·文献综述·

肿瘤标志物对胰腺癌诊断及预后评估作用的研究进展

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摘 要 胰腺癌是目前常见的恶性肿瘤，其发病率与致死率近乎持平。如何提高胰腺癌早期确诊率和胰腺癌的治疗效果是急需解决的问题。肿瘤标志物对胰腺癌患者的筛选、治疗效果评估和监测术后复发的作用正在不断扩大。笔者通过回顾胰腺癌血清和胰液等体液中的肿瘤标志物的研究进展及存在的问题，重点探讨肿瘤标志物对胰腺癌诊断及预后评估的作用。

关键词 胰腺肿瘤；生物标记，肿瘤；综述文献
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Research progress of tumor markers for diagnosis and prognosis estimation of pancreatic cancer

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Abstract Pancreatic cancer is a common malignant tumor currently, and its mortality is nearly equal to its morbidity. How to improve early diagnosis and treatment efficiency of pancreatic cancer has become an urgent issue. The role of tumor markers in screening patients with pancreatic cancer, assessing treatment efficacy and detecting postoperative recurrence has become increasingly important. In this paper, the authors mainly discuss the role of tumor markers for diagnosis and prognosis estimation of pancreatic cancer through reviewing the research progress of tumor makers in the body fluids such as the blood serum and pancreatic juice of pancreatic cancer patients and current problems.

Key words Pancreatic Neoplasms; Biomarkers, Tumor; Review
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胰腺癌是世界上最常见的消化道恶性肿瘤之一[1]，大约有85%的胰腺癌属于胰腺导管腺癌（pancreatic ductal adenocarcinoma cancer，

PDAC）[2]，近年PDAC患者的5年生存率从4%~5%略改善到7%[3]。手术切除是唯一可能治愈PDAC的方法。在早期完全切除术中，淋巴结阴性患者的5年生存率为25%~30%，而淋巴结阳性患者的5年生存率仅为10%[4]。大部分患者在确诊时已处于胰腺癌晚期，仅有15%~20%的患者能够得到及时有效的治疗[2]。

胰腺癌的早期诊断对选择最佳治疗方案并提高PDAC患者的预后具有重要意义。许多肿瘤标

志物与胰腺癌有关联，但CA19-9（carbohydrate antigen 19-9，CA19-9）是目前唯一被食品药品监督管理局（Food and Drug Administration，FDA）认可的对PDAC有监测效能的生物标志物。尽管它普遍用于早期诊断、预后评估以及术后监测复发和转移，但仍具有局限性[5]，因此，急需寻求新的肿瘤标志物对胰腺癌进行早期诊断及预后评估。本文就肿瘤标志物在评估PDAC患者术后复发、转移、治疗效能以及早期诊断PDAC的应用等方面进行综述。

1 诊断标志物

1.1 CA19-9、癌 胚 抗 原（carcinoembryonic antigen，CEA）及其他碳水化合物

CA19-9是目前被最广泛应用于PDAC定位的一种单克隆抗体，也是FDA唯一认可的能对胰腺癌预后有预测作用的标志物[6]。CA19-9诊断PDAC的平均灵敏性与特异性分别为77.5%与77.6%[7]，对有明显病症的PDAC患者来说阳性预测值和阴性预测值分别为72%和81%~96%[8]。但有研究显示在急性胆管炎、胰腺炎、肝癌、胆管癌等患者的血清中可出现假阳性[9]，容易受到血清胆红素的影响而升高，且路易斯（Lewis）血型患者的血清中不表达CA19-9[10]，因此将CA19-9单独作为诊断胰腺癌的指标是不完全准确的。

CEA是从人结肠癌组织中分离出来的一种可溶性蛋白。在胚胎时期生存于肝脏和胰腺，在出生后逐渐下降。当正常细胞发生恶变时，血清CEA水平异常升高。在确定CA19-9的预测能力之前，CEA是唯一用于诊断PDAC的血清抗原[11]，但与CA19-9相比，CEA在诊断胰腺癌时更易出现误诊[12]。因此在临床上，其常应用于临床疗效观察和术后随访的重要指标，与其他肿瘤标志物联合诊断，提高诊断疾病的敏感性和特异性。

联合CA19-9、CEA和其他标志物能提高对胰腺癌患者的诊断。有研究显示CA242（carbohydrate antigen 242，CA242）诊断胰腺癌的敏感性、特异性分别为67.8%、83.3%，CEA诊断的敏感度、特异性为39.5%、81.3%。但CA19-9与CA242联合时，其诊断的灵敏度可高达89%（对特异性无影响）；CA19-9与CEA联合诊断PDAC的灵敏度、特异性为89%、75%[7]。当CA19-9、CEA、CA242三者联合时，PDAC诊断的特异性高达95%，然而诊断的灵敏度出现降低。CA19-9、CEA、CA242与CA125联合时，诊断的灵敏度达90.4%，特异性为93.8%[8]。因此，CA19-9、CEA和其他碳水化合物在临床上对早期诊断PDAC具有重要的意义。

1.2 微小核糖核苷酸（microRNA，miRNA）和其他非编码核糖核苷酸

miRNA影响胰腺发育、胰腺肿瘤的发生和进展。识别胰腺癌中特异的miRNA，不仅可以区别胰腺的良恶性病变，还可以提高胰腺癌的早期诊断率[13]。研究[14-22]发现miR-21、miR-155、miR-196a和miR-210在PDAC患者的胰腺组织、血样、粪便和胰液中表达水平上升，miR-216与miR-217在胰腺组织、粪便、胰液中呈持续下降的趋势。尿中的miRNA浓度可对早期PDAC进行诊断，有研究[6]证实miR-143、miR-22与miR-30e在胰腺癌患者的尿液中水平显著升高。在联合使用miR-143与miR-30e对胰腺癌患者进行诊断时灵敏度为83.3%、特异性为96.2%。将miR-21、miR-155和miR-216联合作为检测PDAC患者时亦得类似的结果（灵敏度与特异性达到83.3%）[23]。Caponi等[24]对miR-21、miR-155和miR-196a进行了特殊标记后，发现它们在导管内乳头状粘液性恶性肿瘤（intraductal papillary mucinous neoplasm，IPMN）与胰腺上皮内肿瘤（pancreatic intraepithelial neoplasia，PanIN）的组织标本中高水平表达，这表明它们也是潜在的生物标记物，特别是用于早期诊断恶性潜能的疾病。

1.3 巨 噬 细 胞 抑 制 细 胞 因 子 1（macrophage inhibitory cytokine 1，MIC-1）与四阶脉冲幅度调制（4 level pulse amplitude modulation，PAM4）

MIC-1是转化生长因子家族的成员，在不同的肿瘤分期中高度表达[25]。有研究[26]显示，与CA19-9相比，MIC-1能更好地从健康对照组中区分出胰腺癌患者，且其对胰腺癌的综合诊断能力明显优于CA19-9，但对胰腺癌和慢性胰腺炎很难区分。Chen等[27]发现PDAC患者血清中检测到MIC-1的灵敏度和特异性分别为79%、86%，且在联合使用MIC-1与CA19-9诊断PDAC的研究中发现

了类似的结果。在CA19-9阴性的患者中，MIC-1的检测灵敏度为63.1%[28]，在很大程度上能够避免对CA19-9阴性的PDAC患者出现漏诊。

PAM4是一种能在胰腺癌早期中表达并在疾病的进展中保存下来的单克隆抗体[29]。Gold等[30]证实与胰腺良性病变相比，PAM4对PDAC的检测总灵敏度为76%，特异性为85%，阳性似然比（positive likelihood ratio，+LR）为4.93；与PAM4相比，CA19-9对PDAC的灵敏度为77%，特异性仅为68%，+LR为2.85（P=0.026）；联合CA19-9与PAM4时，PDAC的检测灵敏度为84%，特异性为82%，对胰腺癌的检出率显著提高。

1.4　钙结合蛋白（calcyclin，Cacy，S100A6）

S100A6是一种钙结合蛋白，在PDAC患者的血清水平中升高。有研究[31]发现胰液中S100A6水平的测定对于区分慢性胰腺炎、PDAC与IPMN具有重要的作用。虽然部分PDAC患者在超声内镜引导下细针穿刺活检（endoscopicultrasonography-fineneedleaspiration，EUS-FNA）的标本中发现S100A6处于高水平状态[32]，但目前为止未能证实循环中血清S100A6水平对胰腺癌具有诊断作用。

1.5　骨桥蛋白（osteopontin，OPN）

OPN是一种具有多功能的分泌蛋白，能在PDAC患者中表达升高，与侵袭性胰腺癌的癌细胞转移生长有关[33]。研究[13]显示血清中高浓度OPN对PDAC患者的检测灵敏度为80%，特异性为97%。OPN能区分出慢性胰腺炎和PDAC患者，同时能区分出早期PDAC患者。虽然OPN的诊断灵敏度低于CA19-9，但是在联合使用OPN、CA19-9与金属蛋白酶组织抑制剂1（tissue inhibitor of metalloproteases 1，TIMP-1）时，诊断灵敏度为87%，特异性为91%[34]，均优于这三种生物标志物单独应用。

1.6　鼠类肉瘤病毒癌基因（kirsten rat sarcoma viral oncogene，KRAS）

KRAS基因是胰腺癌中最常见的突发型致癌基因。近期研究[35]显示KARS突变分析与EUS-FNA样本的细胞逻辑分析结合可使PDAC患者诊断的灵敏度由80.6提高到88.7%。KARS突变患者的总体生存率比无突变的患者小，这表明这KARS基因的检测是用于诊断PDAC和预测生存率的新策略[36]。在细胞学不确定时可用KARS突变进行辅助诊断

PDAC患者，但Singh等[37]没有发现血清中KARS突变的状态与不同的临床病理参数或生存率之间存在明显的相关性。因此，仍需要研究来证实KARS突变可作为PDAC患者潜在的生物标记物。

2　治疗效果的预测指标

2.1　吉西他滨标记

对胰腺癌转移以及在辅助性治疗中发生转移的PDAC患者来说，吉西他滨可作为标准的化疗药物[38]，目前蛋白家族中平衡型核苷转运蛋白（equilibrative nucleoside transporters，ENTs）和集中型核苷转运蛋白（concentrative nucleoside transporters，CNTs）被认为是吉西他滨治疗的生物标记[39]。

2.1.1　人平衡型核苷转运蛋白1（human ENT1，hENT1）　研究[40]发现hENT1升高能够作为吉西他滨治疗中的预测和评价预后效果的标志物，使用免疫组织化学分析对用吉西他滨治疗的晚期PDAC患者进行活检时发现hENT1高度表达，且在吉西他滨治疗检测中发现hENT1高度表达的患者总体生存率与无复发生存率更高。Yamada等[41]进行了不同阶段的PDAC患者治疗前hENT1水平的测定，并将其与用吉西他滨治疗后的切除标本中的hENT1水平对比，发现hENT1是所有PDAC患者以及接受切除术的患者的独立预后预测因子。

2.1.2　人集中型核苷转运蛋白（human CNT3，hCNT3）　hCNTs是第二组吉西他滨的细胞膜转运体，能利用钠梯度转移吉西他滨通过质膜[42]。Maréchal等[43]对45例以吉西他滨为基础治疗的患者分析发现hCNT3高表达患者的3年生存率与hCNT3低表达的患者相比显著延长（54.6% $vs.$ 26.1%，P=0.028）。hCNT3与hENT1联合应用时，hCNT3与hENT1高表达的患者3年生存率为81.1%[43]。

2.1.3　脱氧胞苷激酶（deoxycytidine kinase，dCK）　dCK是一种限速酶，它通过磷酸化将吉西他滨转化为其活化的形式。研究[44]发现dCK信使RNA（mRNA）水平升高能显著延长应用吉西他滨治疗患者的生存期。但考虑到目前有限的数据，仍需要进一步的临床研究证实dCK与hCNT3能否作为评估吉西他滨治疗的标志物。

3 预后标志物

3.1 CA19-9

术后CA19-9正常或术前轻度升高（<100 U/mL）预测预后良好，而CA19-9血清水平术前>100 U/mL或术后>37 U/mL与不良预后有关[8, 24]。此外，胰腺切除术后正常CA19-9的下降趋势亦与生存期延长有关。术后持续升高的CA19-9水平则表明有病灶残留并可能生存期更短。CA19-9术前改变率可以预测切除肿瘤包块患者的生存率。术后的CA19-9水平正常化与提高患者术后生存率有很大的联系，而术后CA19-9的非正常化与发生转移性疾病或术后复发有很大的关联[10]。研究路易斯阳性血伴术后高CA19-9患者的预后情况，发现术后有54.5%的患者发生了局部复发和远处转移，这些患者术后CA19-9再次上升发生在肿瘤复发2~9个月之前[45-46]，术后CA19-9持续性升高可比影像学检测出复发早2周至5个月[11, 47]。但也有研究显示术后CA19-9水平正常化并不等同于良好的预后效果[12, 47]。

3.2 富含半胱氨酸的分泌型酸性蛋白（secreted protein acidic and rich incysteine，SPARC）

SPARC是一种钙结合蛋白，能分泌到细胞外基质并被多种蛋白酶迅速降解，影响细胞的迁移、增殖以及血管生成等[48-50]。SPARC已在紫杉醇治疗中作为预测胰腺癌患者预后的生物标志物。在PDAC切除术后联合吉西他滨与替吉奥胶囊（S-1）或单独使用吉西他滨治疗时，SPARC的高表达与患者的低生存率有关[51]。SPARC对胰腺癌的治疗的研究中，Vaz等[52]发现在PDAC和大部分其他实体性肿瘤中SPARC表达与预后不良有关[53]。SPARC表达的位置在胰腺癌中似乎起决定性的作用。Infant等[54]发现过度表达SPARC的肿瘤周围成纤维细胞能预测PDAC患者预后，肿瘤间质细胞SPARC阳性患者的平均生存期要短于阴性患者（15个月 *vs.* 30个月，*P*<0.001），因此肿瘤间质细胞能延长患者生存期。许多研究[53,55]表明存在肿瘤间质成纤维细胞不代表预后不良，相反，它甚至可以延长总体生存期。

3.3 miRNA

miRNA不仅作为PDAC的潜在诊断标志物，还在预后评估上具有重要的作用。目前，研究证实肿瘤中高度表达miR-21能明显缩短PDAC患者的总体生存期和无病生存期[56]；miR-155与miR-203表达升高，以及miR-34a表达降低使患者总体生存期缩短[57]；miR-221/222在PDAC中过度表达，这说明了miR-221/222基因的表达显著促进生长和侵袭，抑制细胞凋亡。此外，低表达水平miR-218与miR-494以及高表达水平miR-744也与预测PDAC患者的生存率低有关[49-60]。

3.4 预后指数

各种预后标志物的结合构成预后指数。Park等[61]应用5个参数（PS、血红蛋白、白细胞计数、中性粒细胞比值、CEA）将转移性胰腺癌患者分为3个亚组，即低风险组，中风险组和高风险组，三者的平均总体生存期分别为11.7、6.2、1.3个月（*P*<0.001）。对接受姑息性化疗的PDAC晚期患者，Xue等[62]创建由3个临床参数（美国东部肿瘤协作组体能状态评分标准(Eastern Cooperative Oncology Group Performance Status,ECOG PS)、血清CA19-9水平与血清中C反应蛋白水平）组成的预后指数，将胰腺癌晚期患者分为低风险和高风险两组，低风险组与高风险组的平均总体生存期和1年生存率分别为9.9、5.3个月（*P*<0.001）和40.5%、5.9%（*P*<0.05）。预后指数模型的建立是联合不利于患者预后的因素进行统计学分析，这些易于从患者身上获得的预处理参数和预后指数模型可以帮助临床医生识别高危患者，并在临床实践中为胰腺癌晚期患者选择恰当的治疗方法。但目前为止，没有一个可靠的评分系统可用于胰腺导管腺癌患者的常规预后判断[63]。

4 总结与展望

综上所述，早期诊断、及时治疗可极大的提高胰腺癌患者的总体生存率。因此各种肿瘤标志物、血清蛋白、miRNA以及在未来可能满足这些需求的基因标记等，在很大程度上能提高胰腺癌的检出率。联合使用肿瘤标志物能更好地提高胰腺癌的检出率，并在指导治疗和评估预后上具有重要意义。

近年来，基于肿瘤标志物在早期诊断、指导治疗和评估预后等方面具有重要作用，使PDAC患者的治疗效果有所改善。但寻找敏感性高、特异

性强、结果稳定的肿瘤标志物，仍是胰腺癌早期诊断中待解决的问题。相信今后随着技术的发展和胰腺癌分子生物学研究的深入，胰腺癌的早期诊断、预后以及总体生存率将会得到极大的改善。

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