S100P与消化道肿瘤的研究进展

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摘要 S100P是小型钙离子结合蛋白, 属于S100家族成员, 通过细胞内或细胞外功能调节细胞的各种过程, 并参与各种病理过程。越来越多的研究表明, S100P在各种肿瘤细胞中异常表达, 并与肿瘤细胞的生长、转移、化疗药物的耐药、新陈代谢以及不良的临床预后有关。该文主要介绍了S100P在消化道肿瘤中的功能和作用机制, 及其作为新的诊断和药物治疗靶点的可能性。

关键词 S100P; 消化道肿瘤; 调控机制

Current Research Advances in Relationship between S100P and Digestive Cancer

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Abstract S100P is a small calcium-binding protein that belongs to S100 protein family. It functions as extracellular and/or intracellular regulators of diverse cellular processes and participates in various human pathologies. S100P expression was detected in many different cancers, and its expression is associated with tumor growth, metastasis, drug resistant and poor clinical outcome. This review focuses on the functions and mechanisms of S100P, and the S100P protein may serve as a potential biomarker and therapy target in digestive system cancer.

Key words S100P; digestive system cancer; regulation mechanism

引言

近年来, 肿瘤的生物学和病理机制研究取得了一定的成果, 但是肿瘤仍然是威胁人类健康的重大问题[1]。化疗和放射疗法是目前临床治疗肿瘤的常规方法, 但是效果并不理想, 因此亟待新的治疗方法的出现。近几年来的研究主要集中在已知的肿瘤分子生物学机制的基础上, 并寻找新的分子生物学靶点。S100P在肿瘤中的异常表达会通过各种信号通路对肿瘤的生长、增殖、入侵和转移起到重要作用, 因此有可能成为新的分子标志物应用于肿瘤的诊断和治疗[2-7]。本文主要对S100P蛋白在消化道肿瘤中的研究作一综述。

1 S100蛋白家族

S100蛋白家族是一个由20多个成员组成的钙结合蛋白家族, 具有亲和Ca^{2+}的EF手型结构[8-12]。因其能够溶解在100%的饱和硫酸铵(solution in a 100% saturated ammonium sulfate solution)溶液中而得名[13]。

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S100蛋白参与细胞内和细胞外多种活动, 包括蛋白磷酸化、酶的激活、基因的转录调控、细胞骨架成分的动态平衡、细胞增殖和分化等[12]。结构研究表明, S100蛋白家族是由同分异构的两个亚单位组成的, 分为同源二聚体和异源二聚体, 在每个亚基的羧基端均含有一个EF手型钙离子结合区, 其中羧基端含有一个钙离子结合环, 对钙离子具有较高的亲和性, 氨基端结构对钙离子的亲和性较低, 当与钙离子结合后, S100蛋白构象发生改变, 暴露出其与靶蛋白结合的位点, 进而通过与靶蛋白作用发挥生物学效应[14]。钙离子是重要的细胞内第二信使, 一般认为, 在细胞内S100蛋白通过介导Ca^{2+}依赖的信号通路与靶蛋白相互作用[15]。S100蛋白可作为细胞内或细胞间的信号分子[16]。在细胞外, S100蛋白能够结合RAGE(receptor for activated glycation end products)等靶蛋白发挥一系列作用, 涉及多种肿瘤疾病的病理过程[16-17]。

2 S100P基本结构与功能

人*S100P*基因定位于4pl6(4号染色体短臂1区6带), 包含两个外显子和一个内含子[18]。S100P是一种小型钙离子结合蛋白, 由95个氨基酸残基组成, 分子量为10.4 kDa, 于1992年首次从人类的胎盘中获得[19], 属于S100蛋白家族。蛋白结构研究表明, S100P蛋白以二聚体形式存在, 且S100P同源二聚体结构可能比其他S100蛋白家族成员更稳定[15]。S100P分布在细胞核和细胞质基质中, 细胞质S100P主要集中在细胞核周区域[20]。S100P参与了细胞内和细胞间多种细胞过程: 例如在细胞内S100P蛋白可通过介导Ca^{2+}依赖的信号传导途径, 调节蛋白磷酸化及部分酶的活性, 调节细胞周期性生长及增殖分化[12]; 在细胞外, S100P可激活RAGE等靶分子发挥一系列作用, 涉及心脏疾病、多种神经系统疾病和肿瘤疾病等病理过程[21-22]。Parkkila等[23]研究表明, S100P蛋白在许多正常组织中都有表达, 其中表达量最高的是胎盘。S100P在多种肿瘤中过表达, 包括胰腺癌、胃癌、结肠癌、乳腺癌、前列腺癌、胆管癌和卵巢癌, 并且与临床治疗效果相关[2,24-28]。越来越多的研究表明, S100P表达对消化道肿瘤的生长转移具有重要作用。

3 S100P与消化道肿瘤

3.1 食管癌

食管鳞状细胞癌是目前最普遍的肿瘤之一, 但关于其与S100P的研究较少。Ji等[29]用RT-PCR技术检测了62例食管鳞状细胞癌组织中16种S100家族mRNA的表达, 发现与相应的正常组织相比, 癌组织中有11个*S100*基因表达显著下调, 包括*S100A1*、*S100A2*、*S100A4*、*S100A8*、*S100A9*、*S100A10*、*S100A11*、*S100A12*、*S100A14*、*S100B*及*S100P*。另外, Zhi等[30]通过cDNA芯片技术研究了6对食管鳞状细胞癌及相应癌旁组织中14 803个基因的表达, 发现肿瘤组织中有9个基因表达上调, 36个基因表达下调, 并且其中9个基因的异常表达可能和花生四烯酸代谢有关, 包括膜联蛋白I、膜联蛋白II、*S100A8*、*S100A10*、*S100P*、谷胱甘肽过氧化物酶-3、磷脂酰胆碱转移蛋白、醛酮还原酶家族-1及环氧酶-2, 而花生四烯酸代谢途径可能和食管鳞状细胞癌的发生发展有关。

3.2 肝癌

肝癌是导致死亡的三大肿瘤之一。与正常组织相比, S100P在胆管细胞型肝癌中过表达, Kim等[31]利用免疫组织化学、Western blot和RT-PCR技术检测了肝癌组织及其细胞株中S100P的表达, 发现与正常组织相比, 肝癌细胞中S100P高表达。利用siRNA靶向抑制人肝癌细胞株Hep3B中S100P的表达能够抑制肝癌细胞的生长并且促进凋亡, 降低细胞周期相关蛋白cyclin D1和CDK2的活性。S100P在肝癌组织中的异常表达可能通过激活cyclin D1和CDK2来激发有丝分裂的潜能。近年来的研究表明, *S100P*基因可能在介导肿瘤肝转移过程中具有重要作用, 例如Ding等[32]运用基因芯片技术研究原位结肠癌肝转移大鼠模型, 发现APOBEC3G、CD133、LIPC和S100P等在结肠癌的肝转移组织中高表达, 提示这些基因可能在介导结肠癌肝转移的过程中起到重要作用。Barry等[33]通过基因表达谱芯片研究发现, 与正常组织相比, S100P在原位胰腺导管腺癌及其肝转移组织中异常表达。

3.3 胰腺癌

研究表明, 90%以上的胰腺癌中能检测到S100P的表达, 并与肿瘤生长转移有关[34], 而S100P在胰腺癌中特异表达, 在慢性胰腺炎及其他相似炎症性疾病中不表达。Crnogorac-Jurcevic等[3]对胰腺癌的分子水平改变的研究发现, 与正常胰腺细胞相比, 癌组织普遍存在S100蛋白的异常表达, 并且其中变

化最明显的是S100P和S100A6。S100P结合蛋白S100PBP(S100P-binding protein)主要在细胞核或细胞核周区域有表达。在癌前期病变中, S100PBP转移到细胞质, 然而在胰腺导管腺癌和转移病灶中它的表达显著减少。S100PBP表达改变的主要表现为改变细胞的附着力, S100PBP表达升高时附着力显著下降, 反之升高[35]。同时伴随着组织蛋白酶水平的改变, 组织蛋白酶的减少能够降低胰腺导管腺癌细胞的附着力, 从而影响细胞的转移侵袭能力[35]。S100P的另一个靶蛋白是S100PBPR(S100P binding protein Riken), 其与S100P的相互作用受Ca^{2+}和Mg^{2+}的影响。S100PBPR主要出现在细胞核, 同时伴有S100P表达, 实时荧光定量PCR检测发现胰腺上皮内瘤样病变和胰腺导管腺癌都存在S100PBPR和S100P的表达, 原位杂交实验发现S100PBPR在恶性胰腺导管腺癌细胞中表达[4]。此外, S100P还可通过与RAGE相互作用发挥其功能[36]。RAGE是一种多配基受体, 能够与多种分子作用, 包括糖基化终末端产物、S100蛋白、淀粉体蛋白、二性霉素B。RAGE参与了多个重要病理过程, 包括阿尔兹海默病、糖尿病、炎症反应和肿瘤。由S100P激活的RAGE能刺激多个细胞信号通路, 包括MAPK和细胞核因子-κB(NF-κB)信号通路。绝大部分胰腺肿瘤中NF-κB的活性增加, 并且NF-κB活性提高与肿瘤耐药有关。因此, 阻断S100P激活RAGE的作用, 可能提高治疗效率。色氨酸作为小分子能够抑制S100P激活RAGE, 色氨酸结合到S100P上, 从而抑制了S100P与RAGE的相互作用, 降低了S100P介导的肿瘤生长、免疫逃逸和转移[34]。因而抑制S100P与RAGE间的相互作用是胰腺癌治疗新方案的主要思路。

3.4 结直肠癌

Fuentes等[26]研究发现, 与相应的正常结肠组织相比, S100P在结肠癌组织中高表达。并且体外实验表明, S100P与结肠癌的生长、转移、ERK(extracellular-regulated kinase)磷酸化及NF-κB的激活有关。结肠扁平腺瘤极易发展成恶性肿瘤, Kita等[37]在扁平腺瘤和正常结肠黏膜基因表达差异的研究中发现, S100P在结肠扁平腺瘤中异常表达。Tang等[38]研究发现, 对草酸铂和5-氟尿嘧啶同时耐药的细胞株THC8307/L-OHP, 其S100P表达水平升高。与胰腺癌相似, S100P通过与RAGE结合激活受体蛋白活性及关键信号通路, 包括ERK1/2和NF-κB信号通路。正常结直肠黏膜中也有检测到S100P的表达, Birkenkamp-Demtroder等[39]研究发现, 左半结肠*S100P* mRNA的表达是右半结肠的7.6倍。与正常对照组织相比, S100P蛋白及mRNA在结直肠癌组织中的表达明显增高[26,39]。不表达S100P的结肠癌细胞株SW480导入外源性S100P后, 细胞的增殖及迁移能力均明显增强, 且呈现出剂量依赖性与时间依赖性的特点[26]。RAGE拮抗剂可以阻断S100P在结肠癌细胞中对ERK1/2磷酸化的刺激以及NF-κB的活化, 提示S100P通过活化RAGE起作用。但与肝癌及胰腺癌不同的是, RAGE在结肠癌中的表达相对于正常结肠组织并没有增高[26]。我们研究组前期的研究结果发现, 利用慢病毒表达载体携带靶向S100P的shRNA, 抑制结肠癌细胞DLD-1和SW620中的S100P表达, 可以抑制肿瘤细胞体外增殖、克隆形成和侵袭以及裸鼠体内的致瘤性和肝转移能力[40]。S100P的表达与结直肠癌患者临床分期、区域淋巴结转移有关, 而与患者性别、年龄、肿瘤浸润深度及肿瘤复发无明显相关。Kaplan-Meier单因素生存分析结果显示, S100P表达与病人预后无明显统计学意义, 但生存曲线显示S100P低表达患者生存时间较长(数据尚未发表)。

3.5 胃癌

S100P在胃癌中表达, 且与癌细胞的生长转移有关。胃癌中PrP^C(朊蛋白)通过钙结合蛋白提高细胞间Ca^{2+}浓度, 或者通过细胞间Ca^{2+}浓度的积累促进S100P蛋白的表达[41]。Zhao等[42]利用免疫组化组织芯片技术研究了121例胃癌病人标本中S100P的表达, 发现S100P阳性率为52.9%, 并且S100P阳性的病人5年内生存率明显高于S100P表达阴性的病人, 此外, BGC823细胞株过表达S100P能够明显降低草酸铂的半数有效浓度(half-inhibitory concentration IC_{50})。胃癌晚期预后相关蛋白的质谱分析研究表明, S100P表达下调与临床不良预后有关[43]。S100P蛋白的表达对胃癌预后及药物耐药性的影响不同于其他消化道肿瘤, 提示其可能在不同肿瘤中的作用及调控途径存在一定差异。

3.6 S100P表达的调控机制

S100P在消化道肿瘤中的异常表达调控机制尚未完全清楚, 其与多种信号通路有关, 也可能和肿瘤的异质性有关。表观遗传学的改变在肿瘤中可

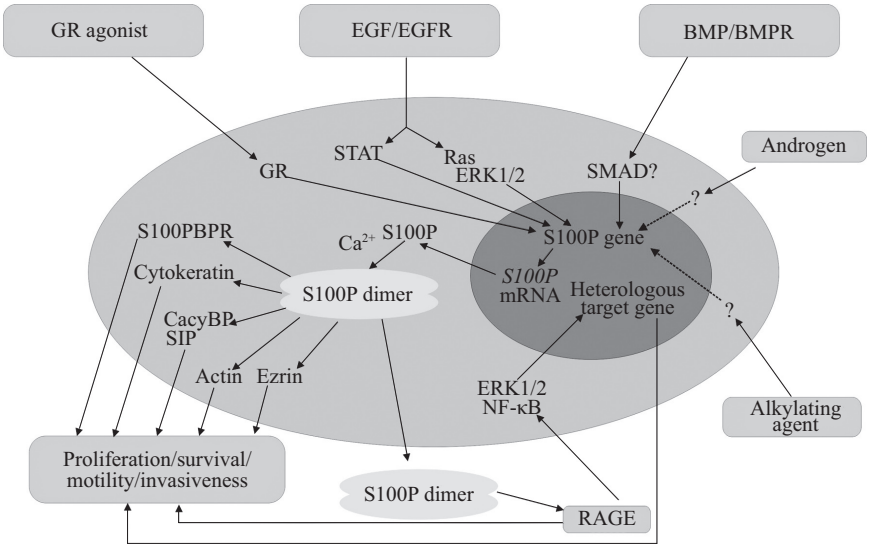
以起到重要的作用, 已有研究发现, 在胰腺癌[44]中S100P的异常表达与基因的甲基化状态有关, 但在结直肠癌以及其他消化道肿瘤中未见相关报道。同样在前列腺癌的细胞水平和组织水平的研究中发现, S100P蛋白的表达与*S100P*基因的低甲基化有关[45]。Hamada等[46]在胰腺癌细胞的研究中发现, BMP-4能够诱导S100P的转录, 但是其具体的通路和作用机制并不十分清楚。BMP-4是上皮间液细胞转换的重要活跃组分, 而上皮间液细胞转换是癌细胞转移的前期表现, 因此通过BMP-4调节S100P的表达合理解释了S100P能够促进肿瘤细胞的转移、侵袭和代谢的现象。

此外, Averboukh等[47]研究发现, S100P表达受雄性激素的调节, 烷化剂也能诱导肿瘤细胞中S100P的选择性上调[48]。同样, 在胸腺癌细胞中孕酮通过孕酮受体调节S100P的表达[49]。

*S100P*转录起始位点核心启动子区域包含大量顺式作用元件, 具有与SMAD、STAT/CREB、SP1/KLF转录因子和糖皮质激素受体(glucocorticoid receptor, GR)的共有序列, 这些结合位点是S100P表达所需的主要顺式作用元件[50], 并与肿瘤细胞中的各种信号通路有关。例如: 在细胞内, 激素通过糖皮质激素受体途径激发S100P的活性, 生长因子则通过相应的跨膜受体[如epidermal growth factor receptor(EGFR)、bone morphogenic factor receptor(BMPR)]影响S100P的表达; 来自这些通路的信号可能由NF-κB转录因子、STAT和SMAD等介导, 通过ERK(extracellular-regulated kinases)途径传递[51-54]。有研究表明, S100P的转录调控受GR影响[55]。因此, EGF和皮质醇能够增强S100P启动子的活性, 而SP-1、MAPK和PI3K等信号通路抑制剂能够降低S100P启动子的活性[54]。体外研究表明, S100P在对一些促生长药物耐药的细胞中的表达明显高于对促生长药物敏感的细胞, 例如环磷酰胺、依托泊苷、甲氨蝶呤、米托蒽醌[56-57]。探讨调控S100P表达的机制, 通过阻断基因表达, 对改善与其相关的预后和耐药性方面可能有一定的帮助。

3.7 S100P的相互作用蛋白

S100P在肿瘤中的作用通路比较复杂, 其在各种肿瘤中发挥作用的具体机制并不完全相同。RAGE是目前研究得比较清楚的信号蛋白, 是S100P的相互作用蛋白之一, 肿瘤中过度表达的S100P可以通过与RAGE结合激活重要的信号通路, 包括ERK1/2和NF-κB信号通路[16,58-59]。有研究表明, 色氨



基于现有的研究表明, GR agonist、EGF、BMP、雄性激素、烷化剂等能够调节*S100P*基因的表达, 同时功能研究揭示, *S100P*启动区具有SMAD、STAT/CREB等结合位点。S100P蛋白主要通过介导Ca^{2+}依赖的信号转导途径, 调节蛋白功能, 从而调控细胞周期和细胞生长增殖等[54,63]。The promoter area of *S100P* has binding sites for SMAD and STAT/CREB, key regulatory elements participating in transcriptional activation of the *S100P* gene. GR agonists, EGF, BMP, Androgen and alkylating agent can regulate the expression of *S100P*. All in all *S100P* can promote cancer progression via its specific roles in cell proliferation, survival, angiogenesis and metastasis. Signal transduction pathways mediating these effects mainly include Ca^{2+} ions[54,63].

图1 S100P调控机制示意图

Fig.1 The regulation mechanism of S100P

酸能够结合S100P阻止其激活RAGE, 从而抑制肿瘤的生长, 并且在动物实验模型中增强吉西他滨的治疗作用[47]。但在不同肿瘤中RAGE的表达是有差异的。在前列腺癌与乳腺癌中, RAGE的表达是上调的; 但在结肠癌与胰腺癌组织中, RAGE的表达相对于正常对照组织并没有增多[26]。除此之外, S100P蛋白还可结合并介导活化Ezrin蛋白、IQGAP1、S100PBPR等。Ezrin是一种多功能蛋白, 参与调解细胞膜骨架结构, 与细胞分化、黏附和转移有关。Ezrin能够被Ga^{2+}依赖的EF手型结构蛋白S100P激活, 促进肿瘤细胞穿越内皮细胞层, 在肿瘤的浸润与转移中起到一定的作用[17]。IQGAP1是一种多功能蛋白, 能够补充信号转导通路中的作用成分, 调节细胞骨架肌动蛋白和动力微管。S100P能够结合IQGAP1, 影响其生物学功能[60]。Dowen等[4]报道, S100PBPR也是S100P的相互作用蛋白。S100P可与泛素化通路的CacyBP/SIP作用, 进而降解β-连环蛋白(β-catenin)[61]。另有研究表明, S100P诱导新陈代谢的最初期的机制是: S100P先与NMIIA结合, 从而影响中心黏附位点(FAS)和细胞的黏附性。S100P过表达降低了其与NMIIA-FAS的组合, 减少了锚定中心, 促进了肿瘤细胞转移[62]。

4 展望

尽管研究表明S100P与多种恶性肿瘤有关, 但是我们仍然不了解S100P与各种靶蛋白间的相互作用机制和其在各种信号通路中的具体功能。研究肿瘤细胞中与S100P协同表达的各种信号蛋白, 将有助于揭示S100P在肿瘤中的具体作用机制。

目前, S100P最可能的应用前景是通过上游调控途径影响S100P的表达水平或者下游转导途径调节S100P蛋白, 从而促进药物对肿瘤的作用。但是通过转录调控S100P来实现对抗肿瘤仍然是非常复杂的, 它受到各种刺激引起的信号通路、细胞类型、生理环境、转录因子水平等的影响。因此, 还需要更多的研究来确定S100P蛋白在肿瘤中的作用, 从而为其在临床中的应用做准备。

总之, 随着近年来对S100P的深入研究, 发现其在多种消化道肿瘤中有着不同程度的异常表达, 且与肿瘤的分期、预后以及耐药性等方面有关, 因此S100P作为一个有潜在价值的肿瘤标记物的地位已经确立。然而, S100P在各种消化道肿瘤中表达的意义不尽相同, 其调节机制及生物学功能有待进一步探讨, 以期使其在消化道肿瘤的诊治与评估中发挥更大的作用。

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