Advances in Clinical Medicine 临床医学进展, 2026, 16(2), 1893-1903
Published Online February 2026 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2026.162584

Hans汉斯

CST1与胰腺癌早期诊断：进展与展望

兰　楮[1]，李春满[1*]，刘中建[2]，付必莽[1]，马朝宇[1]，杨金通[3]，王　朝[1]，张鸿海[1]

[1]昆明医科大学第二附属医院肝胆胰外科四病区，云南　昆明
[2]云南省第一人民医院基础与临床医学研究所，云南　昆明
[3]云南圣约翰医院普外科，云南　昆明

收稿日期：2026年1月6日；录用日期：2026年1月30日；发布日期：2026年2月10日

摘　要

胰腺导管腺癌(Pancreatic Ductal Adenocarcinoma, PDAC)恶性度高、进展隐匿，临床确诊多已失去根治性切除时机，早期识别仍是改善预后的关键环节。围绕“可进入体液检测，并能补足CA19-9不足的候选分泌蛋白”这一需求，本文对PDAC早诊标志物与液体活检研究脉络进行归纳，并重点梳理Cystatin SN (CST1)的生物学特征、检测可行性及与肿瘤进展相关的证据。现有研究显示，ctDNA、CTCs、外泌体及非编码RNA等手段不断推进早诊探索，但受样本量、方法学差异与标准化不足等因素影响，临床可推广性仍有限。CST1属于II型cystatin家族，参与蛋白酶抑制网络失衡调控，在多种消化系统肿瘤中常见上调，并与增殖、迁移、上皮间质转化等过程相关；在PDAC领域，组织高表达与促肿瘤效应已有初步证据，但血清或外泌体层面的诊断效能、动态变化及外部验证仍明显不足。总体而言，CST1更可能作为联合面板的组成部分而非单一筛查指标，其真实增益有赖于前瞻性、多中心研究及统一检测与阈值体系的建立；未来应在高危人群随访与影像不确定人群中检验其临床价值。

关键词

胰腺癌，早期诊断，CST1，液体活检，生物标志物

CST1 and Early Detection of Pancreatic Cancer: Progress and Prospects

Chu Lan[1], Chunman Li[1*], Zhongjian Liu[2], Bimang Fu[1], Chaoyu Ma[1], Jintong Yang[3], Chao Wang[1], Honghai Zhang[1]

[1]Department of Hepatobiliary and Pancreatic Surgery (Ward 4), The Second Affiliated Hospital of Kunming Medical University, Kunming Yunnan
[2]Institute of Basic and Clinical Medicine, The First People's Hospital of Yunnan Province, Kunming Yunnan
[3]General Surgery Department, Saint John's Hospital Yunnan, Kunming Yunnan

Received: January 6, 2026; accepted: January 30, 2026; published: February 10, 2026

[*]通讯作者。

文章引用: 兰楮, 李春满, 刘中建, 付必莽, 马朝宇, 杨金通, 王朝, 张鸿海. CST1 与胰腺癌早期诊断: 进展与展望[J]. 临床医学进展, 2026, 16(2): 1893-1903. DOI: 10.12677/acm.2026.162584

Abstract

Pancreatic ductal adenocarcinoma (PDAC) remains one of the most lethal solid tumors, largely because early disease is clinically silent and current diagnostic pathways rarely identify patients at a stage amenable to curative resection. Although serum CA19-9 is widely used, its performance is constrained by limited sensitivity for early stage tumors, false positives in benign biliary and inflammatory conditions, and biological false negatives in Lewis antigen negative individuals, leaving a substantial gap between clinical need and available tools. With this gap in mind, the present review synthesizes the evolving landscape of PDAC early detection biomarkers and focuses on Cystatin SN (CST1) as a secreted, technically measurable protein candidate that could complement existing strategies. Evidence was appraised by integrating mechanistic findings with clinically oriented studies, with particular attention to specimen type, assay feasibility, study design, and the degree to which results are validated beyond single center case control settings. Across the field, liquid biopsy approaches such as circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), extracellular vesicles including exosomes, and circulating noncoding RNAs have expanded the spectrum of candidate signals. ctDNA enables detection of recurrent driver alterations and provides a direct molecular readout of tumor derived material, yet its sensitivity drops markedly in early stage PDAC where tumor shedding is low, and technical factors such as analytical limits of detection, platform variability, and interference from clonal hematopoiesis complicate interpretation. CTC based assays offer biologically rich information, but the rarity of CTCs in PDAC, phenotypic heterogeneity, and incomplete capture by single marker enrichment methods restrict robust application. Exosome associated cargos, including proteins and nucleic acids, are attractive because vesicular membranes protect contents from degradation and may better reflect tumor microenvironmental crosstalk; however, differences in isolation methods, yield and purity, and the absence of harmonized preanalytical workflows continue to drive between study variability. Circulating miRNA signatures and other noncoding RNAs have shown encouraging diagnostic accuracy in some cohorts, but signal specificity remains vulnerable to confounding by inflammation, pancreatitis, metabolic status, and sample handling. These collective experiences point to a recurring pattern: promising performance in selected cohorts often attenuates when moving toward heterogeneous real world populations, underscoring the importance of standardized assays, appropriate control groups, and external validation. Within this broader context, secreted proteins retain practical advantages because they are compatible with mature clinical laboratory platforms and may be integrated into existing workflows at lower marginal cost than sequencing based assays. CST1 is a member of the type II cystatin family and participates in the cathepsin cystatin protease inhibitor network, which has long been implicated in extracellular matrix remodeling, invasion, and metastatic dissemination. Unlike intracellular cystatins, type II cystatins are secreted into extracellular fluids, a feature that supports measurement in serum or plasma and increases translational plausibility for screening or surveillance applications. Across multiple gastrointestinal malignancies, CST1 is frequently reported to be upregulated and to correlate with aggressive phenotypes and poorer outcomes. Mechanistic studies indicate that CST1 may influence tumor progression by reshaping protease inhibitor balance and engaging oncogenic signaling programs, including pathways linked to proliferation, migration, epithelial mesenchymal transition, and stress adaptation. In PDAC specifically, currently available evidence supports elevated CST1 expression in tumor tissue and suggests pro tumor effects in experimental systems, which together provide biological rationale for further evaluation. At the same time, clinically decisive evidence remains incomplete. Data directly assessing serum or exosomal CST1 in well characterized PDAC cohorts are limited, and key questions remain open, including whether CST1 rises early enough to support detection of resectable tumors, how its levels behave longitudinally during treatment, and how strongly they are influenced by common clinical confounders such as cholestasis, systemic inflammation, renal function, or hemolysis. In addition, cut off selection, batch effects, and platform specific calibration can materially alter performance metrics, making cross study comparisons difficult without shared reference standards. Taken together, CST1 is best viewed at present as a candidate component of a multi marker panel rather than a stand alone screening test, with the most realistic use cases being high risk surveillance, triage of indeterminate imaging findings, or augmentation of CA19-9 based decision making. Future work should prioritize

multicenter prospective validation enriched for early stage disease, rigorous control selection that includes benign biliary and inflammatory conditions, and harmonized preanalytical and analytical protocols so that the incremental value of CST1 can be quantified in clinically relevant pathways.

Keywords

Pancreatic Ductal Adenocarcinoma, Early Detection, CST1, Liquid Biopsy, Biomarker

1. 胰腺癌的严峻临床挑战与生物标志物的迫切需求

1.1. 胰腺癌的流行病学与临床困境

胰腺癌(Pancreatic Ductal Adenocarcinoma, PDAC)是全球范围内最具侵袭性的恶性肿瘤之一。据最新统计，其发病率虽非最高但死亡率几乎与之持平，5 年生存率常低于 10%，被誉为“癌中之王”[1] [2]。其生物学行为和临床特征导致诊治极其困难：1) 早期症状隐匿：胰腺癌早期缺乏特异症状体征，患者多因腹痛、黄疸、消瘦等就诊时已是局部晚期或远处转移，失去手术根治机会[3]。2) 缺乏有效筛查手段：胰腺深藏腹膜后，常规体检和超声难以发现早期病灶。目前尚无针对普通人群或高危人群的高效早期筛查方案[4]。3) 高度侵袭易转移：肿瘤细胞侵袭性极强，早期即可经淋巴、血行途径扩散至远处器官[5]。4) 致密间质屏障：胰腺癌肿瘤微环境富含大量纤维化间质，形成物理和生物屏障，不仅阻碍化疗药物递送，也抑制免疫细胞浸润和功能[6]。超过 80%的患者初诊已属晚期且无法手术，预后极差。为改善这一困境，实现诊断“关口前移”是关键，即在肿瘤早期甚至癌前阶段有效识别患者。因此，生物标志物成为早期诊断的核心工具。理想标志物应能在高危人群中敏感地检出胰腺癌，区分肿瘤与良性胰腺疾病，并可通过血液、尿液等微创途径检测，同时反映肿瘤分期、疗效和进展情况。全球各领域研究者正从基因组、蛋白质组、代谢组等多方面探索候选分子，期望找到可提高胰腺癌早期诊断和预后改善的标志物[2] [7]。

1.2. 传统生物标志物(如 CA19-9)的局限性

胰腺癌临床诊断中最常用的血清标志物是糖链抗原 19-9 (CA19-9)。其诊断灵敏度约 70%~80%，特异度 70%~90%，存在相当比例漏诊和误诊，不足以支持作为普查筛查工具[8] [9]。此外，一些良性疾病(如慢性胰腺炎、胆道梗阻等)也可导致 CA19-9 升高，但约 5%~10%的人群因 Lewis 抗原阴性而先天不产生 CA19-9，这些因素均限制了 CA19-9 的有效性[7]。癌胚抗原 CEA、CA50、CA242、CA125 等传统生物标志物在胰腺癌的诊断和预后监测中有所应用，但它们在早期诊断中的局限性显著[10]-[12]。因此亟需探索新的标志物以提高胰腺癌诊断的灵敏度和特异性[3] [10]。

2. 胰腺癌诊断新兴生物标志物的研究进展

2.1. 液体活检相关标志物

胰腺癌患者外周血中可检出的肿瘤相关分子包括游离 DNA、循环肿瘤细胞及肿瘤来源的外泌体等。循环肿瘤 DNA (ctDNA)：是肿瘤细胞凋亡坏死后释放入血的游离 DNA，可捕获 KRAS、TP53、SMAD4

等突变，动态反映肿瘤异质性，用于胰腺癌的早期检测、疗效监测和预后评估[13] [14]。研究表明，将ctDNA 与 CA19-9 联合检测可在一定程度上提高灵敏度和特异性[13] [14]。然而早期胰腺癌患者血中ctDNA 含量极低，检测阳性率远低于晚期[13]。

非编码 RNA：包括微小 RNA (miRNA)、长链非编码 RNA (Long Non-Coding RNA, lncRNA)和环状RNA (Circular RNA, circRNA)等[15] [16]。有文献报道某些 miRNA 组合(例如 miR-145、miR-150、miR-223、miR-636)用于胰腺癌诊断时，其敏感性和特异性多在 80%~90%，诊断效果上尚未明显优于 CA19-9[15]-[18]。但现有证据主要来源于单中心或小样本队列，且多局限于单一人群，缺乏多中心、大规模前瞻性验证；同时，在样本类型、前处理流程与定量平台等方面尚未形成统一标准，限制了这些标记物向临床常规检测的规范化转化[16]-[20]。

外泌体及其内容物：外泌体是细胞分泌的纳米级胞外囊泡，富含 DNA、各类 RNA 和蛋白质，在体液中稳定存在并介导细胞间通信[21] [22]。胰腺癌患者血浆外泌体总量及特定货物(如 GPC1 阳性外泌体、携带突变 KRAS 的外泌体 DNA、富含 miR-10b/21 等的外泌体 miRNA)均升高，在区分胰腺癌与健康或良性疾病方面显示出较高诊断效能[17] [18] [23]。早期研究报道 GPC1 阳性外泌体对胰腺癌识别的敏感度和特异度极高[23]，但后续研究结果不一，提示其诊断价值存在异质性，需要更大样本验证[21] [22]。相比之下，以 miR-10b、miR-21 等构成的外泌体 miRNA 签名在多项研究中表现稳定，诊断性能优于单一 GPC1，并有望与 CA19-9 联合提高早期检出率[22]。需强调，目前外泌体分离富集技术尚未标准化，不同方法回收率、纯度差异明显，加之外泌体本身异质性高，这些因素均影响检测一致性和可比性，限制其临床推广[21] [22]。

血清多标志物联合：随着检测技术进步，不少研究尝试将 CA19-9 与其他蛋白标志物联用以提高诊断效能[7] [12]。如 CEA 家族成员 CEACAM1 在胰腺癌血清和组织中显著升高，区分胰腺癌与慢性胰腺炎的敏感度和特异度优于 CA19-9，两者联合可提高诊断准确度[7]；黏蛋白 MUC1、MUC4、MUC5AC 在胰腺癌及癌前病变中异常高表达，随肿瘤进展升高，与侵袭转移及化疗耐药相关，将 MUC1 或 MUC5AC 与 CA19-9 联合可一定程度改善早期诊断，但单独应用敏感度仍不足[7] [24]。Growth Differentiation Factor-15 (GDF-15)，在胰腺癌患者血清中持续升高，多项研究及荟萃分析提示其诊断准确度总体上接近 CA19-9 [7] [25] [26]，尤其在 CA19-9 阴性患者中可作为补充标志物，但其在多种炎症性疾病和其他肿瘤中也升高，受炎症及应激影响较大，限制了其作为高特异性筛查标志物的应用[7]。

2.2. 组织分子标志物

DNA 甲基化与基因突变：胰腺导管腺癌分子图谱以 KRAS 驱动突变最常见，并常伴 TP53、CDKN2A、SMAD4 等抑癌基因失活[27]。在组织或 ctDNA 中检测上述突变有助于诊断和复发风险评估，并指导潜在靶向治疗[27]。此外，异常 DNA 甲基化可用于胰腺癌早期检测。研究发现血浆游离 DNA 中 ADAMTS1 和 BNC1 启动子高甲基化在胰腺癌患者中富集，两基因联合检测对局限期胰腺癌的敏感度和特异度均约 95%，显著优于 CA19-9 [28]。不过，多数甲基化标记基于单中心小样本，缺乏大规模前瞻性验证；且高通量甲基化检测成本高、技术复杂，限制了其在常规临床的推广[27] [28]。

3. 半胱氨酸蛋白酶抑制剂(Cystatin)家族与肿瘤

Cystatin 是内源性可逆的半胱氨酸蛋白酶抑制剂，广泛存在于细胞质、胞外基质和体液，在蛋白质降解、抗原提呈、细胞凋亡和组织重塑等过程中调节 Cathepsin 活性，维持细胞稳态[29]-[31]。按结构和定位，Cystatin 分 I 型(胞内，stefin)、II 型(分泌型小分子，如 Cystatin C、SN 等)和 III 型(高分子量含 Cystatin 结构域的血浆蛋白) [29] [30]。Cystatin 通过高亲和结合 Cathepsin B、L、S、K 等抑制其蛋白水解活性，

在肿瘤发生发展中呈“双刃剑”效应：一方面抑制基质降解可限制侵袭转移，另一方面某些成员在慢性炎症、免疫逃逸、肿瘤微环境重塑中促进肿瘤进展[29]-[31]。研究指出，不同实体瘤中 Cystatin 与 Cathepsin 失衡几乎贯穿肿瘤各阶段，包括原位癌形成、基底膜破坏、血管新生和远处转移等[29] [30]。因此，Cystatin 既是理解肿瘤蛋白酶网络紊乱的切入点，也是潜在的诊断和治疗靶点。

II 型 Cystatin (如 Cystatin C、SN 等)由含信号肽的小分泌蛋白组成，成熟蛋白约 100~120 氨基酸，主要存在于细胞外和各种体液中[30] [31]。与局限胞内的 I 型相比，II 型 Cystatin 具有明显的液体活检优势：分泌入血后稳定且易于 ELISA 等方法定量；肿瘤细胞或免疫细胞分泌模式改变可直接反映于体液浓度，适合作为无创诊断和监测标志物[29]-[31]。在多种实体瘤中，II 型 Cystatin 表达改变与肿瘤侵袭性增强、转移风险升高和免疫微环境重塑密切相关[29] [31]。其中 Cystatin SN (CST1)作为 II 型家族的重要成员，在胃癌、结直肠癌、肺癌、肝癌、乳腺癌等多种肿瘤中呈高表达并与预后不良相关，逐渐被视为该家族最具代表性的肿瘤相关标志物之一[32]-[37]。相较其他 II 型成员(如 Cystatin C 在多肿瘤中反而下调且具抑癌作用)，CST1 在大多数恶性肿瘤中持续上调，且其蛋白可分泌入血并稳定存在，赋予其“功能驱动因子”和“可检测标志物”双重属性[29] [31]-[37]。这些特点为本研究聚焦 CST1 作为胰腺癌候选标志物提供理论基础。

4. Cystatin SN (CST1)的生物学特性及其在肿瘤中的研究现状

4.1. CST1 的分子结构、基因调控及分泌分布

CST1 基因位于人 20p11.21，编码含信号肽的前体蛋白，成熟 CST1 约 14 kDa，属分泌型 II 型 Cystatin [30] [31] [38]。CST1 经经典内质网–高尔基途径分泌至细胞外，主要表达于唾液腺、胃黏膜、呼吸道黏膜等，可在唾液、泪液、血浆等体液中检测到[30] [31] [38]。结构上，CST1 与其他 II 型成员相似，具有保守的 QXVXG 基序和 PW 序列，可高亲和结合 Cathepsin B 等半胱氨酸蛋白酶并抑制其活性[29]-[31]。值得注意的是，Kim 等发现 CST1 可在结直肠癌细胞外与 Cystatin C 形成复合物，以更高亲和力抢占 Cystatin C 与 Cathepsin B 的结合位点，部分解除后者对 Cathepsin B 的抑制[39]。提示 CST1 并非仅作为酶抑制剂，还通过调节其他 Cystatin 成员功能，间接放大肿瘤微环境中蛋白酶网络的作用。在检测方法上，目前多采用 qPCR 检测 CST1 mRNA、免疫组化和 Western blot 评估组织蛋白，ELISA 或化学发光法定量血清等体液中的 CST1 蛋白[32]-[37] [40]-[43]。这为后续在胰腺癌开展组织和血清学研究提供了可行技术路径。

4.2. CST1 的生理功能及在非肿瘤疾病中的作用

在生理状态下，CST1 维持口腔和呼吸道黏膜屏障完整性，具抗菌和抗蛋白酶保护作用[29] [38]。免疫学研究发现 CST1 在 2 型炎症相关疾病(如变应性鼻炎、哮喘)中显著上调，由上皮细胞分泌，抑制吸入性变应原蛋白酶活性并调控 Th2 反应，其水平与嗜酸性炎症程度相关[44]。CST1 还可通过调节 ROS 和自噬水平影响细胞存活：Oh 等证实高表达 CST1 的结直肠癌细胞对金剂诱导的细胞死亡更耐受，机制与 CST1 诱导自噬、调节谷胱甘肽还原酶活性、降低 ROS 积累有关[45]。这些结果提示 CST1 在稳态维持和应激适应中具有重要作用，也为理解其在肿瘤化疗耐药中的潜在角色提供线索。

4.3. CST1 在多种实体瘤中的表达谱、功能及临床意义

胃癌：CST1 是胃癌中最早被系统研究的 II 型 Cystatin 之一。Choi 等发现胃癌组织及细胞系中 CST1 mRNA 和蛋白显著升高，过表达 CST1 可促进细胞增殖并抑制 Cathepsin 活性[32]。机制研究表明 CST1 通过 T 细胞因子介导的增殖信号参与胃癌发生，并可激活 Wnt 通路增强细胞迁移侵袭[38] [46]。最新研究揭示 CST1 在胃癌转移中起关键作用：高表达 CST1 通过结合谷胱甘肽过氧化物酶 4 (GPX4)并募集去

泛素酶 OTUB1，抑制 GPX4 降解，降低脂质过氧化和铁死亡水平，促进上皮–间质转化(EMT)及远处转移[46]。且转移性胃癌患者血浆和腹水中 CST1 升高，与不良预后独立相关，提示 CST1 兼具驱动因子和体液标志物双重潜力[46]。

结直肠癌(CRC)：Kim 等发现结肠癌组织中 CST1 高表达，并通过中和 Cystatin C 对 Cathepsin B 的抑制，增强了细胞侵袭和体内转移能力[39]。Yoneda 等首次鉴定 CST1 为 CRC 潜在肿瘤标记物[33]；随后 Li 等构建了 CST1 相关预后列线图模型，显示 CST1 高表达与较差总生存显著相关，是 CRC 患者不良预后的独立因素之一[34] [37]。在检测上，CRC 中常联合组织免疫组化、qPCR 和血清 ELISA 评估 CST1。结果表明 CST1 组织高表达预示预后不良，血清中亦有一定诊断潜力[33] [34] [39]。

非小细胞肺癌(NSCLC)：Cao 等报道 CST1 在肺癌组织中显著上调，其高表达与术后复发、远处转移及更短生存期密切相关，是不良预后独立风险因素[35]。在血清学研究中，Lai 等发现早期 NSCLC 患者血清 CST1 显著高于良性肺结节和健康人，对鉴别早期肺癌具有一定诊断价值，同时血清 CST1 水平低的患者生存率更高[43]。这些结果提示 CST1 可能通过促进 EMT 和影响免疫微环境等机制共同驱动肺癌进展。

肝细胞癌(HCC)：Cui 等观察到 CST1 在 HCC 肿瘤组织和血清中均明显升高，高表达与肿瘤体积大、晚期分期及门静脉癌栓相关，提示预后较差[36]。体外功能实验显示过表达 CST1 可促进 HCC 细胞增殖迁移，敲低 CST1 则显著抑制体内外肿瘤生长[36]。

乳腺癌：Dai 等发现 CST1 在乳腺癌组织中高表达，并与淋巴结转移和晚期分期密切相关，CST1 高表达预示患者预后不良[37]。Liu 等进一步证实 CST1 通过调节 ERα/PI3K/AKT 正反馈环路促进 ER 阳性乳腺癌细胞增殖和 G_1/S 周期转换，揭示了其在内分泌通路中的作用机制[40]。

食管鳞状细胞癌(ESCC)：在 ESCC 中，血清 CST1 显著升高且水平越高预后越差。Wang 等采用化学发光法建立血清 CST1 检测，有助于 ESCC 的早期诊断，并与传统标志物联合应用可提高敏感度；Pi 等在多中心队列中验证了血清 CST1 的诊断和预后价值，其 AUC 约 0.78，术后 1~2 周血清 CST1 水平较术前显著下降，且高术前 CST1 水平是独立的不良预后因素[42] [43]。

综上，除个别肿瘤外，大多数实体瘤中 CST1 均表现为组织和/或血清高表达，并与更强侵袭转移能力及更差预后密切相关[32]-[37] [39]-[43]。这些证据奠定了将 CST1 视为具有“驱动–标志”双重潜力分子的研究基础。

4.4. CST1 表达调控网络

CST1 的异常上调源于多层次调控失衡。转录水平上，部分胃癌研究提示转录因子 HOXC10 可上调 CST1，并激活 Wnt/β-catenin 通路促进迁移侵袭[46]；在 CRC 中，let-7d/CST1/p65 轴被报道可调控细胞增殖和炎症信号，提示 miRNA 也是 CST1 调控网络的重要组成[38] [46]。表观遗传方面，有研究认为 DNA 甲基化和染色质开放状态影响 CST1 启动子活性，但具体机制尚待阐明[31] [38]。此外，在 ESCC 中发现 miR-942-5p 可直接靶向 CST1 mRNA 并抑制其表达，降低细胞迁移侵袭能力，说明 CST1 在某些肿瘤中也受 miRNA 负向调控[42]。总体而言，CST1 处于“转录因子–表观遗传-miRNA-蛋白酶网络”的交汇点，既受多种上游信号调控，又通过影响 Cathepsin 活性以及 ROS/铁死亡、EMT 等通路促进肿瘤进展[31] [39] [46]。

5. CST1 在胰腺癌中的研究进展与潜在机制

5.1. 组织表达特征及与临床病理的关联

与胃癌、结直肠癌等已有大量证据相比，CST1 在胰腺癌(主要指胰腺导管腺癌，PDAC)中的研究有限。较系统的工作主要来自 Jiang 等[47]，该研究通过表达谱分析发现 CST1 在 PDAC 组织中显著上调，

并在差异基因中名列前茅；qPCR、Western blot 和免疫组化在独立样本中验证了 PDAC 组织 CST1 的高表达，染色显示 CST1 主要定位于癌细胞胞质及胞外隙，而邻近正常胰腺组织表达很低[47]。功能实验方面，敲低胰腺癌细胞系中的 CST1 可显著减慢细胞增殖、诱导细胞周期阻滞，并在小鼠异种移植模型中抑制肿瘤生长[47]。同时，CST1 沉默伴随增殖相关蛋白 PCNA、Cyclin D1 下调，提示 CST1 在胰腺癌中具有促细胞增殖作用[38] [47]。尽管该研究未详细分析 CST1 表达与临床分期、转移、神经侵犯等参数的关系，但结合多癌种证据推测，CST1 在 PDAC 中同样可能与更强侵袭性和更差预后相关[32]-[37] [39] [47] [48]。

5.2. 细胞及信号通路层面的潜在机制

综合多癌种研究，推测 CST1 在胰腺癌中可能通过以下机制发挥作用：增强 Cathepsin 介导的基质降解、激活 PI3K/AKT 等增殖存活通路、促进 EMT 相关基因表达，以及降低 ROS 积累和铁死亡敏感性等[29] [39] [46] [47]。需要强调的是，上述机制多数仍未在胰腺癌中直接验证，目前仅有 PI3K/AKT 相关证据来自单一研究[47]；其他推测主要源于跨肿瘤类比及 CST1 在蛋白酶网络中的共性作用。PDAC 以显著致密间质反应(Desmoplasia)为突出特征，胶原与透明质酸沉积可导致间质压升高、微血管塌陷与灌注受限，从而使“蛋白酶–抑制剂”网络对 ECM 重塑、侵袭通道形成及 CAF 激活的调控更具决定性意义[5] [6] [49]。在此背景下，CST1 作为蛋白酶抑制剂并不必然指向“抑制侵袭”，其功能方向更可能取决于：对 Cathepsins 谱系的选择性、胞外/胞周定位，以及与其他 Cystatins (如 CST3)在同一底物竞争框架下的互作。已有研究表明，CST1 可提高胞外 Cathepsin B 的有效活性，并削弱 CST3 对 Cathepsin B 的抑制，等效于在总体上解除部分蛋白水解“刹车”[39]。据此可提出待验证的机制假说：在高间质压、低灌注与免疫抑制并存的 PDAC 微环境中，CST1-Cathepsin B 轴的偏移可能促进基底膜/ECM 降解，并与 MMPs 相关级联反应形成耦联，进一步放大基质重塑信号，同时通过改变 CAF 分泌谱(胶原/透明质酸相关通路)与 ECM 结合因子的释放/加工，间接影响免疫细胞浸润与药物可达性[5] [49]。建议后续在 PDAC 组织(含间质区)采用空间转录组/蛋白组联用，并结合 Cathepsin B 与 MMP 活性读出及 CAF 亚群标记开展分层验证，以区分“肿瘤细胞驱动”与“间质驱动”两类信号在不同分子亚型中的相对贡献[50]。尚待胰腺癌中特异性的体内外实验进一步证实。

5.3. 胰腺癌研究空白与展望

与胃、肠、肺、肝等相比，CST1 在胰腺癌领域仍存在显著空白：1) 缺乏针对胰腺癌患者的大样本血清学研究，目前尚无法回答“CST1 能否弥补 CA19-9 早诊不足”以及“能否用于动态监测”等核心问题；2) 尚无研究评估 CST1 在 0~I 期或家族性胰腺癌高危人群中的筛查价值；3) 除 PI3K/AKT 通路外，缺乏关于 CST1 调控 EMT、铁死亡、免疫微环境等方面的深入机制研究；4) 缺少基于 ROC 曲线的诊断效能评价、联合模型构建、动态监测及预后分层等临床证据。总体而言，现有多组学胰腺癌标志物研究主要聚焦基因突变、ctDNA、miRNA、代谢物和外泌体成分等，CST1 尚未被充分纳入整合分析框架，也反映出其在胰腺癌中属于相对空白但值得深入探索的候选靶点[51]。

6. 研究展望

推动 CST1 用于胰腺癌诊断，还需克服若干挑战。首先，检测方法标准化：应在 ELISA、化学发光等平台间建立统一校准体系和参考值，提高不同研究的可比性[41]-[43] [52]。液体活检研究应尽量统一样本类型与抗凝剂、采血至离心时间/条件、溶血/脂血/黄疸干扰、保存温度与冻融次数，并设置质量控制样本与跨批校准以降低系统误差[53]。鉴于 CST1 约 14 kDa，其在血中稳定性/半衰期、与细胞外囊泡或蛋

白复合物结合比例及其对读数影响仍缺乏系统数据，临床验证除比较病例–对照差异外，还应评估处理条件变化的敏感性(如室温放置、冻融)及批内/批间变异[53]。Cystatin C (CST3)因与 GFR 呈稳定负相关而用于 eGFR 估算及 CKD 风险分层，提示低分子量分泌蛋白的血中水平可能被肾小球滤过能力显著塑形。虽与 CST3“恒定产生”的前提不同，CST1 具有组织特异性且可在肿瘤/炎症状态上调，但从生理学角度，合并 CKD、急性肾损伤或近端小管功能异常时，CST1 仍可能出现累积或清除改变，从而在液体活检场景形成混杂[53] [54]。后续研究建议常规记录肌酐、CST3 与 eGFR，并在统计中进行分层与回归校正；必要时可在入组阶段排除中重度 CKD 并开展敏感性分析，以更可靠地区分“肿瘤相关升高”与“清除障碍导致的假性升高”[54]。其次，多中心大样本验证：未来应设计前瞻性多中心研究系统评估 CST1 的诊断、预后和监测价值，尤其要涵盖早期病例和高危人群[51]。再次，多组学整合分析：将 CST1 与转录组、蛋白组、代谢组及单细胞测序数据结合，探讨其与特定分子亚型、免疫浸润模式和代谢重编程的关联，有助于精准界定其在胰腺癌生物网络中的位置[31] [51]。最后，与现有标志物和影像的联合：可尝试将 CST1 与 CA19-9、CEA、ctDNA 或影像组学特征整合建模，用机器学习优化诊断和预后预测，从而提高早期筛查和个体化管理的效能[51]。

7. 总结

Cystatin SN (CST1)是 II 型 Cystatin 家族中具有代表性的分泌型分子，近年来在多种消化系统肿瘤中被证实高表达并促进肿瘤进展，且可稳定存在于血液中，兼具功能驱动和可检测标志物双重属性。在胰腺癌中尽管研究证据有限，但已显示出 CST1 组织高表达及促增殖作用。结合其分泌特性和跨肿瘤中稳定的预后不良关联，CST1 有望成为胰腺癌早期诊断和预后评估的新型生物标志物。本文系统梳理了胰腺癌的临床挑战、生物标志物研究现状、Cystatin 家族与肿瘤的关系，重点讨论了 CST1 的生物学功能及其在胰腺癌中的研究进展，阐明将血清 CST1 用于胰腺癌早期诊断、分期评估、疗效监测和预后判定的理论基础，并展望其与现有标志物联合应用的前景和未来研究方向，以期为后续开展大规模临床验证提供文献依据和思路指导。

致　谢

感谢所有作者在学术讨论中给予的支持。

声　明

本文无相关利益冲突。

基金项目

昆明医科大学第二附属医院项目(ynIIT2021004)。

参考文献

[1] Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., *et al*. (2021) Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **71**, 209-249. https://doi.org/10.3322/caac.21660

[2] Siegel, R.L., Kratzer, T.B., Giaquinto, A.N., Sung, H. and Jemal, A. (2025) Cancer Statistics, 2025. *CA*: *A Cancer Journal for Clinicians*, **75**, 10-45. https://doi.org/10.3322/caac.21871

[3] Mannucci, A. and Goel, A. (2025) Advances in Pancreatic Cancer Early Diagnosis, Prevention, and Treatment: The Past, the Present, and the Future. *CA*: *A Cancer Journal for Clinicians*, **76**, e70035. https://doi.org/10.3322/caac.70035

[4] Singhi, A.D., Koay, E.J., Chari, S.T. and Maitra, A. (2019) Early Detection of Pancreatic Cancer: Opportunities and Challenges. *Gastroenterology*, **156**, 2024-2040. https://doi.org/10.1053/j.gastro.2019.01.259

[5] Joshi, V.B., Prabhakar, B.S. and Prabhakar, S. (2023) The Cell Biology of Metastatic Invasion in Pancreatic Cancer: Updates and Mechanistic Insights. *Cancers* (*Basel*), **15**, Article No. 2169.

[6] Hartupee, C., Nagalo, B.M., Chabu, C.Y., Tesfay, M.Z., Coleman-Barnett, J., West, J.T., *et al*. (2024) Pancreatic Cancer Tumor Microenvironment Is a Major Therapeutic Barrier and Target. *Frontiers in Immunology*, **15**, Article 1287459. https://doi.org/10.3389/fimmu.2024.1287459

[7] Yang, H., Li, W., Ren, L., Yang, Y., Zhang, Y., Ge, B., *et al*. (2023) Progress on Diagnostic and Prognostic Markers of Pancreatic Cancer. *Oncology Research*, **31**, 83-99. https://doi.org/10.32604/or.2023.028905

[8] Yang, J., Xu, R., Wang, C., Qiu, J., Ren, B. and You, L. (2021) Early Screening and Diagnosis Strategies of Pancreatic Cancer: A Comprehensive Review. *Cancer Communications*, **41**, 1257-1274. https://doi.org/10.1002/cac2.12204

[9] Luo, G., Jin, K., Deng, S., Cheng, H., Fan, Z., Gong, Y., *et al*. (2021) Roles of CA19-9 in Pancreatic Cancer: Biomarker, Predictor and Promoter. *Biochimica et Biophysica Acta—Reviews on Cancer*, **1875**, Article 188409. https://doi.org/10.1016/j.bbcan.2020.188409

[10] He, W., Cui, J., Wang, X., Siu, R.H.P. and Tanner, J.A. (2025) Early-Stage Pancreatic Cancer Diagnosis: Serum Biomarkers and the Potential for Aptamer-Based Biosensors. *Molecules*, **30**, Article 2012. https://doi.org/10.3390/molecules30092012

[11] Meng, Q., Shi, S., Liang, C., Liang, D., Xu, W., Ji, S., *et al*. (2017) Diagnostic and Prognostic Value of Carcinoembryonic Antigen in Pancreatic Cancer: A Systematic Review and Meta-Analysis. *OncoTargets and Therapy*, **10**, 4591-4598. https://doi.org/10.2147/ott.s145708

[12] Kim, H., Kang, K.N., Shin, Y.S., Byun, Y., Han, Y., Kwon, W., *et al*. (2020) Biomarker Panel for the Diagnosis of Pancreatic Ductal Adenocarcinoma. *Cancers*, **12**, Article No. 1443. https://doi.org/10.3390/cancers12061443

[13] Stosic, K., Senar, O.A., Tarfouss, J., Bouchart, C., Navez, J., Van Laethem, J., *et al*. (2023) A Comprehensive Review of the Potential Role of Liquid Biopsy as a Diagnostic, Prognostic, and Predictive Biomarker in Pancreatic Ductal Adenocarcinoma. *Cells*, **13**, Article 3. https://doi.org/10.3390/cells13010003

[14] Al-Shaheri, F.N., Alhamdani, M.S.S., Bauer, A.S., Giese, N., Büchler, M.W., Hackert, T., *et al*. (2021) Blood Biomarkers for Differential Diagnosis and Early Detection of Pancreatic Cancer. *Cancer Treatment Reviews*, **96**, Article 102193. https://doi.org/10.1016/j.ctrv.2021.102193

[15] Seyhan, A.A. (2023) Circulating MicroRNAs as Potential Biomarkers in Pancreatic Cancer—Advances and Challenges. *International Journal of Molecular Sciences*, **24**, Article 13340. https://doi.org/10.3390/ijms241713340

[16] Reese, K., Pantel, K. and Smit, D.J. (2024) Multibiomarker Panels in Liquid Biopsy for Early Detection of Pancreatic Cancer—A Comprehensive Review. *Journal of Experimental & Clinical Cancer Research*, **43**, Article No. 250. https://doi.org/10.1186/s13046-024-03166-w

[17] Mitsunaga, S., Ikeda, M., Ueno, M., Kobayashi, S., Tsuda, M., Miki, I., *et al*. (2025) Robust Circulating MicroRNA Signature for the Diagnosis and Early Detection of Pancreatobiliary Cancer. *BMC Medicine*, **23**, Article No. 23. https://doi.org/10.1186/s12916-025-03849-x

[18] Liu, Y., Feng, W., Liu, W., Kong, X., Li, L., He, J., *et al*. (2019) Circulating LncRNA ABHD11-AS1 Serves as a Biomarker for Early Pancreatic Cancer Diagnosis. *Journal of Cancer*, **10**, 3746-3756. https://doi.org/10.7150/jca.32052

[19] Li, Y., Al Hallak, M.N., Philip, P.A., Azmi, A.S. and Mohammad, R.M. (2021) Non-Coding RNAs in Pancreatic Cancer Diagnostics and Therapy: Focus on LncRNAs, circRNAs, and piRNAs. *Cancers*, **13**, Article No. 4161. https://doi.org/10.3390/cancers13164161

[20] Zhao, R., Han, Z., Zhou, H., Xue, Y., Chen, X. and Cao, X. (2023) Diagnostic and Prognostic Role of circRNAs in Pancreatic Cancer: A Meta-Analysis. *Frontiers in Oncology*, **13**, Article 1174577. https://doi.org/10.3389/fonc.2023.1174577

[21] Chang, C. and Pauklin, S. (2021) Extracellular Vesicles in Pancreatic Cancer Progression and Therapies. *Cell Death & Disease*, **12**, Article No. 973. https://doi.org/10.1038/s41419-021-04258-7

[22] Tiwari, P.K., Shanmugam, P., Karn, V., Gupta, S., Mishra, R., Rustagi, S., *et al*. (2024) Extracellular Vesicular miRNA in Pancreatic Cancer: From Lab to Therapy. *Cancers*, **16**, Article No. 2179. https://doi.org/10.3390/cancers16122179

[23] Melo, S.A., Luecke, L.B., Kahlert, C., Fernandez, A.F., Gammon, S.T., Kaye, J., *et al*. (2015) Glypican-1 Identifies Cancer Exosomes and Detects Early Pancreatic Cancer. *Nature*, **523**, 177-182. https://doi.org/10.1038/nature14581

[24] Manne, A., Ghosh, R., Esho, R. and Pan, S. (2021) Understanding the Clinical Impact of MUC5AC Expression on Pancreatic Ductal Adenocarcinoma. *Cancers*, **13**, Article No. 3059.

[25] Guo, M. and Zhao, H. (2024) Growth Differentiation Factor-15 May Be a Novel Biomarker in Pancreatic Cancer: A Review. *Medicine*, **103**, e36594. https://doi.org/10.1097/md.0000000000036594

[26] Wang, X., Li, Y., Tian, H., Qi, J., Li, M., Fu, C., *et al*. (2014) Macrophage Inhibitory Cytokine 1 (MIC-1/GDF15) as a Novel Diagnostic Serum Biomarker in Pancreatic Ductal Adenocarcinoma. *BMC Cancer*, **14**, Article No. 578.

https://doi.org/10.1186/1471-2407-14-578

[27] Ojha, S., Sessions, W., Zhou, Y. and Aung, K.L. (2025) ctDNA in Pancreatic Adenocarcinoma: A Critical Appraisal. *Current Oncology*, **32**, 589-604. https://doi.org/10.3390/curroncol32110589

[28] Eissa, M.A.L., Lerner, L., Abdelfatah, E., Shankar, N., Canner, J.K., Hasan, N.M., *et al*. (2019) Promoter Methylation of ADAMTS1 and BNC1 as Potential Biomarkers for Early Detection of Pancreatic Cancer in Blood. *Clinical Epigenetics*, **11**, Article No. 59. https://doi.org/10.1186/s13148-019-0650-0

[29] Breznik, B., Mitrović, A., T. Lah, T. and Kos, J. (2019) Cystatins in Cancer Progression: More than Just Cathepsin Inhibitors. *Biochimie*, **166**, 233-250. https://doi.org/10.1016/j.biochi.2019.05.002

[30] Soond, S.M., Kozhevnikova, M.V., Townsend, P.A. and Zamyatnin Jr, A.A. (2019) Cysteine Cathepsin Protease Inhibition: Diagnostic, Prognostic and Therapeutic Potential in Cancer. *Pharmaceuticals* (*Basel*), **12**, Article 87.

[31] Zhang, Z. and Zhan, F. (2023) Type 2 Cystatins and Their Roles in Regulation of Human Immune Responses and Cancer Development. *Cancers*, **15**, Article No. 5363.

[32] Choi, E.H., Kim, J.T., Kim, J.H., Kim, S.Y., Song, E.Y., Kim, J.W., *et al*. (2009) Upregulation of the Cysteine Protease Inhibitor CST1 Contributes to Cell Proliferation and Cathepsin Inhibition in Gastric Cancer. *Clinica Chimica Acta*, **406**, 45-51. https://doi.org/10.1016/j.cca.2009.05.008

[33] Yoneda, K., Iida, H., Endo, H., Hosono, K., Akiyama, T., Takahashi, H., *et al*. (2009) Identification of Cystatin SN as a Novel Tumor Marker for Colorectal Cancer. *International Journal of Oncology*, **35**, 33-40.

[34] Li, T., Hu, W., Zhang, M., Tian, L., Li, J. and Rong, R. (2017) Prognostic Significance of Cystatin SN-Associated Nomograms in Colorectal Cancer. *Oncotarget*, **8**, 115153-115163.

[35] Cao, X., Li, Y., Luo, R., Zhang, L., Zhang, S., Zeng, J., *et al*. (2015) Expression of Cystatin SN Significantly Correlates with Recurrence, Metastasis and Survival Duration in Surgically Resected Non-Small Cell Lung Cancer Patients. *Scientific Reports*, **5**, Article No. 8230. https://doi.org/10.1038/srep08230

[36] Cui, Y., Sun, D., Song, R., Zhang, S., Liu, X., Wang, Y., *et al*. (2019) Upregulation of Cystatin SN Promotes Hepatocellular Carcinoma Progression and Predicts a Poor Prognosis. *Journal of Cellular Physiology*, **234**, 22623-22634. https://doi.org/10.1002/jcp.28828

[37] Dai, D., Li, Y., Chen, B., Du, Y., Li, S., Lu, S., *et al*. (2017) Elevated Expression of CST1 Promotes Breast Cancer Progression and Predicts a Poor Prognosis. *Journal of Molecular Medicine*, **95**, 873-886. https://doi.org/10.1007/s00109-017-1537-1

[38] Liu, Y. and Yao, J. (2019) Research Progress of Cystatin SN in Cancer. *OncoTargets and Therapy*, **12**, 3411-3419.

[39] Kim, J.T., Lee, S.J., Kang, M.A., Park, J.E., Kim, B.Y., Yoon, D.Y., *et al*. (2013) CST1 Neutralizes the Inhibitory Effect of Cystatin C on Cathepsin B Activity. *Cell Death & Disease*, **4**, e974. https://doi.org/10.1038/cddis.2013.485

[40] Liu, Y., Ma, H., Wang, Y., Du, X. and Yao, J. (2019). Cystatin SN Affects Cell Proliferation by Regulating the ER*α*/PI3K/AKT/ER*α* Loopback Pathway in Breast Cancer. *OncoTargets and Therapy*, **12**, 11359-11369. https://doi.org/10.2147/ott.s234328

[41] Chen, Y.F., Ma, G., Cao, X., Luo, R.Z., He, L.R., He, J.H., *et al*. (2013) Overexpression of CST1 Positively Affects Survival of Patients with Surgically Resected Esophageal Squamous Cell Carcinoma. *BMC Surgery*, **13**, Article No. 15.

[42] Wang, J., Yu, L., Sun, Y., Zhang, L., Tu, M., Cai, L., *et al*. (2021) Development and Evaluation of Serum CST1 Detection for Early Diagnosis of Esophageal Squamous Cell Carcinoma. *Cancer Management and Research*, **13**, 8341-8352. https://doi.org/10.2147/cmar.s337497

[43] Pi, Y., Lin, S., Ren, X., Wang, L., Song, Y., Wu, Z., *et al*. (2024) Validation of Serum CST1 Detection for Diagnosis and Poor Prognosis of Esophageal Squamous Cell Carcinoma. *Frontiers in Oncology*, **14**, Article 1337707.

[44] Yan, B., Ren, Y., Liu, C., Shu, L., Wang, C. and Zhang, L. (2023) Cystatin SN in Type 2 Inflammatory Airway Diseases. *Journal of Allergy and Clinical Immunology*, **151**, 1191-1203.e3. https://doi.org/10.1016/j.jaci.2023.02.005

[45] Oh, B.M., Lee, S.J., Cho, H.J., Park, Y.S., Kim, J.T., Yoon, S.R., *et al*. (2017) CST1 Inhibits Auranofin-Induced Cell Death by Autophagy Induction and ROS Regulation via Glutathione Reductase in Colorectal Cancer. *Cell Death & Disease*, **8**, e2682.

[46] Li, D., Wang, Y., Dong, C., Chen, T., Dong, A., Ren, J., *et al*. (2023) CST1 Inhibits Ferroptosis and Promotes Gastric Cancer Metastasis by Stabilizing GPX4 via OTUB1. *Oncogene*, **42**, 83-98.

[47] Jiang, J., Liu, H., Liu, Z., Tan, S. and Wu, B. (2015) Identification of Cystatin SN as a Novel Biomarker for Pancreatic Cancer. *Tumor Biology*, **36**, 3903-3910. https://doi.org/10.1007/s13277-014-3033-3

[48] Yang, J., Luo, G., Li, C., Zhao, Z., Ju, S., Li, Q., *et al*. (2022) CST1 Promotes EMT and Serves as a Prognostic Biomarker in Lung Adenocarcinoma. *BMC Cancer*, **22**, Article No. 589.

[49] Provenzano, P.P., Cuevas, C., Chang, A.E., Goel, V.K., Von Hoff, D.D. and Hingorani, S.R. (2012) Enzymatic Targeting

of the Stroma Ablates Physical Barriers to Treatment of Pancreatic Ductal Adenocarcinoma. *Cancer Cell*, **21**, 418-429. https://doi.org/10.1016/j.ccr.2012.01.007

[50] Moncada, R., Barkley, D., Wagner, F., Chiodin, M., Devlin, J.C., Baron, M., *et al*. (2020) Integrating Microarray-Based Spatial Transcriptomics and Single-Cell RNA-Seq Reveals Tissue Architecture in Pancreatic Ductal Adenocarcinomas. *Nature Biotechnology*, **38**, 333-342. https://doi.org/10.1038/s41587-019-0392-8

[51] Turanli, B., Yildirim, E., Gulfidan, G., Arga, K.Y. and Sinha, R. (2021) Current State of "Omics" Biomarkers in Pancreatic Cancer. *Journal of Personalized Medicine*, **11**, Article 127. https://doi.org/10.3390/jpm11020127

[52] Dikovskaya, M.A., Russkikh, G.S., Loktev, K.V., Johnston, T.P., Gevorgyan, M.M., Voronina, N.P., *et al*. (2021) Cystatin C and Cystatin SN as Possible Soluble Tumor Biomarkers in Choroidal Melanoma. *Radiology and Oncology*, **56**, 83-91.

[53] Inker, L.A., Schmid, C.H., Tighiouart, H., Eckfeldt, J.H., Feldman, H.I., Greene, T., *et al*. (2012) Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. *New England Journal of Medicine*, **367**, 20-29. https://doi.org/10.1056/nejmoa1114248

[54] 上海市肾内科临床质量控制中心专家组. 慢性肾脏病早期筛查、诊断及防治指南(2022 年版) [J]. 中华肾脏病杂志, 2022, 38(5): 453-464.