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PAX-5 在非淋巴造血系统肿瘤中的研究进展

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[摘要] PAX-5 基因是 PAX 基因 (paired box gene) 家族的一员, 其编码的蛋白被称为 B 细胞特异性激活蛋白 (B cell specific activator protein, BSAP), 在 B 细胞的生长和发育过程中具有重要的作用。PAX-5 在 B 淋巴细胞及其来源的肿瘤中可高表达, 尤其是 B 淋巴瘤母细胞淋巴瘤, 是一种用于淋巴造血系统肿瘤诊断与鉴别诊断的可靠标志物。近年来研究发现 PAX-5 可在淋巴造血系统外的恶性肿瘤中异常表达, 例如神经内分泌肿瘤 (Merkel 细胞癌、小细胞癌和大细胞神经内分泌癌、胃肠道神经内分泌肿瘤)、乳腺癌、肝细胞癌、膀胱癌、星形细胞瘤、髓母细胞瘤、口腔鳞状细胞癌等, 造成某些淋巴造血系统肿瘤诊断及鉴别诊断的困难, 而且 PAX-5 与某些恶性肿瘤的进展、转移及预后有关。因此, 研究 PAX-5 在非淋巴造血系统肿瘤中的表达具有重要意义。

[关键词] PAX-5; 非淋巴造血系统; 肿瘤

Research progress of PAX-5 expression in non-lymphoid hematopoietic system tumors

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Abstract PAX-5 gene is a member of PAX gene family. The encoded protein of PAX-5 is called B cell specific activator protein (BSAP) and plays an important role in the growth and development of B cells. PAX-5 is highly expressed in B lymphocytes and their derived tumors, especially in B lymphoblastic lymphomas. It is a reliable marker for the diagnosis and differential diagnosis of lymphoid hematopoietic system tumors. In recent years, studies have found that PAX-5 can be abnormally expressed in malignant tumors outside the lymphatic hematopoietic system, such as neuroendocrine tumors (Merkel cell carcinoma, small cell carcinoma and large cell neuroendocrine carcinoma, gastrointestinal neuroendocrine tumor), breast carcinoma, hepatocellular carcinoma, bladder cancer, astrocytoma, medulloblastoma, oral squamous cell carcinoma and it is related to the progression, metastasis and prognosis of certain malignant tumors. Therefore, it is of great significance to study the expression of PAX-5 in non-lymphoid hematopoietic system tumors.

Keywords PAX-5; non lymphoid hematopoietic system; tumor

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PAX基因(paired box gene)家族是一类人类在胚胎发育过程中能够编码重要转录因子的成对区的基因家族。PAX-5是PAX基因家族一员, 在1989年由Barberis等^[1]确认为一种新的B细胞反式转录因子, 其编码的蛋白被称为B细胞特异性激活蛋白(BSAP)^[2], 在正常B细胞的生长、发育及分化过程中起重要作用。以往PAX-5通常用于淋巴造血系统肿瘤的诊断及鉴别诊断中, 尤其是B细胞淋巴瘤, 而关于其在非淋巴造血系统肿瘤中的表达研究较少。近年有研究^[3-7]报道: PAX-5在多种非淋巴造血系统肿瘤中可异常表达, 在某些恶性肿瘤中有高表达。因此, 研究PAX-5在非淋巴造血系统肿瘤中表达不仅有助于淋巴造血系统肿瘤的诊断及鉴别诊断, 而且对于了解PAX5与肿瘤发生、发展的关系具有重要意义。

1 PAX-5 基因的分类及分布

PAX-5基因位于人类染色体9p13^[8], PAX-5可分为PAX-5a, PAX-5b, PAX-5c, PAX-5d及PAX-5e。其中PAX-5a最重要, PAX-5通常指PAX-5a^[9]。PAX-5a基因含有1 176个核苷酸序列(共包含10个外显子), 其编码的蛋白含有391个氨基酸; PAX-5b基因和PAX-5a基因结构相似, 其主要区别在于前者没有47~212核苷酸序列(缺少第2个外显子); PAX-5c基因结构目前尚不清楚; PAX-5d基因比PAX-5a基因短, 主要区别在于前者没有第605个核苷酸之后的序列(缺少第6~10个外显子); PAX-5e基因更短, 其没有47-212和605个核苷酸之后序列(缺少第2个和6~10个外显子)^[9-10]。

既往研究^[11]报道PAX-5主要在淋巴造血细胞及其来源肿瘤中表达, PAX-5可表达在经典霍奇金淋巴瘤、B细胞及其来源的肿瘤, 例如B淋巴瘤母细胞淋巴瘤、弥漫大B细胞淋巴瘤、套细胞淋巴瘤、滤泡性淋巴瘤等, 而在浆细胞、T细胞及其来源肿瘤, 例如浆细胞瘤、T淋巴瘤母细胞淋巴瘤、NK/T细胞淋巴瘤、外周T细胞淋巴瘤、间变性大细胞淋巴瘤等中均几乎不表达。近年来有研究^[3-7,12]逐渐报道: PAX-5可在非淋巴造血系统外的某些恶性肿瘤中异常表达, 例如神经内分泌肿瘤(Merkel细胞癌、小细胞癌和大细胞神经内分泌癌、胃肠道神经内分泌肿瘤)、乳腺癌、肝细胞癌、膀胱癌、星形细胞瘤等。

2 PAX-5 在非淋巴造血肿瘤中的表达

2.1 神经内分泌肿瘤中的表达

2.1.1 Merkel 细胞癌中的表达

Merkel细胞癌是发生在皮肤的一种神经内分泌肿瘤。研究^[3,13]发现PAX-5在Merkel细胞癌中有较高表达, 其阳性率为70.6%~100%。Dong等^[14]在2005年发现PAX-5不仅局限于B淋巴细胞, 还可以在Merkel细胞癌中表达。Mhaweck-Fauceglia等^[13]和Buresh等^[15]的研究也证实这一观点, PAX-5可作为Merkel细胞癌诊断的标志物。Merkel细胞癌的来源一直是研究的热点, PAX-5, TdT以及多种免疫球蛋白(IgH和Igk)在Merkel细胞癌中表达, 使B细胞是Merkel细胞癌来源的观点开始被大家关注^[16]。

2.1.2 肺神经内分泌肿瘤中的表达

肺神经内分泌肿瘤可分为类癌、不典型类癌、小细胞癌、大细胞神经内分泌癌4个肿瘤亚型和特发性弥漫性神经内分泌细胞增生, 其占有肺肿瘤的20%~30%^[17]。PAX-5在各种肺神经内分泌肿瘤中表达差别较大, 低、中级别神经内分泌肿瘤(类癌和不典型类癌)中几乎不表达, 在高级别神经内分泌肿瘤(小细胞癌和大细胞神经内分泌癌)中表达较高^[18]。肺大细胞神经内分泌癌中PAX-5阳性率为67%^[18], 而除个别研究报道PAX-5在肺小细胞癌中不表达外^[19], 肺小细胞癌中PAX-5阳性率为43.8%~91.7%^[20-21]。因此, PAX-5可用于低、中级别神经内分泌肿瘤和高级别神经内分泌肿瘤之间的鉴别诊断。Kanteti等^[21]研究发现: PAX-5异常表达可提升c-Met的表达, 从而增加肺小细胞癌的转移, PAX-5可能是一个肺小细胞癌潜在的治疗靶点。还有研究^[20,22]发现: 在肺小细胞癌中, 若PAX-5阳性则提示患者预后较差, 提示PAX-5可以作为一个判断肺小细胞癌预后的标志物。PAX-5在非小细胞癌肺癌(肺鳞癌和肺腺癌)中几乎不表达^[23], 其可用于非小细胞肺癌与高级别神经内分泌肿瘤的鉴别诊断。

2.1.3 胃肠胰神经内分泌肿瘤中的表达

根据中国胃肠胰神经内分泌肿瘤专家共识(2016年版)^[24], 胃肠胰神经内分泌肿瘤(gastroenteropancreatic neuroendocrine neoplasms, GEP-NENs)包括所有高、中、低分化的神经内分泌肿瘤, 其中NETs是指高、中分化的神经内分泌肿瘤, 而NEc则是指低分化的神经内分泌癌。叶郁红等^[4]研究发现: PAX-5在NET中不表达, 在NEc中

可表达(其阳性率为43.9%),而且PAX-5的表达和肿瘤的大小、淋巴结转移及临床分期有显著相关性,即肿瘤体积大、有淋巴结转移及临床分期高时其高表达。PAX-5着色部位主要在细胞核,而最近文献[25]报道:在高分化直肠内分泌肿瘤(类癌)中,PAX-5可以着色在细胞质(以颗粒状形式),这一特点可用于直肠类癌与其他神经内分泌肿瘤的鉴别诊断。

2.2 乳腺癌中的表达

PAX-5在乳腺癌中可高表达。Benzina等^[5]研究报道PAX-5在乳腺癌中的表达率为97.6%(298/306),一方面可以抑制乳腺癌浸润和转移,另一方面可以增加乳腺癌细胞的黏附能力。PAX-5根据结构不同可分为多种亚型,Vidal等^[26]研究发现:乳腺癌中可检测到PAX-5 α mRNA,而不能检测到PAX-5 β mRNA,并指出PAX-5 α mRNA可通过影响 β -CATENIN/LEF/TCF复合体来阻止乳腺癌的浸润、转移。相反,Ahmed等^[27]研究发现:乳腺癌低表达PAX-5 α mRNA,高表达PAX-5 β mRNA,两者在乳腺癌的发生发展中具有重要的作用,PAX-5 β mRNA在高级别乳腺癌中表达较高,并指出PAX-5 β mRNA与P53,CA15-3有正相关性。而在Mhaweche-Fauceglia等^[13]研究中,164个乳腺癌病例中仅有1例乳腺癌PAX-5阳性,其结果与多数研究结果相反。与PAX-5在B细胞淋巴瘤中的作用相反,PAX-5异常表达可抑制乳腺癌的进展和转移。目前,PAX-5在乳腺癌中高表达及其在乳腺癌中的作用机制尚不清楚。Harquail等^[28]研究发现:乳腺癌中miRNAs可以抑制PAX-5的表达,PAX-5不受miRNAs控制是PAX-5在乳腺癌中异常高表达的原因之一。Benzina等^[29]的研究指出:PAX-5与FAK(focal adhesion kinase)具有负相关性,并且通过实验^[30]证实PAX-5可以通过阻断FAK信号通路阻止乳腺癌的恶性进展,其具体机制为PAX-5通过影响FAK抑制物(p53和miR-135b)和FAK激活物(NF κ B)从而抑制FAK介导的信号通路。

2.3 肝细胞癌中的表达

基因的甲基化在肝细胞癌的发生和发展过程中具有重要的作用,肝细胞癌中甲基化PAX-5 mRNA可异常高表达,甲基化PAX-5可作为检测肝细胞癌的标志物^[31-32]。Liu等^[6]的研究发现:PAX-5 mRNA在原发性肝癌中表达下调,甲基化PAX-5在原发性肝癌中增加,PAX-5是一种肝细胞癌的抑制物,其机制可能是通过影响p53基因实现的。Mžik

等^[33]的研究也指出甲基化PAX-5 mRNA在肝癌中高表达,并且发现甲基化PAX-5在63岁以上肝癌患者年龄组明显增高。乙肝和丙肝是导致肝癌的重要原因之一,而Shitani等^[32]报道:甲基化PAX-5在无乙肝丙肝组肝细胞癌、乙肝组肝细胞癌和丙肝组肝细胞癌中没有明显差异。因此,PAX-5可能是肝细胞癌的一种抑制物,甲基化PAX-5可作为肝细胞癌检测的可靠标志物。

2.4 膀胱癌中的表达

关于PAX-5在膀胱癌中表达的研究较少。PAX-5在正常尿道上皮不表达,而在膀胱癌中可表达,在蛋白水平其表达率为10%~82.7%^[7,34],在mRNA水平其表达率为79%~82%^[35-36]。Denzinger等^[34]的研究报道,膀胱癌中PAX-5仅有10%的表达率,并且与临床病理特征没有相关性。相反,Babjuk等^[7]的研究指出:PAX-5在膀胱癌中异常表达(阳性率为82.7%),并且膀胱癌中高表达PAX-5组与弱表达或无表达组相比较,高表达组3年无复发和无进展生存率较低,PAX-5水平与膀胱癌预后相关。Babjuk等^[36]的另一项研究发现:PAX-5与膀胱癌的分期、分级以及膀胱癌中p53高表达没有相关性。

2.5 神经系统肿瘤中的表达

Stuart等^[12]报道:PAX-5在星形细胞瘤的恶性进展中具有重要作用,在恶性程度高的肿瘤中表达增高。Stuart等^[37]的另一项研究显示:在弥漫型星形细胞瘤中,PAX-5与P53呈负相关,P53基因包含1个PAX-5的结合位点(位于P53第一个外显子),与PAX-5结合后可抑制P53的表达。Kozmik等^[38]报道:PAX-5与髓母细胞瘤的肿瘤细胞的增殖呈正相关,而与神经分化呈负相关。Czapiewski等^[39]研究显示:PAX-5在嗅神经母细胞瘤中表达仅22.7%(3/11),但若是其高表达PAX-5,则患者预后较差。

2.6 口腔及消化系统肿瘤中的表达

口腔白斑是口腔黏膜显著的白色斑块,属于潜在恶性病变,而口腔鳞状细胞癌是口腔常见的恶性肿瘤之一。Norhany等^[40]研究显示:PAX-5在口腔鳞状细胞癌形成中具有重要作用,尤其在肿瘤形成的早期,其可在口腔白斑和口腔鳞状细胞癌中表达,其阳性率分别为42%(11/26)和78%(39/50),而甲基化PAX-5与舌鳞状细胞癌也相关^[41]。Kurimoto等^[42]研究报道敲除PAX-5使食管鳞

状细胞癌的癌细胞增殖明显增加, 可以导致顺铂耐药, 而甲基化PAX-5在食管鳞状细胞癌具有重要作用, 其可以作为预测食管鳞状细胞癌预后不良和对顺铂敏感性的指标。Hirabayashi等^[43]研究发现: 结直肠癌中甲基化PAX-5也明显增加, 尤其是右半结肠癌, 而甲基化PAX-5对结直肠癌的转移、化疗敏感性可能有影响。

3 结语

PAX-5作为一种标志物, 在淋巴造血系统肿瘤中的应用已被广泛熟知, 而PAX-5在非淋巴造血系统肿瘤中的表达了解不多。虽然由于研究技术和方法的原因使得某些研究结果不尽相同, 但是新近文献报道证实PAX-5在某些非淋巴造血系统肿瘤中异常高表达, 在鉴别淋巴造血系统来源的肿瘤和某些非淋巴造血系统肿瘤时, 易将其误诊。PAX-5还与某些恶性肿瘤的临床病理特征和预后具有相关性。因此, 进一步研究PAX-5在非淋巴造血系统肿瘤中的表达谱及其机制具有重要的意义。

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