Serum Syndecan-1: A Novel Biomarker for Pancreatic Ductal Adenocarcinoma

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INTRODUCTION: Syndecan-1 (SDC1) has multiple functions in tumorigenesis in general and specifically in pancreatic cancer. We aimed to evaluate SDC1 as a diagnostic and prognostic biomarker in patients with pancreatic ductal adenocarcinoma (PDAC).

METHODS: In this case-control study, patients newly diagnosed with a biopsy-proven PDAC were enrolled alongside healthy individuals in a derivation-validation cohort design. Serum SDC1 was measured by enzyme-linked immunoassay. The diagnostic accuracy of SDC1 levels for diagnosing PDAC was computed. A unified cohort enriched with additional early-stage patients with PDAC was used to evaluate the association of SDC1 with survival outcomes and patient characteristics.

RESULTS: In the derivation cohort, serum SDC1 levels were significantly higher in patients with PDAC (n = 39) compared with healthy controls (n = 20) (40.1 ng/mL, interquartile range 29.8–95.3 vs 25.6 ng/mL, interquartile range 17.1–29.8, respectively; P < 0.001). The receiver operating characteristic analysis area under the curve was 0.847 (95% confidence interval 0.747–0.947, P < 0.001). These results were replicated in a separate age-matched validation cohort (n = 38 PDAC, n = 38 controls; area under the curve 0.844, 95% confidence interval 0.757–0.932, P < 0.001). In the combined-enriched PDAC cohort (n = 110), using a cutoff of 35 ng/mL, the median overall 5-year survival between patients below and above this cutoff was not significantly different, although a trend for better survival after 1 year was found in the lower level group (P = 0.06). There were 12 of the 110 patients with PDAC (11%) who had normal CA 19-9 in the presence of elevated SDC1.

DISCUSSION: These findings suggest serum SDC1 as a promising novel biomarker for early blood-based diagnosis of pancreatic cancer.

INTRODUCTION
Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer death with dismal prognosis (1). Despite improvements in therapeutic strategies, the estimated 5-year survival rate of PDAC is only 8% mainly because it is usually diagnosed at very late stages (2). This is due to its asymptomatic nature at early stages together with the lack of efficient screening tests for early detection (3,4). The earliest genetic event in the progression of the normal ductal epithelia to premalignant pancreatic intraepithelial neoplasia is the KRAS oncogene mutation, which functions as a tumorigenesis driver (5–7).

Syndecan-1 (SDC1), a member of the transmembrane heparan sulfate proteoglycans family, is predominantly expressed on the basolateral membrane surface of epithelial cells (8). It mediates cell adhesion; participates in cell proliferation, migration, and cell-matrix interactions; and promotes wound healing by regulating immune functions (9,10). During infection, inflammation, and tissue injury, serum levels of SDC1 increase sharply, contributing to diverse pathophysiological events (11–13).

In the context of tumorigenesis, SDC1 regulates multiple functions, including tumor cell attachment, growth, proliferation, and angiogenesis through different signaling pathways (e.g., Wnt pathway activation) (14,15). Altered SDC1 expression is
associated with the presence and progression of various tumors (16–19) and specifically in PDAC as was recently published in a landmark study by Yao and colleagues. Oncogenic KRAS induces SDC1 overexpression on the cell surface, where it regulates macropinocytosis, a critical metabolic pathway that fuels PDAC cell growth and promotes tumor progression (20). In another study, patients carrying KRAS somatic mutations had higher SDC1 mRNA expression than those without mutations, suggesting a role for SDC1 as a KRAS effector and expression signature (21).

To the best of our knowledge, despite the pivotal role of SDC1 in PDAC tumorigenesis, serum levels of SDC1 have not been investigated in patients with pancreatic cancer. Therefore, this study was undertaken to evaluate the diagnostic and prognostic performance of serum SDC1 in patients with pancreatic cancer.

METHODS

Design and patient population
This case-control study was conducted at the Sheba Medical Center, a tertiary academic center in Israel. We included patients newly diagnosed with EUS-guided or surgically obtained histologically proven PDAC. The derivation cohort comprised of newly diagnosed patients with PDAC and healthy control individuals, who were prospectively and sequentially recruited between October 2019 and October 2020. A validation cohort was thereafter enrolled comprising additional prospectively recruited age-matched healthy individuals and PDAC patient serum samples obtained from the Sheba Medical Center’s Tissue Bank Repository. For the purpose of subgroup assessment, we divided patients into one group and enriched with additional patients with PDAC who underwent upfront surgery between September 2014 and October 2019, and whose serum were similarly stored in the Sheba Tissue Bank.

In all patients, serum tests for the tumor markers CA 19-9 and SDC1 analysis were performed at baseline before any surgical or oncological treatment. Retrieved data from medical records included demographics, smoking habits, presence of diabetes, germline testing (if performed), localization of the tumor, clinical/pathological staging, performance of surgery, and censor date (December 2020/death). Patients were excluded from the study if they were unable to provide informed consent or suffered from systemic active infectious diseases, autoimmune disorders, or other known extrapancreatic malignancies. All patients signed an informed consent (either for this study or for the tissue bank), and the study was approved by our institutional ethics review board.

Staging and size of the tumor
PDAC staging was classified either by the TMN system/American Joint Committee on Cancer staging for PDAC or by 3 clinically distinct patient groups: resectable (T1-3, stages 1 and 2), locally advanced (T4, stage 3), and metastatic disease (M1, stage 4). Staging was determined based on imaging modalities (typically computed tomography scans) for non-recteable tumors and pathologically determined for resectable ones. For locally advanced tumors in which neo-adjuvant treatment was given before surgery, we considered preoperative staging for the purpose of categorization.

Tumor size was determined by measuring its diameter, based on either pathology reports whenever surgery was performed or cross-sectional imaging/endoscopic ultrasound reports.

Study endpoints
The primary outcome was the diagnostic accuracy of serum SDC1 to differentiate between patients with PDAC and healthy individuals. Secondary outcomes included the utility of this biomarker to distinguish between different tumor stages, its association with survival outcomes, and with patient and tumor characteristics.

Soluble SDC1 analysis
Venous blood was collected and centrifuged at 3,000g for 10 minutes. The obtained serum was then stored at −80 °C. Samples provided by the Sheba Pancreatic Cancer biorepository were stored at −80 °C at all times after serum extraction. Serum SDC1 concentrations were determined using a human SDC1 enzyme-linked immunosorbent assay (Diaclone Research, Besancon, France) according to the manufacturer’s instructions. Serum SDC1 concentrations were reported as ng/mL, and the technicians were blinded of any clinical data.

Statistical analysis
Categorical variables were described as frequency and percentage and compared using the χ2 test or Fisher exact test. Continuous variables were described as median and interquartile range (IQR), and comparisons between categories were performed using Mann-Whitney U and Kruskal-Wallis tests. Associations between SDC1 levels and categorical variables were assessed using Spearman correlation coefficient, and associations between SDC1 levels and continuous variables were assessed using linear regression analysis. The association with survival outcomes, and with patient and tumor characteristics, was evaluated using the survival-ROC package version 1.0.3 in R: a language and environment for statistical computing (The R Foundation for Statistical Computing, version 3.3.3, 2017).

RESULTS

Patient characteristics
The derivation cohort was comprised of 39 patients and 20 healthy individuals, and the validation cohort included 38 patients and 38 age-matched healthy individuals. Patient characteristics in the derivation and validation groups are summarized in Table 1. The median age of patients with PDAC was 68 and 70 years in the derivation and validation groups, respectively. Patients with PDAC were significantly older than the healthy controls in the derivation cohort. Patient characteristics, tumor location or size, tumor staging, and CA 19-9 levels were comparable between the derivation and validation groups. Actionable germline pathogenic variants were found in 8 patients in the 2 groups (BRCA 1/2–6, MSH6–1, CHEK2–1). Significantly more patients with PDAC in the validation group underwent surgery compared with the derivation group (20 vs 9, P = 0.007), including 3, 5, and 1 patients in stage disease I, II, and III,
Table 1. Patient demographics and baseline characteristics

|                      | Derivation cohort | Validation cohort | P-valuea |
|----------------------|-------------------|-------------------|----------|
|                      | PDAC, N = 39      | Control, N = 20   |          |
|                      |                   |                   |          |
| Age, median (IQR), yr| 68 (63–74)        | 31 (27–36)b       | 0.617    |
| Male sex, N (%)      | 19 (48.7)         | 9 (45.0)c         | 0.420    |
| Diabetes, N (%)      | 22 (56.4)         | 18 (47.4)         | 0.427    |
| Smoking, N (%)       | 13 (33.3)         | 12 (31.6)         | 0.869    |
| Tumor localization, N (%) |                  |                   |          |
| Head                 | 30 (76.9)         | 25 (65.8)         | 0.06     |
| Body/tail            | 9 (23.1)          | 13 (34.2)         |          |
| Staging, N (%)       |                   |                   |          |
| 1                    | 4 (10.3)          | 6 (15.8)          | 0.376    |
| 2                    | 11 (28.2)         | 12 (31.6)         | 0.764    |
| 3                    | 4 (10.3)          | 5 (13.2)          | 0.576    |
| 4                    | 20 (51.3)         | 15 (39.5)         | 0.298    |
| Tumor size, median (IQR), mm | 28 (23–40)     | 30 (25–41)        | 0.865    |
| Germline mutation, N (%) | 3 (7.7)          | 5 (13.2)          | 0.970    |
| CA 19-9 ≥ 37 U/mL, N (%) | 31 (79.5)        | 33 (86.8)         | 0.389    |
| Baseline CA 19-9, median (IQR), U/mL | 392 (71–3,198) | 394 (92–1,502) | 0.854    |
| Surgery, N (%)       | 9                 | 20                | 0.007    |
| Upfront              | 5                 | 20                |          |
| After neo-adj.       | 4                 | 0                 |          |
| IQR, interquartile range 25–75; PDAC, pancreatic ductal adenocarcinoma. |
| aBetween derivation and validation PDAC cohorts. |
| bP-value < 0.001 between PDAC and control patients. |
| cP-value not significant between PDAC and control patients. |
| dP-value = 0.03 between PDAC and control patients. |

respectively, in the derivation group and 6, 11, and 3 patients, respectively, in the validation group.

Serum SDC1 level diagnostic accuracy for PDAC—primary outcome
In the derivation cohort, the median serum SDC1 level was significantly higher in the PDAC group compared with healthy controls (40.1 ng/mL, IQR 29.8–95.3 vs 25.6 ng/mL, IQR 17.1–29.8, respectively; P < 0.001, Figure 1a). On ROC analysis, AUC was 0.847 (95% confidence interval [CI] 0.747–0.947, P < 0.001, Figure 2a).

In the validation cohort, the median serum SDC1 level was also significantly higher in the PDAC group compared with healthy controls (50.5 ng/mL, IQR 35.1–73.2 vs 32.2 ng/mL, IQR 29.0–36.5, respectively; P < 0.001, Figure 1b). The ROC analysis AUC was 0.844 (95% CI 0.757–0.932, P < 0.001) in the validation cohort (Figure 2b).

A cutoff level of 30 ng/mL serum SDC1 showed a sensitivity of 75% and a specificity of 75% in the derivation group and a sensitivity and specificity of 95% and 37%, respectively, in the validation group. A cutoff level of 26 ng/mL of serum SDC1 showed a

Figure 1. (a) Box-plot representation of median serum syndecan-1 levels in patients with pancreatic ductal adenocarcinoma (PDAC) vs healthy controls (derivation cohort). (b) Box-plot representation of median serum syndecan-1 levels in patients with PDAC vs healthy controls (validation cohort).
Diagnostic utility of serum SDC1 for PDAC staging—secondary outcome

To evaluate the diagnostic value of SDC1 for PDAC staging, we enriched our cohort with early-stage patients undergoing upfront surgery ($n = 33$), generating a combined total cohort size of 110 patients. The serum SDC1 level was not significantly different among patients with different tumor stages (median [IQR]: stage 1 [$N = 15$] −43.7 ng/mL [24.8–68.6]; stage 2 [$N = 44$] −45.5 ng/mL [30.2–95.0]; stage 3 [$N = 14$] −37.4 ng/mL [32.1–59.7]; and stage 4 [$N = 37$] −40.2 ng/mL [31.2–63.7]; $P = 0.854$) (Figure 3a).

Similarly, the SDC1 level was not significantly different when comparing metastatic ($n = 37$) vs nonmetastatic ($n = 73$) PDAC groups (median [IQR] 40.2 ng/mL [31.2–63.7] vs median [IQR] 43.7 ng/mL [31.3–84.0], respectively; $P = 0.877$) (Figure 3b).

Serum SDC1 for association analysis and survival prediction

Association between baseline characteristics, tumor location, tumor size, CA 19-9 levels, and serum SDC1 are presented in Table 2. Serum SDC1 was higher in patients with tumor location in the head of pancreas vs body/tail localization ($P = 0.019$) and was not significantly associated with age, sex, smoking habits, diabetes, tumor size, germline mutation, and elevated CA 19-9 level ($\geq 37$ U/mL). However, stage IV disease was equally distributed between patients with pancreatic head or body/tail localization (71.8% vs 53.1%, respectively, $P = 0.076$). Remarkably, a subset of patients, with normal CA 19-9 (<37 U/mL) had elevated serum levels of SDC1. Twenty out of 110 patients (18.1%) had normal serum CA 19-9, of whom 5 (25%) had metastatic disease and the rest (75%) had stage 1–2 disease. Twelve of these 20 patients (60%) had serum SDC1 $\geq 35$ ng/mL, of whom 3 (25%) had metastatic disease and the rest had stage 1–2 disease.

Overall, 47 of the 110 patients (42.7%) survived with a median follow-up time of 11 months (IQR 5–28). Kaplan-Meier analysis of overall survival during the follow-up period (Figure 4) shows that the median overall survival of patients with baseline serum SDC1 $<35$ vs $\geq 35$ ng/mL was not significantly different (24.0 months [CI 12.1–35.8] vs 14.0 months [CI 4.7–23.2], respectively; $P = 0.153$), although there was a trend towards better survival after 12 months in patients with serum levels $< 35$ ng/mL ($P = 0.066$).
DISCUSSION

The early diagnosis of pancreatic cancer remains elusive and challenging, making easily obtained biomarkers a necessity. This study was conceived based on basic and translational studies indicating the involvement of SDC1 in PDAC’s tumor biology and aimed to explore this molecule’s role as such a biomarker. The results indicate that baseline serum SDC1 levels were significantly elevated in patients with PDAC, across all stage groups, compared with healthy individuals in both the derivation and validation cohorts. However, it was not correlated with either disease staging or overall survival. In cutoff levels of 26 and 30 ng/mL, serum SDC1 displayed a high sensitivity for diagnosing patients with PDAC. Owing to the observed low specificity of the above thresholds, it practically demonstrates that serum SDC1 can be an accurate biomarker for PDAC, but not as a screening tool in the general population with a low index of suspicion for a disease.

The discovery and utilization of novel biomarkers that also have a defined pathophysiological role in the tumorigenesis of PDAC can potentially improve diagnostic and clinical evaluation (22). Moreover, a better understanding of the role of the cell surface protein repertoire (surfaceome) that interacts with KRAS in PDAC progression may shed light on additional therapeutic targets for PDAC (21,23). Indeed, growing evidence indicates that among the multiple changes seen in malignant transformation, SDC1 expression, which is the best characterized of the 4 syndecan family members, often undergoes significant alterations (14,17). In general, SDC1 expression is downregulated in gastrointestinal malignancies and the loss of epithelial SDC1 has been associated with high tumor bulk, high histologic grade, and shorter overall and recurrence-free survival in gastric cancer, colorectal adenocarcinoma, and hepatocellular carcinoma (24,25). Conversely, PDAC is the only gastrointestinal malignancy in which SDC1 levels are upregulated, which correlates with accelerated tumor growth, as determined by in situ hybridization and immunohistochemistry (26).

Two recent published studies have linked SDC1 levels with mutated overexpressed KRAS, the initiating step in most PDACs, which cooperate to induce a malignant phenotype. In the first study, the authors found that patients carrying KRAS somatic mutations had higher SDC1 mRNA expression than those without mutations and that this gene signature elevated mortality (21). The second study demonstrated that in a low-glutamine medium, SDC1 knockout cells with upregulated KRAS, reduced albumin intake capacity, and consequently reduced cell proliferation (20). Therefore, SCD1 seems to serve as a KRAS effector and plays a crucial role in macropinocytosis (a type of endocytosis) in KRAS-driven PDAC.

SDC1 extracellular domains (ectodomains) are constitutively shed by proteolytic cleavage at the juxtamembrane site (27). Increased shedding of SDC1 to the serum has been shown by our lab and others to occur in multiple inflammatory conditions and in the setting of tissue injury (11,28). However, in tumorigenesis, there are multiple lines of evidence suggesting that shed SDC1 is responsible for enhancing the activity of cancer cells and has a role in tumor progression (29,30). A recent study involving breast cancer patients demonstrated higher levels of serum SDC1 compared with healthy individuals, correlating with tumor size (31). To the best of our knowledge, this is the first study reporting the shedding of SCD1 in PDAC to serum, adding another piece of evidence to its importance.

Although our understanding of the pathways causing SCD1 shedding in PDAC, as well as its significance in tumor development, is limited, there are several possible mechanisms. First, accelerated SDC1 ectodomain shedding can be attributed to

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**Table 2. Association between serum syndecan-1 levels, patient’s characteristics, and tumor features**

| Characteristic          | Serum syndecan-1 ng/mL, median (IQR) | P-value |
|-------------------------|--------------------------------------|---------|
| Age                     | 0.003<sup>a</sup>                    | 0.975   |
| Sex                     | 0.792                                |         |
| Male                    | 43.7 (32.2–69.6)                     |         |
| Female                  | 40.2 (29.0–73.3)                     |         |
| Smoking                 | 0.556                                |         |
| Yes                     | 41.8 (30.6–63.0)                     |         |
| No                      | 43.7 (31.2–80.2)                     |         |
| Diabetes                | 0.744                                |         |
| Yes                     | 42.3 (31.0–87.1)                     |         |
| No                      | 43.5 (32.1–67.9)                     |         |
| Germline mutation       | 0.818                                |         |
| Yes                     | 45.2 (32.3–110.7)                    |         |
| No                      | 43.0 (30.3–71.7)                     |         |
| Localization of PDAC    | 0.019                                |         |
| Head                    | 48.0 (32.4–94.6)                     |         |
| Body/tail               | 37.2 (28.9–49.3)                     |         |
| Tumor size              | –0.006<sup>a</sup>                  | 0.946   |
| CA 19-9 ≥ 37 U/mL       | 0.190                                |         |
| Yes                     | 43.7 (32.3–75.7)                     |         |
| No                      | 37.2 (28.9–52.5)                     |         |

*IQR, interquartile range 25–75; PDAC, pancreatic ductal adenocarcinoma.

<sup>a</sup>Data are presented as Spearman rank correlation coefficient.
upregulated cell surface SDC1, probably reflecting a large tumor mass, as was shown in other malignancies (25,31). Alternatively, the shedding can be attributed to overexpression of hepanase (HPA), an endoglycosidase that specifically degrades the heparan sulfate chains of SDC1, which has been correlated with cancer cell invasion and lymph node metastasis in patients with PDAC (32). HPA can mediate enhanced SDC1 shedding within the tumor microenvironment through upregulation of matrix metalloproteinase-9 (MMP9), which seems to be associated with an aggressive phenotype (32). At the same time, the HPA/SDC1 axis promotes the upregulation of fibroblast growth factor 2 (FGF2) which in turn promotes SDC1 shedding by MMP7 in PANC-1 cells (33). In our study, serum SDC1 levels were associated with tumor location in the head of the pancreas, which can reflect either a larger tumor mass than body/tail localization or a higher degree of cell invasion within the microenvironment and lymph nodes, although not significantly shown to be more metastatic. Although we did not find tumor size to be correlated with SDC1 levels, it may not reflect the true tumor burden because of inaccurate measurement by cross-sectional imaging or the lack of reported data regarding tumor volume, possibly a more reliable marker of tumor mass.

Biological markers can serve patients differently in the various stages of PDAC. In this study, serum SDC1 levels were equally elevated across all stage groups, which clinically means that it can distinguish between normal and very early disease stages of PDAC. In addition, a trend in difference in survival curve for an SDC1 cutoff level of 35 ng/mL, independent of cancer staging, is remarkable, although shown after 1 year and was lessened after longer periods. These findings rationalize targeting SDC1 as a therapeutic treatment (28), as was recently shown in multiple myeloma, in which indatuximab ravtansine (BT062), an SDC1 antibody, has been successfully used in stabilizing or improving the disease in almost 80% of the patients (34). In addition, the SDC1 gene has been recently reported to be targeted by microRNA-494, which decreases mRNA and protein expression levels of SDC1 in the pancreatic cancer cell line and delays tumor growth in a xenograft mouse model (35).

Our study has several limitations. First, we had a small number of patients with resectable disease, which reflects the real-life proportion of patients diagnosed at this stage (15%), which might have precluded our ability to reliably analyze this group. Moreover, several inherent shortcomings of the American Joint Committee on Cancer staging system (e.g., inadequate evaluation of lymph node status, and lack of consideration of margins of resection in patients who are not candidates for surgery) may lead to an understaging of resectable or locally advanced disease and misclassification. Nevertheless, the same results were obtained when patients were classified according to patient groups. Second, high-risk patients with nonmalignant pancreatic diseases, specifically premalignant cystic diseases and chronic pancreatitis, were not included and compared with patients with PDAC. Thus, it is unknown whether SDC1 can be equally used as a reliable biomarker between these groups. Third, serum SDC1 was measured only in 1 time point before any treatment, which limits our ability to study its prognostic role and its correlation to treatment. Finally, our cohort is from a relatively homogenous Israeli population and extrapolation to more heterogenous populations may be limited.

In conclusion, this study showed that serum SDC1 is elevated in patients with PDAC compared with normal individuals. In addition to its potential as a diagnostic marker, either alone or possibly in combination with other biomarkers, it can also potentially serve as a therapeutic target in light of its biological role in PDAC progression and associated genetic tumor alterations, specifically in KRAS. More prospective studies are needed to test and verify the clinical utility of serum SDC1 in PDAC and in premalignant pancreatic lesions, and subsequently, clinical studies should be conducted in which clinical decisions are taken on the basis of the protein level.

CONFLICTS OF INTEREST
Guarantor of the article: Doron Yablecovitch, MD.
Specific author contributions: Talia Golan, MD, and Ido Laish, MD contributed equally to this work. D.Y.: conceptualization and writing; S.B-H.: supervision and methodology; I.L.: supervision and writing; T.G.: supervision, methodology, and data acquisition; O.P., M.Y., and E.F: methodology and data acquisition; M.N., I.L., E.S., A.L., and M.L.: data acquisition; T.S.: visualization; S.N., L.S., and R.D.: methodology; M.R-G.: data acquisition, reviewing, and editing. All the authors involved in critical revision of the manuscript for important intellectual content and approved the final version of the manuscript.

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Study Highlights

WHAT IS KNOWN

✓ Pancreatic ductal adenocarcinoma (PDAC) is one of the leading causes of cancer death with dismal prognosis.
✓ There is an unmet need for the early detection of novel biomarkers.
✓ Syndecan-1 (SDC1) has a pivotal role in PDAC tumorigenesis.

WHAT IS NEW HERE

✓ Serum levels of SDC1 have not been investigated in pancreatic cancer.
✓ We report for the first time that serum SDC1 levels are higher than healthy individuals compared with patients with PDAC.

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