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文献综述 REVIEW

抗酒石酸酸性磷酸酶在恶性肿瘤中的研究进展

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背景资料
抗酒石酸酸性磷酸酶(type 5 acid phosphatase 5, ACP5)是酸性磷酸酶家族中的一种高度保守的金属蛋白酶, 是骨吸收和破骨细胞活性的良好标志物, 当恶性肿瘤发生骨转移和骨破坏时血清ACP5含量明显增高.

Role of tartrate-resistant acid phosphatase in malignant tumors

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Abstract
The acid phosphatase 5, tartrate resistant or tartrate-resistant acid phosphatase (ACP5/TRACP/TRAP) is a metalloproteinase of the acid phosphatase family, which is a good marker of bone resorption and osteoclast activity. It has recently been found that the expression of ACP5 in a variety of tumors is significantly higher than that in matched normal tissues. These suggest that ACP5 may play an important role in the occurrence and development of tumors.

Key Words: ACP5; Hepatic carcinoma; Gastric carcinoma; Gallbladder carcinoma; Breast cancer; Bone metastasis

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摘要
抗酒石酸酸性磷酸酶(type 5 acid phosphatase/tartrate-resistant acid phosphatase, ACP5/TRACP/TRAP)是酸性磷酸酶家族中的金属蛋白酶, 是骨吸收和破骨细胞活性的良好标志物. 近来发现ACP5在多种肿瘤中的表达比配对正常组织中的表达显著上调, 该现象提示, ACP5可能肿瘤的发生发展中起到一定的作用.

关键词: 抗酒石酸酸性磷酸酶; 肝癌; 胃癌; 胆囊癌; 乳腺癌; 骨转移

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研发前沿

目前有很多学者对ACP5在恶性肿瘤中的指标进行了大量的研究, 证明ACP5在肿瘤的发生、发展及转移中都起着一定的作用. ACP已经作为一类诊断标志物和干预的工具已经广泛应用于临床, 这对ACP5在临床的应用奠定了基础.

核心提要: 抗酒石酸酸性磷酸酶(type 5 acid phosphatase 5, ACP5)是酸性磷酸酶家族中的一种金属蛋白酶, 而近年研究开始揭示ACP5在恶性肿瘤中的作用, 本文通过复习相关文献, 对ACP5近年来与相关恶性肿瘤病理特征及预后等方面的研究进展作一综述.

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0 引言

抗酒石酸酸性磷酸酶(type 5 acid phosphatase 5, ACP5)是一种在自然界中广泛存在的酶, 存在于许多动物和植物中[1]. 目前, ACP作为一类诊断标志物和干预的工具已经广泛应用于临床. ACP是的一组在pH低于7的条件下发挥作用最好的同工酶[2], ACP通常以不同的形式存在于人体大多数组织及体液中, 在细胞中ACP不仅定位于溶酶体, 同时也存在于细胞核、胞液、微粒体及高尔基体. 根据对酒石酸盐抑制的反应, 将具有抗抑制效应的ACP同工酶分为两类, 即ACP1与ACP5. ACP1只存在于红细胞中, 因而将血浆或血清中的ACP5称为抗酒石酸酸性磷酸酶(ACP5/tartrate resistant/tartrate-resistant acid phosphatase, ACP5/TRACP/TRAP), ACP5是酸性磷酸酶家族中的金属蛋白酶, 主要位于破骨细胞及单核细胞, 是骨吸收和破骨细胞活性的良好标志物. ACP5根据来源不同, 将破骨细胞来源者称为5b, 非骨源性者为5a, 两者具有不同的功能[2]. 近来发现ACP5在多种肿瘤的发生、发展及转移过程中起到一定的作用.

1 ACP5基因的特点

*ACP5*基因位于人类19号染色体(19p13.2-13.3)和小鼠9号染色体上[3]. 蛋白质测序提示, ACP5 DNA在整个哺乳动物中是高度保守的, 同时*ACP5*基因已经在猪、大鼠、人和小鼠类中成功克隆并测序[3]. ACP5由8个外显子和7个内含子组成, mRNA 1640 bp, 编码信号肽的为281.343 CDS区(coding sequence): 281.1258, 编码成熟肽的为: 344.1255, 分子量大约37 kDa, 编码的蛋白质含325个氨基酸, 包括21个氨基酸的信号肽和304个氨基酸的成熟肽, 成熟肽能够分泌到血液中发挥重要作用.

相关报道

以往ACP5研究多集中在骨质疏松、关节炎、肾病、骨肿瘤和肿瘤骨转移等骨吸收性疾病, 而最近的研究表明许多恶性肿瘤组织ACP5呈现不同程度的高表达.

2 ACP5的生理特性

ACP5的具体生理功能还不太清楚, 但目前认为其功能主要有骨桥蛋白/骨涎蛋白去磷酸化, 活性氧(reactive oxygen species, ROS)的产生, 铁转运以及作为一种细胞生长和分化的因子[4,5]. 现已证实ACP5广泛表达在树突状细胞、激活的巨噬细胞和破骨细胞/巨噬细胞系, 在各种组织中以骨组织中ACP5表达最高[6,7]. 在破骨细胞中, ACP5位于溶酶体, 高尔基体和囊泡的皱褶边界区域[8]. 相关研究[9]显示, ACP5敲除的小鼠表现出轻度的骨硬化, 与破骨细胞活性降低有关, 并且, 随着年龄的增长, 这会导致骨皮质增厚和缩短, 股骨远端形成球状畸形, 并且骨骺随着软骨矿化的延迟而扩大. 然而在ACP5过表达转基因小鼠则表现出轻度骨质疏松症, 这与成骨细胞活性和骨骼合成的增加有关[10-12].

3 ACP5与肿瘤骨转移的关系

基于ACP5的特性, 以往ACP5研究多集中在骨质疏松[13-18]、关节炎[19,20]、结节病[21]、肾病[22-25]、免疫性疾病[26-28]、代谢性疾病[29,30]、甲状旁腺亢进[31]、骨肿瘤[32,33]和肿瘤骨转移等骨吸收性疾病. 最近的相关研究[34,35]显示心血管疾病患者ACP5水平也显著升高. 当恶性肿瘤发生骨转移和骨破坏时血清ACP5含量明显增高, 可作为恶性肿瘤预后不良及监测骨转移发生的血清学指标[36-39]. 其主要原因可能是ACP5的活性增强会影响细胞间钙桥的链接, 促进肿瘤细胞解离, 扩散和浸润.

Chao等[40]、Voorzanger-Rousselot等[41]以及Korpela等[42]的研究均显示, 乳腺癌骨转移时, 血清ACP5含量显著升高, 提示ACP5能够很好地预测及监测乳腺癌骨转移的程度. 同时对于那些已发生骨转移, 同时在进行抗肿瘤治疗的乳腺癌患者来说, 监测ACP5能够很好地显示药物抗肿瘤骨转移作用的效果, 并且能够预测乳腺癌骨转移患者的生存预后[43-46]. 相关研究[17,38,47-51]显示, 在前列腺癌骨转移患者中, 血清ACP5浓度显著升高, 能很好地反应转移灶中破骨作用, 通过监测前列腺癌患者的血清ACP5的水平, 可以很好地反映肿瘤的生长状态, 同时对判断肿瘤的进展、预测前列腺癌骨转移的发生具有重要的临床意义. 但是, 研究[48,49]也表明, 血清ACP5的水平并不能很好地预测前列腺癌骨转移患者的生存预后. 相关研究[52,53]显

示, 在肺癌骨转移中, ACP5水平也明显增高.

4 ACP5与恶性肿瘤的联系

ACP5对恶性肿瘤本身同样具有重要意义, 与他可以发生在不同系统, 不同器官的肿瘤中, 并且与肿瘤的发生发展有密切的联系, 而且这种联系有对肿瘤的转移、迁徙有很大的影响. 新近研究发现, 一些未发生骨转移的上皮性恶性肿瘤血清ACP5含量也明显增加, 提示其肿瘤细胞自身能合成和分泌ACP5, 同时其表达水平与这些恶性肿瘤进展、侵袭转移能力及预后密切相关, 高水平表达的恶性肿瘤一般进展迅速, 侵袭能力强, 比较容易发生转移和复发, 且预后也较差.

4.1 肝癌 Chan等[54]通过光谱核型分析显示在肝癌(hepatocellular carcinoma, HCC)中ACP5出现了频繁的下调. 他们对10株肝癌细胞系进行FISH实验, 实验显示有6株细胞系的第19p染色体有结构的变异, 其中有4株易位到了其同源染色体上. 通过荧光标记探针, 物理作图可以看到断裂点在19p13.12和19p12之间. 同时, 他们检测了肝癌组织中ACP5的表达情况, 发现肝癌肿瘤组织中ACP5表达与正常肝脏组织相比降低18倍. 同时, 乙型肝炎病毒(hepatitis B virus, HBV)诱导的肝硬化引起的肝癌病例中, ACP5表现出相当高的表达抑制作用, 这表明ACP5在HBV诱导的肝癌发生发展中发挥更重要的作用. 然而, Xia等[55]研究发现却得出了相反的结果. 他们的研究发现, ACP5在肝癌组织中的表达比癌旁组织中的表达显著增高, 同时, ACP5过表达和微血管浸润, 肝癌分化以及TNM分期有关; 此外, ACP5阳性的HCC患者比阴性的患者预后要差. 多因素生存分析揭示, ACP5是疾病复发和术后低的生存的一个独立的和显著的危险因素. Transwell小室实验以及常规的转移模型表明上调的ACP5能促进肝癌的侵袭和肺转移, 而将ACP5敲除后, 能够明显的减弱Foxm1促进侵袭和肺转移的作用. 在肝癌中, ACP5的表达与FoxM1的表达呈正相关, 并且他们的共表达与HCC的预后较差有关. 总之, ACP5在肝癌中的作用和机制仍不明确, 其表现到底是促癌作用还是抑癌作用, 或者说具有双刃剑作用, 这仍需要进一步研究探寻.

4.2 胃癌 相关研究[56-58]发现, 在诱发小鼠前胃癌和大鼠胃癌癌变过程中, ACP5活性从总体上呈增强趋势, 有远处转移的胃癌患者的预后很差. Kawamura等[56]研究发现, ACP5在胃癌组织比正常癌旁黏膜组织表达明显增高. 分析ACP5的表达与胃癌患者临床病理资料发现, ACP5与淋巴结转移, 腹膜播散以及TNM分期具有明显的相关性. 同时, 多因素分析显示ACP5的表达是腹膜播散的独立危险因素. 此外, ACP5高表达患者的生存时间更短. ACP5表达水平可能是胃癌腹膜转移和生存预后标志物.

4.3 胆囊癌 吕芳等[59]研究胆囊良恶性病变组织中ACP5表达水平发现, 胆囊腺癌ACP5表达阳性率明显高于癌旁组织、腺瘤性息肉和慢性胆囊炎胆囊上皮. 同时在所有胆囊癌病例中, 中或低分化腺癌、肿瘤最大直径≥2 cm、淋巴结转移阳性和侵犯周围组织患者的ACP5表达阳性率明显高于那些高分化、肿瘤最大直径<2 cm、无淋巴结转移和未侵犯周围组织的病例. 上述结果提示部分胆囊腺癌细胞本身能够分泌ACP5, 其表达水平可能与胆囊腺癌发生发展、侵袭转移以及生存预后明显相关, 但是其确切作用机制有待更深入研究.

4.4 乳腺癌 Honig等[60]发现乳腺癌组织中ACP5表达高于正常组织. 而Adams等[61]研究也支持上述结果, 他们同时检测了不同乳腺癌细胞系中ACP5的表达情况, 也发现在多种乳腺癌细胞株中TRAP均有表达. Krumpel等[62]研究化学酶抑制剂CD13对ACP5抑制作用时发现, CD13能很好地抑制表达TRACP的乳腺癌细胞株MDA-MB-231的侵袭和迁移, 同时发现CD13是通过阻断TRACP5b来发挥抑制作用的.

4.5 肺癌 Gao等[63]研究ACP5在肺腺癌中的表达情况发现, ACP5的高表达与淋巴结转移, TNM分期以及病理分化显着相关. 从单变量生存分析及多变量Cox回归分析显示, ACP5表达的高表达是肺腺癌生存的独立预后因素.

4.6 结肠癌 How等[64]研究发现, 即结直肠腺癌患者中, ACP5高表达的患者5年生存率增加约20%, 疾病特异性死亡风险降低47%以上. 同时, 该研究还发现上述预后的改善与巨噬细胞表达ACP5相关, 并且意味着ACP5作为结肠癌中的潜在生物标志物.

4.7 其他恶性肿瘤 相关研究[53]显示, ACP5在黑色素瘤、卵巢癌中高表达, 并与其预后相关.

5 展望

ACP5不仅是一种反应骨吸收的标志, 同时他的表达也影响着肿瘤的发生和发展. 从目前

创新盘点

本文复习近年来相关文献, 从分子病理学、肿瘤学、肿瘤转移机制、治疗及预后等方面对ACP5的研究进展予以综述.

应用要点

目前ACP5的研究逐步涉及到肿瘤领域, 抗酒石酸酸性磷酸酶在肿瘤组织中的变化是否也出现在血清中, 为将来临床诊断及预后提供帮助.

的研究来看, 多种恶性肿瘤细胞自身能够表达ACP5(包括肝癌、胃癌、胆囊腺癌、结肠癌、乳腺癌等). 因此使得ACP5在肿瘤中有更独特的研究价值. 根据ACP5在正常组织和肿瘤组织中的表达差异, 已经有学者开始研究针对ACP5的检测方法应用于肿瘤诊断. 而联合其他检测指标, 则能增加肿瘤诊断的灵敏性和准确性. 随着人们对ACP5的进一步认识, 针对ACP5的靶向治疗措施将也将得到进一步研究探索, 为肿瘤的诊治提供一个新的方向.

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名词解释

酸性磷酸酶(ACP): 是一种在自然界中广泛存在的酶, 在人类中通常以不同的形式存在于大多数组织及体液中, 在细胞中ACP不仅定位于溶酶体, 同时也存在于细胞核、胞液、微粒体及高尔基体.

同行评价

本文选题新颖, 文章脉络清晰, 从分子病理学、肿瘤学、肿瘤转移机制、治疗及预后等方面对ACP5作了详细的综述, 对加深ACP5的认识有很大意义, 对临床有一定参考价值.

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