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# 核苷酸转运体表达与吉西他滨治疗胰腺癌患者临床疗效相关性的研究进展

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**摘要：目的** 探讨核苷酸转运体表达与吉西他滨抗胰腺癌临床疗效相关性的研究进展。**方法** 通过查阅国内外文献，对相关研究归纳、总结进行综述。**结果** 吉西他滨是胰腺癌化疗的一线药物，较大个体化差异和有效率偏低是目前临床应用的挑战，核苷酸转运体是吉西他滨摄取入细胞的内吞转运体，它的蛋白或 mRNA 表达可能与接受吉西他滨治疗胰腺癌患者的临床疗效和不良反应相关，但尚未达成共识。**结论** 核苷酸转运体表达与吉西他滨抗胰腺癌临床疗效的相关性还需要进一步研究，为吉西他滨在胰腺癌中实现临床个体化治疗提供参考依据。

**关键词：**吉西他滨；胰腺癌；核苷酸转运体；基因多态性；临床疗效；不良反应
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## Nucleoside Transport Expression Associated with Clinical Response of Gemcitabine in Pancreatic Cancer

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**ABSTRACT: OBJECTIVE** To introduce the research progress on the nucleoside transport expression associated with clinical response in pancreatic cancer who treated with gemcitabine. **METHODS** The domestic and international articles were reviewed to summarize the relevant studies. **RESULTS** Gemcitabine is the first-line Chemotherapeutic agent for treatment of pancreatic cancer, but high interpatient variability and low response rate has been the major challenge faced by clinicians, Cellular uptake of gemcitabine is mediated by nucleoside transporters,expression (including protein and mRNA) of nucleoside transport may be associated with clinical response and adverse effect in pancreatic cancer, who were treated with gemcitabine. But it has not reach the consensus in clinic. **CONCLUSION** The future study will fouce on nucleoside transport expression

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associated with clinical response of gemcitabine in pancreatic cancer, provided the basis on presonalized treatetment option for pancreatic cancer patients.
**KEY WORDS:** gemcitabine; pancreatic cancer; nucleoside transport; single nuelsoside polymorphisms; clinical response; adverse effect

胰腺癌是发病隐匿、进展迅速且预后差的恶性肿瘤，最新调查显示，我国胰腺癌发病率为5.96/100 000，呈明显上升趋势，提高胰腺癌患者的存活率和生存期是当今医学研究的热点之一[1-2]。近年来，尽管对胰腺癌的研究取得一定进展，但对失去手术机会中晚期及术后复发的患者，仍缺乏有效治疗手段，而化疗是延长这类患者生存期的主要手段，也是术后辅助的治疗手段。

吉西他滨(Gemcitabine，2,2-difluorodexycytidine)属脱氧胞苷类似物，是细胞周期特异性抗肿瘤药，主要作用于 DNA 合成期，也可阻止细胞从合成前期向合成期进展。在胰腺癌的辅助、姑息治疗和同步放化疗中，吉西他滨均是基础药物，但临床有效率仍然偏低(约 20%)，部分患者可能还遭受血液系统毒性等不良反应[3-4]。分子标志物预测抗肿瘤药物的疗效和不良反应是当前肿瘤研究热点，寻找能预测吉西他滨疗效的生物标志物也迫在眉睫。核苷酸转运体(nucleoside transporters，NTs)是吉西他滨摄取入细胞发挥细胞毒作用的关键，Mackey 等[5]认为 NTs 的活性与吉西他滨摄取入癌细胞的量有关，在对多种实体瘤模型的研究发现，NTs 不表达或低表达的癌细胞，会减少吉西他滨摄入细胞的量，从而引起耐药。Mori 等[6]通过 RT-PCR 法检测了 5 种胰腺癌和胆道癌细胞株的 hENT1 mRNA 表达水平，研究其与吉西他滨敏感性的相关性，结果显示吉西他滨的半数抑制浓度($IC_{50}$)与 hENT1 mRNA 表达水平呈负相关($r$=–0.900，$P$=0.037)，并认为上调 hENT1 mRNA 可以增加吉西他滨对癌细胞株的敏感性。临床研究也显示 NTs 的表达与接受吉西他滨化疗胰腺癌患者生存期和无疾病进展期具有相关性[7-8]。为了证明 NTs 是否为吉西他滨的生物标志物，本研究通过查阅国内外文献，进行归纳、分析，将胰腺癌患者的核苷酸转运体表达与吉西他滨的临床疗效和不良反应相关性研究作综述。

## 1 核苷酸转运体

吉西他滨是一类亲水化学物，不能以自由扩散的形式进入细胞内，需借助于细胞膜上的核苷酸转运体摄取进入细胞。在体内，核苷酸转运体分为平衡型核苷酸载体(human equilibrative nucleoside transports，hENTs)和浓聚型核苷酸载体(human concentrative nucleoside transporters，hCNTs)。hENTs 是单纯扩散性载体，由 SLC29 基因编码，主要有 SLC29A1 和 SLC29A2 2 种亚型，分别编码 hENT1 和 hENT2；hCNTs 属主动转运载体，由 SLC28 基因编码，主要有 SLC28A1、SLC28A2 和 SLC28A3 3 种亚型，分别编码 hCNT1、hCNT2 和 hCNT3，它们的分子学信息见表 1[9-10]。研究显示 SLC29A1 是吉西他滨主要转运体和底物，而 SLC28A1 和 SLC28A3 是吉西他滨次要转运体和底物[6]。

**表 1** 核苷酸转运体的分子学信息

**Tab. 1** Molecular information of nucleoside transport

| 基因 | 基因亚型 | 表达转运体 | 染色体位置 | 氨基酸数 | 分子量/KDa | 是否吉西他滨的底物 |
|---|---|---|---|---|---|---|
| SLC29 | SLC29A1 | hENT1 | 6p21.1b | 465 | 52 | 是 |
| | SLC29A2 | hENT2 | 11q13 | 465 | 52 | 否 |
| SLC28 | SLC28A1 | hCNT1 | 15q25.3a | 650 | 71 | 是 |
| | SLC28A2 | hCNT2 | 15q21.1a | 658 | 72 | 否 |
| | SLC28A3 | hCNT3 | 9q21.32c | 691 | 77 | 是 |

## 2 核苷酸转运体表达与吉西他滨临床疗效的相关性

### 2.1 SLC29A1 表达与吉西他滨临床疗效的相关性

SLC29A1 表达(蛋白和 mRNA 的表达)与接受吉西他滨化疗胰腺癌患者的临床疗效相关性见表 2，多数学者认为 SLC29A1 表达可作为吉西他滨的预后标志物[8,11-17]。ESPAC-3 研究将 176 例胰腺癌切除患者，用吉西他滨作为辅助化疗药物，考察 SLC29A1 表达对生存期(overall survival，OS)的影响，发现 SLC29A1 高表达和低表达患者的 OS 分别是 26.2 月和 17.1 月($P$=0.002)[11]。Morinaga 等对 27 位胰腺癌术后患者使用吉西他滨化疗，采用免疫组化分析 SLC29A1 蛋白表达，发现高表达者和低表达者的 OS 分别是 22.2 月和 11.8 月($P$=0.024)，无疾病进展期(disease-free survival，DFS)分别是 9.3 月和 7.3 月($P$=0.022)，结果表明 SLC29A1 高表达患者的 OS 和 DFS 显著增加[12]。但也有研究认为 SLC29A1 表达不会影响胰腺癌患者的 OS 和 DFS[18-19]。

**表 2** 核苷酸转运体表达与吉西他滨临床疗效的相关性

**Tab. 2** Nucleoside transport expression associated with clinical response in pancreatic cancer patients treated with gemcitabine

| 表达基因 | 分析样本 | 抗体/探针 | 评分标准 | 总样本(高表达数) | OS(月)或危险比均值(95%CI)，*P* 值 | DFS(月)或危险比均值(95%CI)，*P* 值 | 参考文献 |
|---|---|---|---|---|---|---|---|
| SLC29A1 | 蛋白 | 鼠单抗 | 中位数评分：<br>阴性<48 分；阳性≥48 分 | 176(99) | 低表达=17.1 (14.3~23.8)<br>高表达=26.2 (21.1~31.4)<br>*P*=0.002 | 未报道 | [11] |
| | 蛋白 | 兔多抗 | 染色阳性肿瘤细胞百分比评分：<br>低表达=0~3；高表达=4~6 | 27(16) | 低表达=11.8 (6.9~16.6)<br>高表达=22.2 (11.5~32.9)<br>*P*=0.024 | 低表达=7.3 (3.6~11.1)<br>高表达=9.3 (4.2~14.5)<br>*P*=0.022 | [12] |
| | mRNA | 引物自制 | mRNA 的中位数 | 56(30) | 低表达=23.6；高表达=20.0<br>*P*=0.302 | 未报道 | [13] |
| | mRNA | 引物自制 | Capan-1 制作 mRNA 标准曲线：<br>低表达<0.5；高表达≥0.5 | 40(14) | 低表达=16.5；高表达=45.0<br>*P*=0.011 | 低表达=8；高表达=25<br>*P*=0.11 | [14] |
| | 蛋白 | 兔多抗 | 染色强度划分：<br>低表达=0~1 级；<br>高表达=2~3 级 | 109(78) | 低表达=13；高表达=38<br>*P*=0.001 | 低表达=17；高表达=30<br>*P*=0.004 | [15] |
| | 蛋白 | 鼠单抗 | 染色强度分数<br>低表达<80；高表达≥80 | 45(19) | 危险比：高表达=1<br>低表达=3.88 (1.78~8.92)<br>*P*=0.007 | 危险比：高表达=1<br>低表达=3.55 (1.65~7.63)<br>*P*=0.005 | [16] |
| | mRNA | Hs00191940 (Applied Biosystems) | 染色强度划分：<br>阴性=0~3；阳性≥3 | 45(39) | 危险比：阳性=1<br>阴性=3.04 (1.45~6.37)<br>*P*=0.0037 | 危险比：阳性=1<br>阴性=2.34 (1.22~4.77)<br>*P*=0.011 | [17] |
| | mRNA | Hs00191940 (Applied Biosystems) | GAPDH/目标基因比划分：<br>低表达：<1.06<br>中表达：1.06~1.38<br>高表达：≥1.38 | 105(26) | 低表达=8.48 (7.01~9.95)<br>中表达=15.74 (13.84~17.63)<br>高表达=25.69 (17.64~33.74)<br>*P*≤0.001 | 低表达=5.85 (2.75~8.95)<br>中表达=10.09 (9.63~10.54)<br>高表达=12.68 (2.89~22.47)<br>*P*=0.02 | [18] |
| SLC28A1 | mRNA | Hs01085706_m1 (Applied Biosystems) | mRNA 的中位数 | 32(16) | 低表达=34.4；高表达=13.2<br>*P*=0.009 | 无显著差异 | [29] |
| SLC28A3 | 蛋白 | 鼠单抗 | 染色强度划分：<br>低表达<150；高表达≥150 | 45(22) | 危险比：阳性=1<br>阴性=3.08 (1.42~6.67)<br>*P*=0.0028 | 危险比：阳性=1<br>阴性=2.27 (1.12~4.65)<br>*P*=0.02 | [16] |

SLC29A1 表达与吉西他滨抗胰腺癌临床疗效相关性尚未达成共识，可能有以下 3 点原因，第一：样本分析方法不同。目前临床多采用免疫组化分析蛋白、RT-PCR 法分析 mRNA 来评估 SLC29A1 表达，在免疫组化分析中，各研究使用的抗体不同，包括鼠单抗、多抗、兔抗体等，而 RT-PCR 法分析 mRNA，各研究内参基因或探针也不同；第二：阳性/阴性、高表达/低表达的评分标准不一。SLC29A1 的表达多用阳性和阴性、高和低表达来判断，各研究按中位数、蛋白染色强度等不同标准评分；第三：各临床研究样本量均相对较少，尚无多中心、大样本的研究报道[20-23]。尽管 SLC29A1 表达作为吉西他滨的生物标志物尚存矛盾，但多篇 Meta 分析研究却认为 SLC29A1 高表达者接受吉西他滨化疗的临床获益显著高于低表达者，并认为 SLC29A1 表达是吉西他滨治疗胰腺癌最具潜力的预后标志物[24-26]。

**2.2** SLC28A1 和 SLC28A3 表达与吉西他滨临床疗效的相关性

除了 SLC29A1 外，SLC28A1 表达可能也与吉西他滨对胰腺癌细胞化疗的敏感性相关[27]。Bhutia 等[28]发现 SLC28A1 在胰腺癌中的表达比正常胰腺细胞要低，而低表达的 SLC28A1 易引起胰腺癌细胞耐药，减弱吉西他滨的临床疗效，并建议把 SLC28A1 表达作为胰腺癌耐药的潜在标志物。但 Mohelnikova 等[29]对 32 例胰腺癌患者用吉西他滨为基础药物化疗，却发现 SLC28A1 高表达患者的 OS 低于低表达者，分别是 13.2 月和 34.3 月(*P*=0.009)。SLC28A3 也是吉西他滨的次要转运体，Maréchal 等[16]认为高表达的 SLC28A3 患者，采用

吉西他滨治疗具有更好的收益。但目前 SLC28A1 和 SLC28A3 表达对接受吉西他滨化疗的胰腺癌患者临床研究还较少，SLC28A1 和 SLC28A3 表达能否作为吉西他滨化疗的标志物还有待更深入研究。

## 3 核苷酸转运体表达与吉西他滨不良反应的相关性

吉西他滨的不良反应包括流感样症状、恶心呕吐、蛋白尿等，其中血液系统毒性(包括粒细胞减少症和血小板减少症等)是吉西他滨最严重的不良反应。因此在每个化疗周期前，患者的粒细胞绝对计数应<1 500×$10^6$·$L^{-1}$，血小板计数需达到 100 000×$10^6$·$L^{-1}$，若达不到要求，需减少吉西他滨给药剂量或延迟给药时间。

Maréchal 和 Farrell 等研究认为 SLC29A1 表达与吉西他滨引起血液系统毒性的发生率和严重程度均无相关性[16, 30]。但 Tanaka 等[31]通过对 SLC29A1 基因多态性研究发现 SLC29A1 rs9394922 CC 携带者与 CT/TT 携带者发生 3~4 级中性粒细胞减少症发生率分别是 22.9%和 43.4%，$P$=0.017；Okazaki 等[32]发现 SLC28A3 rs7867504 中 AA 携带者发生 3~4 级中性粒细胞减少症显著高于 AG/GG 携带者，发生率分别为 42.3%和 25.7%，$P$=0.035；而其他位点如 SLC29A1 rs324148、rs760370 和 SLC28A1 rs2242047、rs2242048 等未发现与吉西他滨的血液系统毒性相关。目前，核苷酸转运体的表达与吉西他滨的血液毒性报道不一致，可能是由于不同研究中吉西他滨的治疗方案不同，包括吉西他滨单药化疗、以吉西他滨为基础的联合化疗或同步放化疗等。

## 4 讨论

除了 SLC29A1 和 SLC28A1 外，SLC22A1、SLC22A2、SLC22A3 等转运体也可能是胰腺癌患者潜在的标志物，其中有研究者认为 SLC22A3 高表达者具有更长的生存期[29]。Pressler 等[33]发现，与正常胰腺组织相比，胰腺癌中 SLCO1B1 表达较高。因此核苷酸转运体在胰腺癌中的异常表达，与胰腺癌的预后和不良反应是否具有相关性，还有待于更多更深入的研究。

分子标志物预测抗肿瘤药物的疗效是当前研究热点，吉西他滨在辅助、新辅助、姑息治疗或同步放化疗中均是胰腺癌的基础治疗药物，但临床接受吉西他滨化疗的胰腺癌患者有效率仍然偏低，而且部分患者还要承受吉西他滨所带来的血液系统毒性等不良反应。因此，寻找能预测吉西他滨疗效的生物标志物显得尤为重要，核苷酸转运体作为吉西他滨摄取入细胞，发挥细胞毒作用的关键一步，目前大多数研究认为 SLC29A1 表达(蛋白或 mRNA 表达)能作为吉西他滨化疗的预后标志物，但仍需谨慎对待这一结论，因为目前各研究多为单中心、小样本的研究，为确定 SLC29A1 表达是吉西他滨的生物标志物，接下来的研究需在扩大研究样本的前提下，采用统一纳入样本标准、统一样本分析方法、统一评分标准来评估 SLC29A1 表达与接受吉西他滨化疗胰腺癌患者的 OS 和 DFS 的相关性。

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