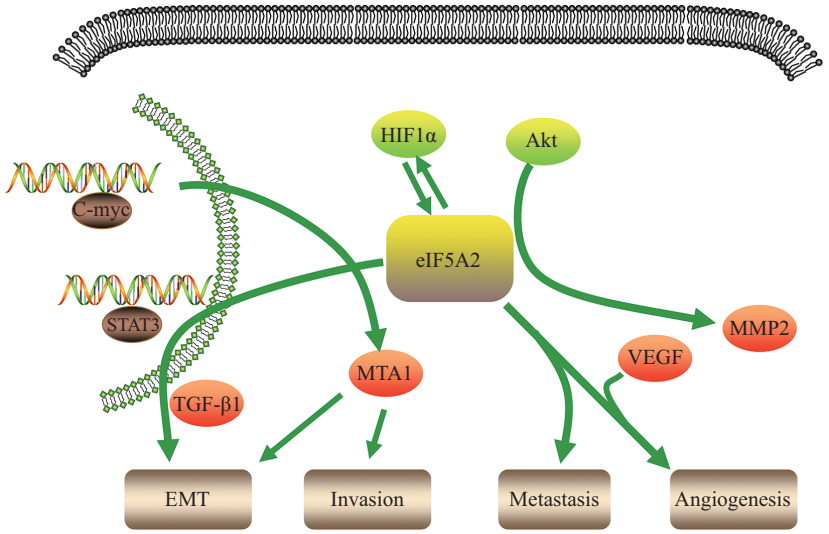
挥了作用[25,41-42]。

eIF5A2在不同细胞中的调控机制尚不完全清楚, 尤其是各通路中的下游靶点。就目前而言, 在结直肠癌中, 受*c-myc*基因影响, eIF5A2调节下游与转移相关蛋白1(metastasis associated 1, *MTA1*)基因, 使其表达升高, 从而增强细胞侵袭能力, 在*eIF5A2*基因被敲除后, 侵袭减弱, 同时EMT过程受到抑制[27]。膀胱癌中, eIF5A2刺激信号转导及转录激活子3(signal transducer and activator of transcription 3, STAT3)进行细胞核定位, 使转化生长因子-β1(transforming growth factor-beta 1, TGF-β1)的启动子大量富集并开始翻译, 诱导EMT过程, 因此膀胱癌细胞侵袭能力增强[25]。在黑色素瘤中, eIF5A2是磷酸化酶丝氨酸/苏氨酸激酶(serine/threonine kinase, Akt)的下游靶点。基质金属蛋白酶-2(matrix metallopeptidase-2, MMP-2)的活力和黑色素瘤细胞的侵袭性会随着eIF5A2的表达增加而增强[43]。对食管鳞状肿瘤细胞进行一段时间的缺氧处理后, 其中一个重要发现是, 缺氧诱导因子1α(hypoxia inducible factor 1 alpha subunit, HIF1α)会与eIF5A2在血管生成上形成复杂的相互作用[19], eIF5A2蛋白与HIF1α启动子的上游一段区域结合, 从而调控其转录的进行。另外, 当eIF5A2过表达时, 血管内皮生长因子(vascular endothelial growth factor, VEGF)的表达也随之升高, 说明eIF5A2在血管再生中也起了作用[19]。综上所述, eIF5A2的异常表达影响了多个致癌基因, 在多条通路中参与了肿瘤的侵袭和转移(图2)。

4 靶向eIF5A2的肿瘤治疗

由于eIF5A独有的羟腐赖氨酸翻译后修饰特性, 人们逐步将肿瘤治疗策略转移到与之相关的分子通路上, 以期获得更好的效果。DHS和DOHH是形成羟腐赖氨酸残基过程中必不可少的酶, 它们是目前肿瘤治疗和药物开发的主要突破口[2]。化学抑制剂、直接靶向DOHH的miRNA与顺铂、5-氟尿嘧啶等化疗药物联合使用, 也是正在探索的方向[7,29,36,44]。

作为eIF5A2的抑制剂, GC7可调节其表达水平, 在神经胶质瘤中, 一定剂量的GC7能抑制神经胶质瘤细胞的生长[11]。在非小细胞肺癌NCI-H1299中, 低浓度的GC7虽不能改变细胞的活性, 但提高了顺铂的细胞毒性, 间接提高了化疗药物的作用, 另外GC7还能阻止A549细胞的EMT进程[44]。GC7与西妥昔单抗联用可明显提高非小细胞肺癌细胞对西妥昔单抗的敏感性[34]。药物环吡酮胺和去铁酮已被证明是DOHH的抑制剂[45-46], 环吡酮胺能有效抑制体外培养的胰腺肿瘤细胞生长[47]。含羞草素是一种天然提



MTA1: 转移相关蛋白1; STAT3: 信号转导及转录激活子3; TGF-β1: 转化生长因子-β1; Akt: 磷酸化酶丝氨酸/苏氨酸激酶; MMP-2: 基质金属蛋白酶-2; HIF1α: 缺氧诱导因子1α; VEGF: 血管内皮生长因子。

MTA1: metastasis associated 1; STAT3: signal transducer and activator of transcription 3; TGF-β1: transforming growth factor-beta 1; Akt: serine/threonine kinase; MMP2: matrix metallopeptidase 2; HIF1α: hypoxia inducible factor 1 alpha subunit; VEGF: vascular endothelial growth factor

图2 肿瘤中与eIF5A2相关的信号通路

Fig.2 The signal pathway associated with eIF5A2 in tumors

取的化合物, 被证明具有抑制DOHH活性的作用, 通过与不同的miRNAs联用抑制DOHH的合成, 从而降低前列腺癌细胞的生长速度[48]。

药物与抑制剂的联用是目前研究较多的, 那么在核酸水平是否也存在有效的方法抑制eIF5A2的表达呢？在结直肠癌细胞中, eIF5A2的表达明显升高, 而miRNA-203的表达则是下降的, 曾有报道显示, miRNA-203通过绑定在*eIF5A2*的3′端非翻译区而使eIF5A2在转录和翻译水平都降低了, 因此减少了结直肠癌细胞的转移、侵袭[42]。类似的情况也出现在胃癌中, miR-30b一般在胃癌组织和相关细胞系中表达较低, 但过表达的miR-30b能促进胃肿瘤细胞的凋亡, 同时抑制其增殖和侵袭, 其可能的机理与miRNA-203相近, 通过绑定在*eIF5A2*的3′端非翻译区来调控eIF5A2的表达[49]。在核酸水平上, 对eIF5A2的限制普遍采用反义DNA或RNA干扰技术, 有报道称, 利用慢病毒将shRNA转入食管鳞状细胞癌的细胞内, 使eIF5A2的表达下降, 发现肿瘤细胞对5-氟尿嘧啶、紫杉醇等化疗药物的敏感性明显增强[29]。另有人报道, 应用纳米技术使siRNA靶向抑制eIF5A2的表达, 这种纳米粒子复合物具有更高效的抗肿瘤活性[50]。

5 总结

eIF5A的两个亚型中, 主要以eIF5A1的表达和分布为主, eIF5A2则更多地与人类多种肿瘤疾病相关。近年来随着对eIF5A2研究的深入, 人们不断发现eIF5A2在肿瘤中的作用, 它可能是一个潜在致癌基因, 同时也是多种肿瘤的预后标记物。由于其独有的翻译后修饰特性, 越来越多的研究者将目光放在了抑制剂和靶向药物应用开发上, 以期提高治疗效果。不论是eIF5A2的抑制剂单用或与化疗药联用, 对eIF5A2高表达的肿瘤都有较好地治疗效果, 且eIF5A2在正常人体组织中表达低, 抑制剂对正常细胞的作用小, 副作用相对较低, 这是以eIF5A2作为靶向治疗的优点。然而在一些eIF5A2表达较低的肿瘤中, 以上提及的治疗方法效果不甚理想, 因此具有一定局限性, 已有文章提出eIF5A2靶向药物存在细胞毒性强弱的疑问[34]。eIF5A2用于靶向治疗的另一个关键是其细胞内的定位, 例如eIF5A2的前体是如何穿梭细胞核转化为成熟eIF5A2的。

但eIF5A2在不同肿瘤中表达的潜在分子基础仍不清楚, 对肿瘤细胞转移侵袭的调控机制是未来亟待解决的问题, *eIF5A2*基因敲除的小鼠可能不失为一种好的研究模型。eIF5A2与肿瘤的密切关系可能蕴含着eIF5A2促进细胞癌变的重要证据, 它的翻译后修饰和细胞内基本功能需要进一步研究。鉴于eIF5A2具有翻译起始功能, 影响了部分mRNA的活性, 而在肿瘤细胞内利用核糖体图谱的技术[2], 可以明确eIF5A2对基因的影响, 提示与eIF5A2有关的肿瘤形成机制, 找到更为合适的靶向或干预治疗方法, 这可能是一条未来研究eIF5A2表达与肿瘤关系的出路。

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