

含缬酪肽蛋白与消化系统肿瘤

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收稿日期: 2005-09-10 接受日期: 2005-09-30

摘要

含缬酪肽蛋白(valosin-containing protein, VCP)即p97, 是一种广泛存在的膜结合糖蛋白, 在细胞活性中有着广泛的功能, 其总的特点是作为类似分子伴侣的作用在内质网相关的蛋白降解及细胞周期调控中起重要作用. 已有许多研究证实: VCP的表达水平与食道癌、胃癌、结直肠癌、肝癌、胰腺癌等消化系统恶性肿瘤的临床病理特征之间密切相关. VCP表达水平高者, 出现复发及转移早, 无瘤生存期短, 预后差. 本文就近年来有关VCP表达水平与消化系统肿瘤相关性的文章进行了回顾.

关键词: 急性胰腺炎; 急性脑损伤; 发病机制

尹义梅, 穆建平, 张晓岚. 含缬酪肽蛋白与消化系统肿瘤. 世界华人消化杂志 2005;13(22):2672-2676
<http://www.wjgnet.com/1009-3079/13/2672.asp>

0 引言

在我国消化系统恶性肿瘤的死亡率较高, 其中胃癌居各种恶性肿瘤死亡率的首位^[1], 胃癌的5 a生存率仅约20%^[2]. 近年来, 由于诊断技术的不断提高, 消化系统肿瘤的早期发现比率不断提高, 患者的预后得到显著改善. 进展期的患者选择合理的治疗方案, 对于提高生存率至关重要, 有些病人的全身转移就发生在外科治疗后, 甚至是根治术后; 即便是严格的TNM分期, 同一病理分期的患者的预后, 也有大大的不同, 这可能是在手术时就有患者发生了微转移. 因此, 有效的判断胃癌的进展和预后, 对于合理选择治疗方案、提高生存率非常重要. 近年来越来越多的研究显示, 含缬酪肽蛋白(valosin-containing protein, VCP)对消化系统肿瘤的进展和预后具有预测价值.

1 VCP的结构

VCP是与多种细胞活性相关的三磷酸腺苷酶超家族(ATPases associated with various cellular activities, AAA)中的一员, 是糖基磷脂酰肌醇连接的转铁蛋白同系物, 最初发现于黑色素瘤细胞表面, 是一种膜结合糖

蛋白, 其相对分子质量为 M_r 97 000, 又称黑色素转铁蛋白或p97, 它有着广泛的分布, 在酵母、两栖动物及昆虫中均有同系类似物存在^[3,4]. VCP是一个可溶性似环六聚体, 由250个氨基酸残基组成的N端、2个保守的ATP结合域和C端组成. N端的250个氨基酸残基包含有Walk A、B基序, 这是ATP结合和水解的重要结构, N端能结合多泛素链, 负责识别底物. VCP的2个保守的ATP结合域D1、D2区域有高度的序列相似性, 负责类似分子伴侣的活性, 在VCP的ATP酶循环中, D1环是其稳固性所必需的, 在热诱导的活性中发挥作用. D2环控制主要的ATP酶活性, 主要执行构象改变^[5]. 在色氨酸荧光性及胰蛋白酶分析中发现^[6], 只有在D2环完整存在条件下, ATP/ADP与VCP结合才能使其构象改变, 使被束缚的底物发生张力改变, 导致蛋白络合物被分解或底物的伸展.

2 VCP的生物学功能

2.1 调控细胞增殖 无论在植物细胞细胞膜融合和细胞质分裂的过程中, 还是在哺乳动物细胞发生有丝分裂时, 必须有VCP同系类似物cdc48p或者VCP存在才能保证高尔基体能平等分配到子细胞中, 才能使纺锤体断开, 与染色体的分离最后完成^[7]. Uchiyama *et al*^[8]将注射了p97的细胞进行检测, 证实VCP存在才能保证高尔基体的分解和组装, 从而促进细胞的分裂与增殖. zhang *et al*^[9]将人4.1带-相关蛋白-酪氨酸磷酸酯酶1(the human band 4.1-related protein-tyrosine phosphatase, PTPH1)导入NIH3T3细胞中, 发现PTPH1的异常表达能抑制细胞的生长, 而PTPH1通过VCP的去磷酸化作用实现对细胞生长的调控. Huyton *et al*^[10,11]亦证实VCP的去磷酸化作用对于细胞周期的进展至关重要.

2.2 激活T细胞 Egerton *et al*^[12]研究发现, 在由T细胞受体引起一系列快速的细胞蛋白的酪氨酸磷酸化致T细胞激活时, 无论从鼠科动物、猪, 还是人的蛋白纯化测序中发现, VCP是T细胞受体早期酪氨酸磷酸化的底物, 在T细胞的激活中发挥重要作用.

2.3 维持内环境稳态 内质网中错误折叠蛋白的蓄积, 可以引起内环境稳态的失衡, 导致内质网应激, 致细胞程序化死亡. 内质网相关降解(endoplasmic reticulum-associated degradation, ERAD)是一个蛋白质量控制机制. Zhong *et al*^[13], Rao *et al*^[14]及Hirabayashi *et al*^[15,16]先后在实验中发现: 在ERAD过程中, VCP是反常折叠蛋

白的识别因子和病理效应器, 陪伴底物从内质网到细胞质中, 通过泛素蛋白酶体(ubiquitin proteasome, Ub-Pr)途径降解^[17-21]. Ub-Pr系统是真核细胞中的一种蛋白降解途径, 主要降解细胞内泛素化的蛋白质. 泛素经过泛素活化酶E1、泛素结合酶E2、泛素连接酶E3等一系列催化步骤结合底物蛋白, 形成泛素-底物蛋白复合物, 使底物进入26S蛋白酶体内实现泛素化降解^[22]. VCP是此泛素介导的蛋白酶降解过程中多泛素链上的标记因子, VCP的缺失导致Ub-Pr的抑制和泛素化蛋白的蓄积. VCP同泛素化的蛋白通过直接结合在其N末端至底物的多泛素链上, 而且其N末端在Ub-Pr中是必需的.

2.4 对核转录因子- κ B 的调控作用 有研究证实^[23], VCP的抗凋亡作用及促肿瘤转移作用是通过激活核转录因子NF- κ B(Nuclear-Factor kappa B, NF- κ B)信号转导通路实现的. NF- κ B的活化在抵抗细胞凋亡中的重要作用已被广泛证实. NF- κ B是由Rel蛋白家族中的成员以二聚体形式组成的转录因子. 细胞静息时, NF- κ B与其抑制因子(inhibitor of Nuclear-Factor kappa B, I- κ B)结合成无活性的复合物存在于细胞浆中, I- κ B遮蔽着NF- κ B的基因定位序列. 当细胞受到细菌、病毒、炎性细胞因子、肿瘤坏死因子、电力辐射及化疗药物等外界因子刺激时, I- κ B发生磷酸化并迅速降解, NF- κ B被激活, 转入细胞核内调控一系列基因表达. VCP对NF- κ B信号通路的作用是通过调控I- κ B实现的. I- κ B的失活导致NF- κ B的持续活化, 其发生包括I- κ B的磷酸化及Ub-Pr途径的降解作用. 已有研究证明: VCP确与I- κ B呈免疫复合物沉淀. VCP与泛素化的I- κ B的络合物与NF- κ B解离, 使NF- κ B激活. 在这个过程中, VCP在I- κ B和26S蛋白酶之间提供一个物质上和功能上的链, 并在Ub-Pr的降解中发挥重要作用, 缺乏VCP导致I- κ B代谢受阻, NF- κ B活性下降; VCP增高, 则NF- κ B的活性增强, 进而表达出抗凋亡和促肿瘤转移的作用.

VCP的所有活性, 已被证明^[24-27], 直接或间接的由泛素依赖的蛋白降解途径Ub-pr调控, 在此途径中VCP是作为一个普遍存在的分子伴侣来标记多种底物, 到蛋白酶处降解. 由于底物的多样性也形成了VCP在许多看起来并不相关的细胞活性中起作用^[28,29]. 这些底物有: 有丝分裂的细胞周期蛋白、细胞周期的蛋白的激酶抑制剂P27、原癌基因产物P53、c-myc、c-Jun、I- κ B. Asai *et al*^[23]应用VCP转染小鼠的骨肉瘤细胞株Dunn, 研究了VCP是否影响NF- κ B活性. 融合状态的Dunn细胞, VCP水平低, 磷酸化的I- κ B增加, NF- κ B活性近乎停止; 应用肿瘤坏死因子 α 刺激时, Dunn/VCP细胞则表现出持续的NF- κ B活化. 进一步研究证实, VCP的抗凋亡作用, 由于持续的NF- κ B的激活及直接的P-I- κ B活性减低.

3 VCP表达水平与消化系统肿瘤临床病理和预后的关系

Yamamoto *et al*^[30-35]先后对食道癌、胃癌、结直肠癌、肝癌、胰腺癌进行了VCP表达水平的研究应用免疫组织化学方法分析以上肿瘤切除物中VCP的表达水平, 并与同系无瘤相关组织进行对比, 将VCP表达水平弱于或等于同系无瘤相关组织定为水平1, 强于同系无瘤相关组织定为水平2, 结果显示, 食道癌、胃癌、结直肠癌、肝癌及胰腺癌组织中VCP呈水平2表达率达61.4-71.3%, 与肿瘤的大小、浸润程度、组织学类型、病理分期等密切相关, VCP高水平表达的患者易于淋巴结转移及复发; 相反则预后较好. 并对胃癌患者治疗后复查, 在早期胃癌中VCP表达水平1者, 5 a无瘤生存率100%, VCP表达水平2者, 5 a无瘤生存率90.4%; 在进展期胃癌中VCP表达水平1者, 5 a无瘤生存率85.7%, VCP表达水平2者, 5 a无瘤生存率51.8%, $P < 0.05$, 有明显的统计学差异. 证实VCP表达水平可以作为胃癌患者进展和预后预测因素.

Yamamoto *et al*又进行了结肠良恶性肿瘤间VCP表达水平的研究, 发现VCP在8例结肠腺瘤中全部呈低水平表达, 在10例结肠癌中全部呈高水平表达. Yamamoto, Tomita, Hoshida *et al*在食道癌、结直肠癌、肝癌中各选取病历, 分别为10例、8例和11例, 应用RT-PCR技术, 测定VCP mRNA, 比较其与VCP蛋白表达之间的关系, 发现VCP蛋白水平与VCP mRNA表达量显著正相关, 证明了免疫组织化学测定VCP水平的可靠性.

越来越多的实验证实, VCP的表达水平在消化系统肿瘤组织中比同系非瘤组织中的表达水平明显增高, 与肿瘤的大小、浸润深度、组织学类型、血管或淋巴管的转移及淋巴结的转移有明显的相关性. 组织学TNM分级与VCP水平相结合分析后认为, 无论是早期, 还是进展期, VCP表达水平对肿瘤都有提示和预测作用, 而与年龄、性别及肿瘤生长部位等未见相关关系. 有人在非小细胞性肺癌、前列腺癌、齿龈癌等病例中用同样的方法测定VCP水平^[36-38], 分析后得出与肿瘤的病理分型及转移等有显著相关性的结论.

诸多实验的多变量分析显示: 免疫组织化学方法测定VCP水平, 对于消化系统肿瘤的转移和复发是独立的预示因子.

总之, 由于VCP存在的广泛性^[39-51]、在细胞活动中的基础性^[52-67], 包括膜融合、细胞分裂周期调控、细胞内蛋白的运输和调控以及细胞凋亡等活动中, 均可见其重要作用. 目前比较肯定的抗凋亡及促肿瘤转移作用是通过激活核转录因子NF- κ B信号转导通路实现的. NF- κ B信号转导通路在肿瘤细胞代谢过程中的作用有研究证实^[68,69]. 因此可以预见, VCP对于肿瘤的转移与预后可能有预示作用. 在目前微创治疗日益成熟的今天, 能提前预示转移风险, 对于肿瘤患者合理的选择治疗极为有利.

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ISSN 1009-3079 CN 14-1260/R 2005 年版权归世界胃肠病学杂志社

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世界华人消化杂志 2004年 5月;12(5):1009-1014

中国首次载人航天航天员主着陆场区医疗保障及救护

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目的: 探讨中国首次载人航天主着陆场区航天员医疗保障及救护的经验体会. 方法: 结合我们参加中国首次载人航天航天员医疗保障及救护的体会, 8次在直升机上的医疗救护演练经验, 2次突发意外事故乘直升机远距离实施医疗救护的体会, 多次在载人航天医疗救护车上的医疗救护演练体会. 并参考国内外相关资料, 对载人航天航天员意外伤害提出有效的防治预案. 结果: 主要针对首飞载人航天航天员可能发生意外伤害的原因, 创新地把一个高质量的ICU全天候前移至草原上、沙漠里, 载体是载人航天医疗救护直升机及医疗救护车, 可以确保意外情况下航天员的安全. 创造了反应速度第一; 技术装备第一. 使救治规则、卫勤保障原则更趋于合理, 抢救成功率更高. 载人航天医疗保障系统在装备、方案、试验等方面能满足安全性的要求. 航天员主着陆场的医疗卫勤保障工作能够体现急救医学“快速反应, 立体救护”的理念. 载人航天医疗救护直升机在航天员的医疗保障及救护中起着十分重要的作用, 他有机动性强、速度快、飞行高度较低的优点, 在草原及沙漠地区都可着落实施救护. 结论: 返回着陆场区的航天员实施快速医疗救护, 能保障航天员安全, 圆满完成载人航天任务.

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