

SLC25A10 marks a proliferative, MYC-associated state in stomach adenocarcinoma and declines with advancing stage

Xiao Ruifeng

Taihe Hospital

Xue Shanle

Affiliated Rehabilitation Hospital of Fujian University of Traditional Chinese Medicine

Zhao Juanhua

Taihe Hospital

Wu Xuan

wx821115@163.com

Affiliated Rehabilitation Hospital of Fujian University of Traditional Chinese Medicine

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Abstract

Background. *SLC25A10* (solute carrier family 25 member 10) transports metabolites across the inner mitochondrial membrane and has been implicated in ferroptosis resistance. Its diagnostic and prognostic value in stomach adenocarcinoma is unknown.

Methods. We analyzed whole-transcriptome profiles from 412 stomach adenocarcinoma tumors and 36 adjacent normal tissues (The Cancer Genome Atlas) and tested the stage association in 483 gastric adenocarcinomas on a different platform (GSE84437). Differential expression, diagnostic performance, survival, pathway activity and immune composition were assessed by standard methods, with enrichment complemented by CIBERSORT.

Results. *SLC25A10* was higher in tumors than adjacent tissue (area under the receiver operating characteristic curve 0.798, 95% confidence interval 0.740–0.856). Expression fell across stages in both cohorts (discovery: $P = 0.024$, trend $P = 0.003$; independent: median 9.48 at T1 to 8.77 at T4, $P = 0.002$; age- and sex-adjusted beta = -0.172 per stage, $P < 0.001$). Nodal stage was unrelated ($P = 0.60$), and expression was not an independent prognostic factor (multivariable hazard ratio 0.99, 95% CI 0.71–1.38; $P = 0.95$). Enrichment analysis implicated *E2F* targets, *MYC* targets V1, mTORC1 signaling, the mitotic spindle, DNA repair and glycolysis, with negative enrichment of inflammatory response, myogenesis and epithelial-mesenchymal transition. High expression was linked to reduced adaptive immunity and M0 macrophage expansion ($\rho = 0.355$, false discovery rate = 2.6×10^{-12}).

Conclusions. *SLC25A10* describes a proliferative, myeloid-biased tumor state that narrows as stage advances. The prognostic association was negative in 412 patients, and the two immune deconvolution methods agreed only in part. Prospective and experimental confirmation is required before clinical application.

INTRODUCTION

Stomach adenocarcinoma is the fifth most common malignancy worldwide and the fourth leading cause of cancer death [1, 2], and its burden continues to rise in China [3, 4] and worldwide [5–9]. Treatment is centered on surgery with chemotherapy or radiotherapy, and targeted and immune checkpoint therapies have added options for advanced disease [10–13]. Diagnosis nevertheless remains late in most patients. Early symptoms are non-specific, available tests have limited sensitivity, and no single molecular marker of adequate sensitivity and specificity exists for screening [14, 15]. The search for such a marker has been shaped by the metabolic programs that distinguish malignant from normal gastric epithelium [16–18].

SLC25A10 belongs to the mitochondrial carrier family and mediates metabolite transport across the inner mitochondrial membrane, thereby linking energy metabolism, redox balance and stress responses [19]. It exports succinate from the matrix to the cytoplasm and then to the extracellular space, where secreted succinate engages *SUCNR1* on tumor-associated macrophages and drives M2 polarization. The

protein also functions as a mitochondrial glutathione importer. Raising its activity raises mitochondrial glutathione, activates the glutathione-*GPX4* axis and suppresses mitochondria-dependent ferroptosis [20]. Knockdown in lung adenocarcinoma impaired mitochondrial function and promoted ferroptosis [21, 22], and the carrier regulates cancer cell growth by a separate route [25]. Work in other malignancies has linked *SLC25A10* to inhibition of ferroptosis and to cisplatin resistance [27]. Inhibin beta A has been shown to drive tumor progression through macrophage M2 polarization together with mitochondria-dependent ferroptosis suppression [26], a combination that parallels the metabolic and immune phenotypes examined here. *SLC25A10* has also been implicated in radioresistance [23] and ferroptosis resistance in hepatocellular carcinoma [24], and nuclear translocation of its isoform 3 has been linked to chemoresistance [33]. It is upregulated across solid tumors with an *in silico* association with reduced survival [18]. Because succinate export and glutathione import both influence immune cell phenotype, *SLC25A10* sits at the intersection of tumor metabolism and immune regulation, which is why we examined it in stomach adenocarcinoma.

Here we characterize *SLC25A10* expression in stomach adenocarcinoma by testing diagnostic performance, the association with stage and survival, pathway activity and immune composition. Profiling and survival analysis used TCGA-STAD data, pathway activity was assessed by gene set enrichment analysis (GSEA) and gene set variation analysis (GSVA) against the Hallmark collection, and immune infiltration was estimated by single-sample gene set enrichment analysis (ssGSEA) and cross-validated by CIBERSORT deconvolution. To test whether the stage association was specific to one cohort or platform, the analysis was repeated in GSE84437, an independent 483-case Korean cohort in the Gene Expression Omnibus (GEO) profiled on an Illumina exon array. We report the negative prognostic result explicitly, and we state the limits of the immune analysis rather than presenting two partially discordant deconvolution methods as a single consistent finding.

METHODS

Data acquisition and preprocessing

All data are publicly available. Whole-genome expression profiles in transcripts per million (TPM), clinical annotations and copy number variation data for stomach adenocarcinoma (TCGA-STAD) were downloaded from The Cancer Genome Atlas via the UCSC Xena platform (<https://tcga.xenahubs.net>); normal tissue expression came from the Genotype-Tissue Expression project; gene set definitions came from the Molecular Signatures Database (MSigDB, <https://www.gsea-msigdb.org/gsea/msigdb>). Tissue distribution of *SLC25A10* across 51 normal human tissues was taken from the Human Protein Atlas and GTEx consensus datasets (Fig. S1).

An independent cross-platform cohort tested whether the stage association reproduced outside TCGA. We analyzed GSE84437, a Korean cohort of 483 stomach adenocarcinomas on the Illumina HumanHT-12 V3.0 exon array (GPL6947). *SLC25A10* abundance was retrieved from probe ILMN_1804090 (RefSeq NM_012140.3; Entrez Gene 1468), the only *SLC25A10* exon probe on the array, and T and N stage, age,

sex, vital status and overall survival from the GEO sample annotations. Maximum follow-up in this cohort is 161 days (median 70 days), so survival analyses are reported as short-term survival and not as prognostic outcomes.

In TCGA-STAD, the analytic set for expression comparisons comprised 412 tumors and 36 adjacent normal tissues. Numbers available for each clinical variable differed: 412 for sex and race, 407 for age and 388 for stage. Empty-string stage entries were treated as missing, and stage was collapsed from AJCC subcategories to four levels before analysis. Models that required complete covariate data were fitted on smaller subsets: 383 patients for the logistic regression, and 370 for the multivariable Cox model.

Differential expression and diagnostic analysis

SLC25A10 expression was compared between 412 stomach adenocarcinoma tumors and 36 adjacent normal tissues by two-sided Wilcoxon rank-sum test, with Cliff's delta as the effect size. Cross-cohort comparisons partly separate technical differences and inflate apparent discrimination. No external normal stomach cohort was therefore added, and the area under the curve reported here is a conservative within-cohort estimate. The curve was computed with the pROC package (version 1.19.1) and the operating point taken at the Youden index.

Associations with clinical characteristics were assessed by Fisher's exact test for categorical variables, the Kruskal-Wallis test across ordered categories, and Spearman correlation for ordered stage. Variables that reached significance were additionally assessed under bootstrap resampling.

Enrichment analysis

Patients were stratified into high- and low-expression groups at the cohort median (206 per group). Genes were ranked by the difference in mean $\log_2(\text{TPM} + 1)$ expression between groups, and classic GSEA was performed against the Hallmark collection (50 gene sets, v2024.1.Hs) [32] with 1,000 gene-set permutations and random seed 20261007. Nominal P values were derived from the permutation null distribution and adjusted by the Benjamini-Hochberg method. As a complement, pathway activity was quantified per tumor by GSVA (R package version 2.6.6) [33] using the same collection and correlated with *SLC25A10* (Fig. S2). The two strategies separate transcriptional covariation from pathway-level co-enrichment, which reduces the risk of spurious associations.

Immune infiltration analysis

Immune infiltration was quantified in 412 tumors by ssGSEA using curated marker sets covering T, B, natural killer, myeloid and mast populations [28, 29]; after removing duplicated sets that differed only in the naming of identical genes, 38 unique populations were retained. These scores are computed from

whole-transcriptome data and share a substantial number of genes, so they are not independent of one another. Immune deconvolution was therefore performed with CIBERSORT (counting matrix torture by iterative regression of small subsets of traits; Newman et al., 2015 implementation as distributed in the IOBR R package) using the LM22 leukocyte signature matrix, which estimates absolute fractions of 22 subsets by support vector regression [30, 31]. The marker gene list is provided in Data S1. Correlations were computed on the 412 tumors with expression values available, and P values were corrected by the Benjamini-Hochberg procedure.

Gene-level copy number data for SLC25A10 were obtained from the National Cancer Institute Genomic Data Commons (GDC) using the TCGA-STAD Gene Level Copy Number dataset (files named TCGA-STAD.<uuid>.gene_level_copy_number.v36.tsv, retrieved on October 12, 2026). Two alternative GDC representations were explicitly excluded to avoid mixing algorithms: the ASCAT3 files (ascat3.gene_level_copy_number.v36.tsv) and the continuous absolute_log2 files. SLC25A10 (ENSG00000183048, chr17:81712236–81721016) copy number is reported by the GDC as total copy number, which was grouped as hemizygous loss [1], diploid [2] or gain (≥ 3). The GDC returned gene-level profiles for 53 patients, of which 48 also had a primary tumour sample in the expression matrix used for the main analysis, and these 48 were carried forward (Fig. S6).

Survival analysis

Overall survival, disease-specific survival and progression-free interval were compared between median-defined expression groups by Kaplan-Meier curves with the log-rank test. Independent prognostic value was assessed by univariable and multivariable Cox proportional hazards models following established TCGA survival workflows [30]; the proportional hazards assumption was assessed by the Schoenfeld residual test [34]. Survival in GSE84437 was analyzed as short-term survival as described above.

Statistical analysis

All analyses were performed in R (version 4.6.1) using the survival (version 3.8.6), data.table (version 1.18.6.1), GSVA (version 2.7.22) and pROC (version 1.19.1) packages. Hazard ratios (HR) and confidence intervals (CI) are reported throughout. Expression deviated from normality in both tumor and normal groups (Shapiro-Wilk test, both $P < 0.05$), so group differences were assessed by two-sided Wilcoxon rank-sum tests rather than Student's t test. Effect size was quantified with Cliff's delta. Multiple testing was controlled by the Benjamini-Hochberg false discovery rate, correlations by Spearman's rank correlation, survival differences by the log-rank test and independence by multivariable regression. All tests were two-sided with a threshold of $P < 0.05$.

RESULTS

SLC25A10 is elevated in stomach adenocarcinoma and separates tumor from normal tissue

SLC25A10 was higher in 412 stomach adenocarcinoma tumors than in 36 adjacent normal tissues (Wilcoxon rank-sum $P = 3.13 \times 10^{-9}$; Cliff's delta = 0.595; Fig. 1a). The within-cohort receiver operating characteristic curve gave an area under the curve of 0.798 (95% CI 0.740–0.856), which is good but not sufficient for discrimination (Fig. 1b). At the Youden-optimal cut-off of 3.175 $\log_2(\text{TPM} + 1)$, sensitivity was 0.643 and specificity 0.861. *SLC25A10* is not tissue-restricted, with the highest normal-tissue levels in liver (179.7 nTPM) and stomach (22.3 nTPM) ranking twenty-fifth of the thirty highest-expressing normal tissues (Fig. S1). Expression did not differ by age group ($n = 132$ aged 60 years or younger; $n = 275$ older than 60 years) or sex ($n = 145$ female; $n = 267$ male) (Fig. 1c, d; Table 1).

Table 1

Clinical characteristics of patients with stomach adenocarcinoma stratified by SLC25A10 expression

Characteristic	Category	Total	Low	High	P	Test
Age, years	Mean +/- SD	65.6 +/- 10.7	66.1 +/- 11.1	65.0 +/- 10.3	0.315	Student's t-test
Age group, n (%)	<= 60	132 (32.4)	64 (15.7)	68 (16.7)	0.672	Fisher's exact test
Age group, n (%)	> 60	275 (67.6)	141 (34.6)	134 (32.9)	-	Fisher's exact test
Sex, n (%)	Male	267 (64.8)	130 (31.6)	137 (33.3)	0.536	Fisher's exact test
Sex, n (%)	Female	145 (35.2)	76 (18.4)	69 (16.7)	-	Fisher's exact test
Race, n (%)	White	260 (63.1)	139 (33.7)	121 (29.4)	0.026	Fisher's exact test
Race, n (%)	Black or African American	12 (2.9)	2 (0.5)	10 (2.4)	-	Fisher's exact test
Race, n (%)	Other	140 (34.0)	65 (15.8)	75 (18.2)	-	Fisher's exact test
Stage, n (%)	Stage I	58 (14.9)	19 (4.9)	39 (10.1)	0.003	Kruskal-Wallis test
Stage, n (%)	Stage II	122 (31.4)	54 (13.9)	68 (17.5)	-	Kruskal-Wallis test
Stage, n (%)	Stage III	169 (43.6)	89 (22.9)	80 (20.6)	-	Kruskal-Wallis test
Stage, n (%)	Stage IV	39 (10.1)	23 (5.9)	16 (4.1)	-	Kruskal-Wallis test

Note Percentages are calculated within each variable's available cases, so denominators differ across rows: n = 412 for sex and race, n = 407 for age and n = 388 for stage. The multivariable logistic model used the 383 patients with complete age, sex, stage and race data. Column headings give the size of the two expression groups across the whole cohort (206 each); within an individual variable the two columns therefore need not each contain 206 patients, because patients with missing values for that variable are omitted. The low- and high-expression groups were defined by the median SLC25A10 value (cut-off = 3.4900 log₂(TPM + 1)). Race was grouped as White, Black or African American, and other. The P value shown for sex, race and stage is the overall P value across all categories of that variable. All P values are two-sided. CI, confidence interval; SD, standard deviation; STAD, stomach adenocarcinoma

Expression declines across disease stage in two independent cohorts

In TCGA-STAD, expression differed across stage (Kruskal-Wallis $P = 0.02$, $n = 388$), and the decline across stage levels was monotone (Jonckheere-type trend $P = 0.003$; odds ratio 0.686 per stage level; Table 2).

Table 2
Association between SLC25A10 expression and clinicopathological characteristics

Variable	Comparison	OR_CI	P
Age	per 1 year	0.985 (0.966–1.005)	0.136
Sex	Male vs Female	1.060 (0.689–1.631)	0.791
Stage	II vs I	0.629 (0.317–1.221)	0.176
Stage	III vs I	0.444 (0.229–0.836)	0.013
Stage	IV vs I	0.321 (0.130–0.766)	0.012
Race	Black vs White	5.679 (1.416–38.089)	0.029
Race	Other vs White	1.139 (0.731–1.778)	0.566
Note Odds ratios from multivariable logistic regression adjusted for age, sex, stage and race, referencing stage I. The association with self-reported race was confined to a subgroup of 12 patients and did not survive bootstrap resampling; it is reported as exploratory only. All P values are two-sided. OR, odds ratio; CI, confidence interval			

The same pattern appeared in GSE84437. Median log2 *SLC25A10* abundance across T1 to T4 was 9.48, 9.11, 8.76 and 8.77 (Kruskal-Wallis $P = 0.002$; Spearman rho = -0.138, $P = 0.004$). The inverse relationship was stronger when early and advanced disease were compared directly (I-II $n = 46$ versus III-IV $n = 387$, $P < 0.001$) (Fig. S5a, b). After adjustment for age and sex, the per-stage effect was beta = -0.1723 (95% CI -0.3026 to -0.0420; $P < 0.001$), close to the TCGA estimate (beta = -0.1153, 95% CI -0.2106 to -0.0201; $P = 0.02$) (Fig. S5c). Nodal stage was unrelated ($P = 0.60$), consistent with TCGA.

SLC25A10 is not an independent prognostic factor

Kaplan-Meier curves for overall survival, disease-specific survival and progression-free interval did not differ significantly between groups (Fig. 2). The corresponding HRs were 0.84 ($P = 0.28$), 0.91 ($P = 0.66$) and 0.92 ($P = 0.62$). Median survival was in fact numerically longer in the high-expression group for overall survival (1,095 vs 794 days) and progression-free interval (1,376 vs 1,287 days). No subgroup by age, race or sex reached significance (Fig. 3); the Black or African American subgroup was not analyzed (12 patients, 7 deaths). The proportional hazards assumption held for all covariates (Schoenfeld global $P = 0.92$), and excluding the most influential case did not alter the *SLC25A10* estimate (HR 0.998).

In univariable Cox models, stage III versus I (HR 2.44, 95% CI 1.33–4.50; $P = 0.004$), stage IV versus I (HR 3.95, 95% CI 1.96–7.94; $P < 0.001$) and age (HR 1.02 per year, 95% CI 1.01–1.04; $P = 0.008$) were associated with overall survival, whereas *SLC25A10* expression (high vs low HR 0.84, 95% CI 0.61–1.15; $P = 0.28$), sex ($P = 0.23$) and stage II ($P = 0.24$) were not. The multivariable model confirmed this pattern:

stage remained highly significant ($P = 2.90 \times 10^{-6}$) and age remained significant (HR 1.03 per year; $P = 0.001$), but *SLC25A10* was not an independent predictor (HR 0.99, 95% CI 0.71–1.38; $P = 0.95$) (Table 3).

Table 3
Univariable and multivariable Cox proportional hazards models for overall survival

Characteristic	Comparison	Uni_HR	Uni_P	Mul_HR	Mul_P
SLC25A10 expression	SLC25A10 expression (High vs Low)	0.84 (0.61–1.15)	0.2834	0.99 (0.71–1.38)	0.9520
Age	Age (per 1 year)	1.02 (1.01–1.04)	0.0083	1.03 (1.01–1.05)	0.0005
Sex	Sex (Male vs female)	1.23 (0.88–1.73)	0.2310	1.13 (0.80–1.61)	0.4873
Stage	Stage (II vs I)	1.49 (0.77–2.87)	0.2375	1.63 (0.84–3.15)	0.1476
Stage	Stage (III vs I)	2.44 (1.33–4.50)	0.0041	2.67 (1.44–4.96)	0.0018
Stage	Stage (IV vs I)	3.95 (1.96–7.94)	0.0001	5.44 (2.65–11.16)	< 0.001
Note The multivariable model used the 370 patients with complete age, sex, stage and survival data; univariable models used all available patients for each variable (388 for <i>SLC25A10</i> expression). The two columns differ because they were fitted on different subsets, not because any covariate was excluded on the basis of its univariable P value. Age was analyzed as a continuous variable. Stage entered the models as three indicator variables referencing stage I; the joint Wald test for stage gave $P = 2.90 \times 10^{-6}$ in the multivariable model. The proportional hazards assumption was satisfied for all covariates (Schoenfeld global $P = 0.92$). HR, hazard ratio; CI, confidence interval. All P values are two-sided					

High expression marks a proliferative, relatively epithelioid program

Twenty-six of 50 Hallmark gene sets were enriched between the *SLC25A10*-high and -low groups ($FDR < 0.05$; Fig. 4). The nine most significant were *E2F* targets (NES = 6.16), *MYC* targets V1 (NES = 5.38), mTORC1 signaling (NES = 4.27), mitotic spindle (NES = 3.57), DNA repair (NES = 3.21), glycolysis (NES = 3.03), inflammatory response (NES = -3.36), myogenesis (NES = -2.81) and epithelial mesenchymal transition (NES = -2.73). Positive scores indicate activation in *SLC25A10*-high tumors and negative scores suppression. GSVA in individual tumors reproduced the same pattern, the strongest correlations being *E2F* targets ($\rho = 0.353$, $P = 2.18 \times 10^{-13}$), G2M checkpoint ($\rho = 0.351$), spermatogenesis ($\rho = 0.345$) and *MYC* targets V1 ($\rho = 0.323$, $P = 2.53 \times 10^{-11}$) (Fig. S2).

Immune composition is myeloid-biased at high *SLC25A10*

By ssGSEA, 36 of 38 populations correlated negatively with *SLC25A10* at FDR < 0.05. The exceptions were Th17 cells ($\rho = 0.024$, FDR = 0.64) and neutrophils. The strongest inverse associations were CD4 effector naive cells ($\rho = -0.494$, FDR = 3.7×10^{-25}), mast cells ($\rho = -0.474$), basophils ($\rho = -0.471$), central-memory CD4 T cells ($\rho = -0.467$), central-memory CD8 T cells ($\rho = -0.458$) and naive CD8 T cells ($\rho = -0.458$) (Fig. 5, left panel).

Marker sets in this analysis are collinear, so the analysis was repeated by CIBERSORT deconvolution. The result was less uniform: 10 of 22 subsets reached FDR < 0.05. The largest increase was in M0 macrophages ($\rho = 0.355$, FDR = 2.6×10^{-12} ; Fig. 5, right panel; Fig. S3). The largest decreases were resting mast cells ($\rho = -0.291$, FDR = 2.0×10^{-8}), eosinophils ($\rho = -0.206$), M2 macrophages ($\rho = -0.171$), naive B cells ($\rho = -0.170$) and monocytes ($\rho = -0.167$; Fig. S4).

SLC25A10 copy number gain is frequent but poorly coupled to expression

Gene-level copy number could be retrieved for 48 of the 412 tumours in the expression matrix. *SLC25A10* was diploid in 31 cases (64.6%), amplified in 16 (33.3%) and hemizygotously deleted in 1 (2.1%); the amplified fraction exceeded the 50% expected under a neutral model (exact binomial $P = 0.0293$). Copy number was, however, only weakly related to expression: the Spearman correlation between copy number and $\log_2(\text{TPM} + 1)$ was $\rho = 0.1313$ ($P = 0.374$) and the Pearson correlation $r = 0.1017$ ($P = 0.491$), and expression did not differ significantly across copy number categories (Kruskal-Wallis $P = 0.0956$). Amplified tumours showed a numerically higher median expression than diploid tumours (3.612 versus $3.067 \log_2(\text{TPM} + 1)$) but the difference did not reach significance (Wilcoxon $P = 0.109$, Cliff's $\delta = 0.29$), so the copy number difference accounts for little of the expression variation (Fig. S6a-c).

The copy number state was not significantly associated with the expression groups (Fisher exact $P = 0.0687$) and did not differ between early and advanced disease (I-II $n = 26$ versus III-IV $n = 20$, Kruskal-Wallis $P = 0.102$), which argues against amplification driving the decline in *SLC25A10* that accompanies advancing stage. Amplified tumours did, however, have shorter overall survival than diploid tumours (log-rank $P = 0.0228$). In a Cox model treating copy number as a continuous variable, each additional copy was associated with a hazard ratio of 2.284 (95% CI 1.368–3.816, $P = 0.0016$), and the association persisted after adjustment for stage (HR 2.548, 95% CI 1.362–4.765, $P = 0.00342$; Schoenfeld global $P = 0.186$, so the proportional hazards assumption holds). These survival estimates rest on 45 cases and 17 events and are therefore exploratory (Fig. S6d).

DISCUSSION

SLC25A10 separated stomach adenocarcinoma from adjacent normal tissue with an area under the curve of 0.798 (95% CI 0.740–0.856) and a specificity of 0.861 at the Youden cut-off. This is short of what would be needed to displace established markers such as CEA and CA19-9, for two reasons. The analysis was confined to a single cohort, so the estimate is conservative and would need validation in

independently processed specimens before it could serve as a performance benchmark. *SLC25A10* is also broadly expressed, and its highest normal-tissue levels are in liver, so any circulating assay would need a threshold that separates tumor from metabolically active background tissue. Its value may lie as a component of combined diagnostic models rather than as a stand-alone test [33].

The clearest finding here is the inverse, graded relationship between *SLC25A10* expression and stage. The pattern was monotone rather than a single significant contrast, it held under bootstrap resampling, and it was replicated in a 483-case cohort on a different platform with a similar adjusted per-stage effect. That the association was independent of age and sex also matters, since it implies *SLC25A10* levels are unlikely to be confounded by the demographic composition of a cohort. *SLC25A10* therefore appears to be highest in well-differentiated, early-stage tumors and to fall as disease progresses, the opposite of the pattern usually reported for markers of the proliferative compartment. The association with self-reported race was confined to a 12-patient subgroup and did not survive resampling; because race categories in TCGA reflect social as well as biological determinants, we do not treat it as biological.

This inverse stage association sits alongside the proliferative pathway signature we observed, and the two are not easily reconciled. One explanation is that *SLC25A10* labels a proliferative state characteristic of well-differentiated tumors: as disease progresses, tumors lose this state and acquire inflammatory and stromal programs, which is why negative enrichment of inflammatory response and epithelial mesenchymal transition accompanies the decline in *SLC25A10*. The data at hand cannot separate this from the simpler possibility that *SLC25A10* is correlated with histologic differentiation, since no grading data were available in the cohort. An independent differentiation score or direct staining would be needed.

SLC25A10 was not an independent prognostic factor for overall survival in the discovery cohort, and no survival endpoint or subgroup reached significance. In the same cohort, stage and age accounted for far more of the survival variation, so *SLC25A10* adds little prognostic information to established clinical variables. We report the negative result explicitly because single-gene prognostic claims are common in this literature and rarely survive multivariable adjustment. It also changes how the gene should be read: the data support *SLC25A10* as a descriptor of tumor state rather than as a prognostic marker.

Functional context comes from mechanism studies in other tumor types. *SLC25A10* exports succinate, engaging *SUCNR1* on tumor-associated macrophages and driving M2 polarization; it also imports mitochondrial glutathione, so that increasing its activity raises mitochondrial glutathione, activates the glutathione-GPX4 axis and suppresses mitochondria-dependent ferroptosis [20]. Knockdown in lung adenocarcinoma impaired mitochondrial function and promoted ferroptosis [21, 22], and the carrier has been associated in silico with reduced survival in lung and breast cancer [18]. It also maintains mitochondrial glutathione import and redox capacity [35], and transports malate [34], which connects glycolysis to fatty acid synthesis. *SLC25A10* must also be distinguished from *SLC25A42*, a family member that promotes gastric cancer growth by enhancing *CPT2*-dependent fatty acid oxidation to

confer ferroptosis resistance [36]; the two transport different substrates and serve different redox roles, so evidence for one cannot be transferred to the other.

The immune analysis needs more caution, and its limits are better stated than smoothed over. Both methods scored broad reductions in adaptive immune populations, but they agreed in direction and significance for only two populations, naive B cells and resting dendritic cells, and in direction alone for one further population. The strongest ssGSEA signals, involving CD4 effector naive, central-memory CD4 and naive CD8 T cells, did not reach significance by deconvolution, and the follicular helper T cell increase detected by CIBERSORT ran opposite to the negative ssGSEA score for the same population. The 38 ssGSEA populations did not include a memory B cell category, so no statement about that subset can be made. Both approaches do point to a compositional reweighting rather than a uniform loss of immunity, with M0 macrophage expansion the single strongest immune association, accompanied by increases in activated mast cells and follicular helper T cells and reductions in resting mast cells, eosinophils and monocytes. *SLC25A10*-high stomach adenocarcinoma is therefore better described as shifted towards a less differentiated, myeloid-dominant state than as globally immune-excluded.

Several limitations constrain the conclusions. All analyses relied on public databases, and TCGA-STAD clinical annotation is incomplete for several variables, which restricts the sample available for multivariable adjustment. The design is correlational throughout. The stage association was replicated and the immune analyses cross-validated between two independent algorithms, but no perturbation experiment was performed, so the mechanisms proposed above remain hypotheses. Direct testing would require single-cell and spatial profiling, measurement of succinate and glutathione in situ, and co-targeting experiments combining *SLC25A10* inhibition with *SUCNR1* antagonism or *GPX4*-directed ferroptosis strategies. Clinical assays would also need validation in multicenter cohorts where tumor and control specimens are processed identically.

LIMITATIONS

The following limitations constrain the conclusions of this study:

1. The study is entirely computational. No perturbation experiment was performed, so the mechanistic links described above (succinate export, glutathione import, ferroptosis resistance) remain hypotheses rather than demonstrated effects in this disease.
2. The discovery cohort is of moderate size (412 tumors) and several clinical variables are incompletely annotated, which restricts the sample available for multivariable adjustment to 370 patients with complete data.
3. Prognostic analyses were negative. We report this explicitly, but it means the study cannot claim any prognostic utility for *SLC25A10* in stomach adenocarcinoma.

4. 4. The two immune deconvolution methods agreed in direction and significance for only two of 38 populations, and the marker sets used by ssGSEA are not independent of one another; the immune findings should therefore be read as hypothesis-generating.
5. 5. Histologic differentiation grade was unavailable in the cohort, so we cannot distinguish *SLC25A10* as a marker of a proliferative state from *SLC25A10* as a correlate of differentiation alone.
6. 6. The diagnostic estimates are within-cohort and therefore optimistic by construction; no external normal stomach cohort was available, and the independent cohort was used only to test the stage association.
7. 7. Short-term survival in GSE84437 (maximum follow-up 161 days) cannot be interpreted conventionally and was not used as prognostic evidence.

The copy number analysis addresses a specific weakness of the expression-based comparisons. Because *SLC25A10* sits on chromosome 17q22 and is amplified in about a third of the tumours examined here, the possibility that the observed differences in expression simply reflect copy number rather than transcriptional regulation had to be excluded. It is largely excluded: copy number correlates only weakly with expression ($\rho = 0.1313$), expression does not differ significantly between amplified and diploid tumours, and the expression decline across stage persists independently of copy number status. The clinical association of amplification with shorter survival is consistent with the amplification being functionally relevant even when it accounts for only a modest share of expression variance, but it is derived from a small number of cases and events and is offered as a hypothesis for future study rather than as a prognostic claim.

CONCLUSIONS

In 412 stomach adenocarcinoma tumors and an independent 483-case cohort, *SLC25A10* was elevated relative to adjacent normal tissue and declined monotonically with stage. After adjustment for age and sex, the effect per stage level was of similar magnitude in the two cohorts. Pathway analysis assigned the corresponding state to a proliferative, *MYC*-associated program with suppressed inflammatory response. Immune deconvolution identified a shift towards myeloid dominance led by M0 macrophage expansion rather than a uniform loss of adaptive immunity. *SLC25A10* was not an independent prognostic factor once stage and age were accounted for. The gene is best regarded as a descriptor of tumor state that declines with progression; any diagnostic or therapeutic application would require prospective validation and experimental confirmation.

Declarations

Conflicts of interest

All authors have completed the ICMJE uniform disclosure form. The authors have no conflicts of interest to declare.

consent to publish

Not applicable.

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None.

Author Contribution

XR conceived and designed the study, performed all bioinformatics analyses, and drafted the manuscript. XS and ZJ participated in data collection and verification of the clinical annotations. XW supervised the study, resolved methodological questions, and revised the manuscript critically. All authors read and approved the final manuscript.

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Disclosure of generative artificial intelligence. A large language model-based writing assistant was used in the preparation of this manuscript, specifically for language editing, conversion of non-American to American English, and formatting assistance. The tool was not used for study design, data generation, data analysis, statistical testing, or the interpretation of results. All analyses, statistical tests, figures and conclusions are the work of the authors, who have checked the terms of use of the tool, verified the accuracy of all content against the underlying data, and take full responsibility for the integrity of the work, including the accuracy of its references.

CONTRIBUTIONS

(I) Conception and design: Xiao Ruifeng; Wu Xuan.

(II) Administrative support: Wu Xuan.

(III) Provision of study materials or patients: Not applicable; all data analysed in this study are publicly available.

(IV) Collection and assembly of data: Xiao Ruifeng; Xue Shanle; Zhao Juanhua.

(V) Data analysis and interpretation: Xiao Ruifeng; Zhao Juanhua; Wu Xuan.

(VI) Manuscript writing: All authors.

(VII) Final approval of manuscript: All authors.

FOOTNOTE

Reporting checklist

The authors have completed the STARD reporting checklist. All data analyzed in this study are openly available.

Data availability statement

All data analysed in the present study are publicly available. Transcriptome and clinical data for stomach adenocarcinoma, together with gene-level copy number data, were obtained from The Cancer Genome Atlas via the UCSC Xena platform (<https://tcga.xenahubs.net>); copy number was additionally retrieved for SLC25A10 from the National Cancer Institute Genomic Data Commons as the TCGA-STAD Gene Level Copy Number dataset (<https://portal.gdc.cancer.gov/projects/TCGA-STAD>, files named TCGA-STAD.<uuid>.gene_level_copy_number.v36.tsv, retrieved October 12, 2026). Normal tissue expression came from the Genotype-Tissue Expression project; Hallmark gene sets from MSigDB (<https://www.gsea-msigdb.org/gsea/msigdb>); and the independent validation cohort from the Gene Expression Omnibus under accession GSE84437 (<https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE84437>). The LM22 leukocyte signature matrix used for CIBERSORT deconvolution is distributed with the CIBERSORT source code at <https://github.com/IOBR/IOBR>. No new data were generated. A source data workbook containing the tables underlying every number reported here is provided as Data S2, including the copy number tables, and the complete analysis code is provided as Data S3.

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37. Supplemental. figure legends.

Figures

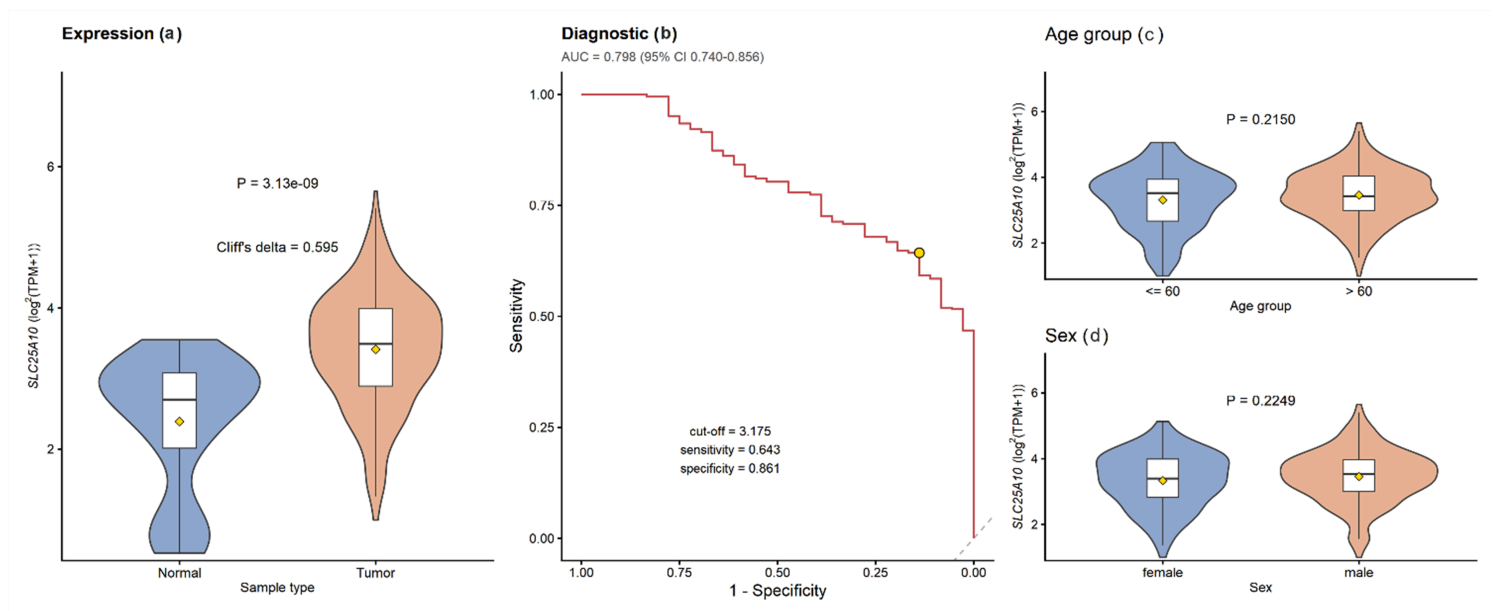


Figure 1

Expression of SLC25A10 in stomach adenocarcinoma (STAD) and its relationship to clinical characteristics (a) Distribution of SLC25A10 expression in 412 STAD tumors and 36 adjacent normal tissues; P value from a two-sided Wilcoxon rank-sum test (b) Within-cohort receiver operating characteristic (ROC) curve for distinguishing tumors from adjacent normal tissues; area under the curve 0.798 (95% confidence interval 0.740-0.856), gold point marks the Youden-index cut-off (3.175), sensitivity 0.643, specificity 0.861 (c) Expression by age group (n=132 aged 60 years or younger; n=275 older) (d) Expression by sex (n=145 female; n=267 male). Violins show the distribution, boxes the interquartile range and median, diamonds the mean. Case counts by Fisher's exact test were likewise not significant (P=0.67 and P=0.54), so panels c and d agree in direction with Table 1

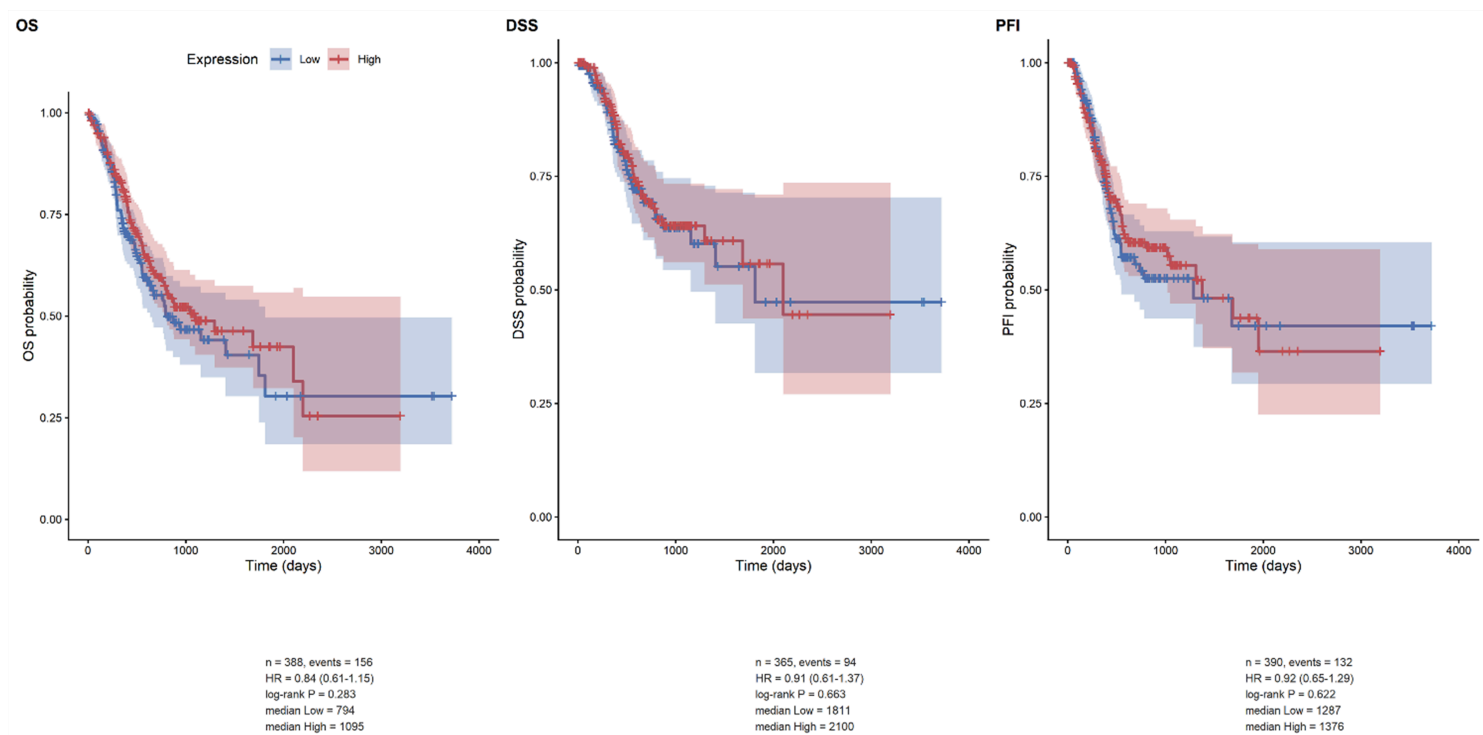


Figure 2

Kaplan-Meier survival curves for overall survival (OS), disease-specific survival (DSS) and progression-free interval (PFI) in TCGA-STAD patients stratified by median SLC25A10 expression. Patients were split at the cohort median (3.4900 log₂(TPM+1)); shading indicates 95% confidence intervals. Panels show, left to right, OS, DSS and PFI. Hazard ratios (High vs Low) with 95% confidence intervals, two-sided log-rank P values, numbers at risk and median survival are printed below each panel; none reached significance (OS HR=0.84, P=0.28; DSS HR=0.91, P=0.66; PFI HR=0.92, P=0.62)

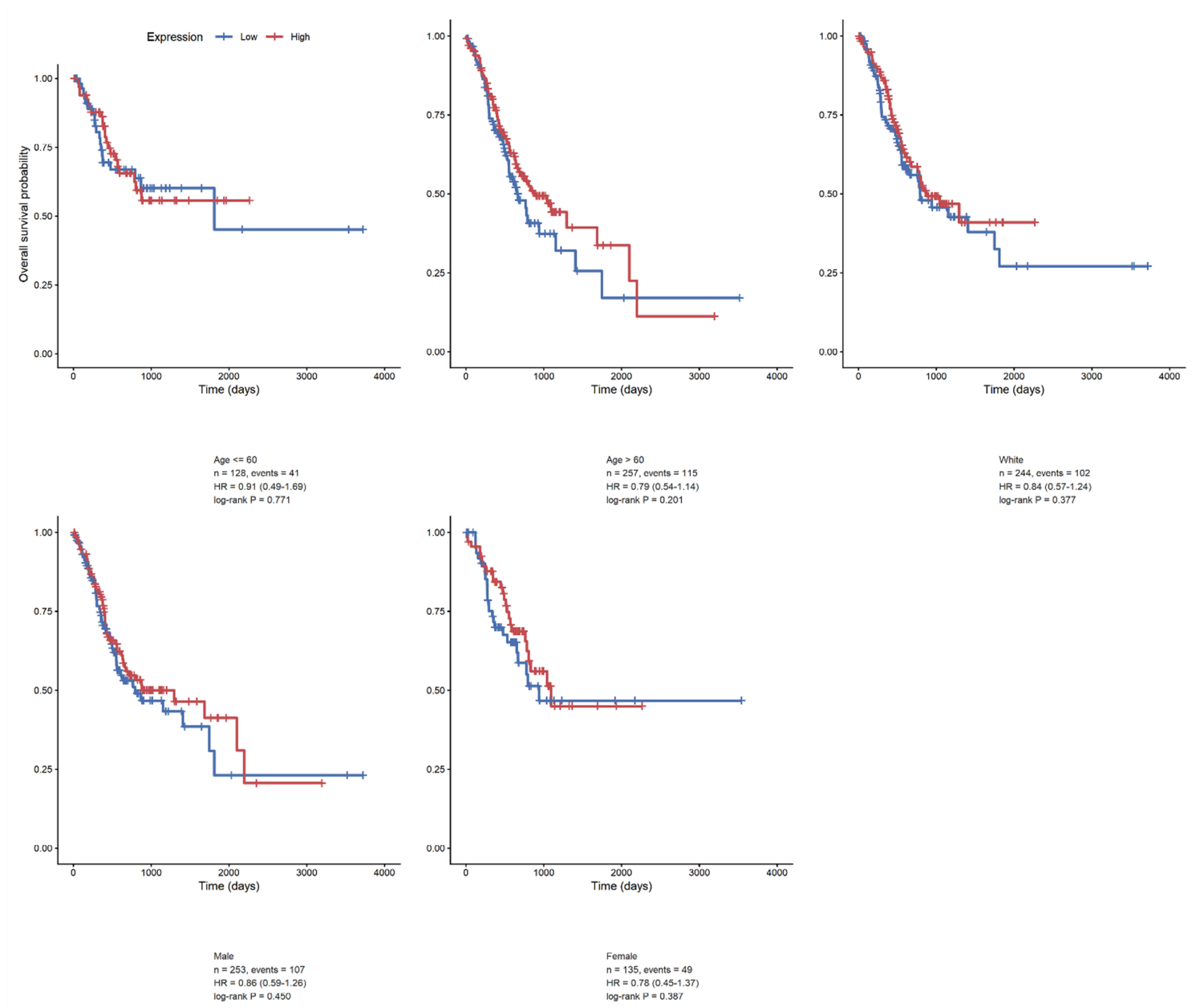


Figure 3

Subgroup Kaplan-Meier analyses of overall survival. Subgroups were defined by age, race and sex; the five panels show age 60 years or younger, age older than 60 years, White patients, male patients and female patients. Patients within each subgroup were split at the cohort median. The subgroup name and full statistics are printed below each panel; n is the number of patients with available follow-up data, smaller than the group size in Table 1. No subgroup reached significance. The Black or African American subgroup was not analyzed (12 patients, 7 deaths). HR, hazard ratio; CI, confidence interval

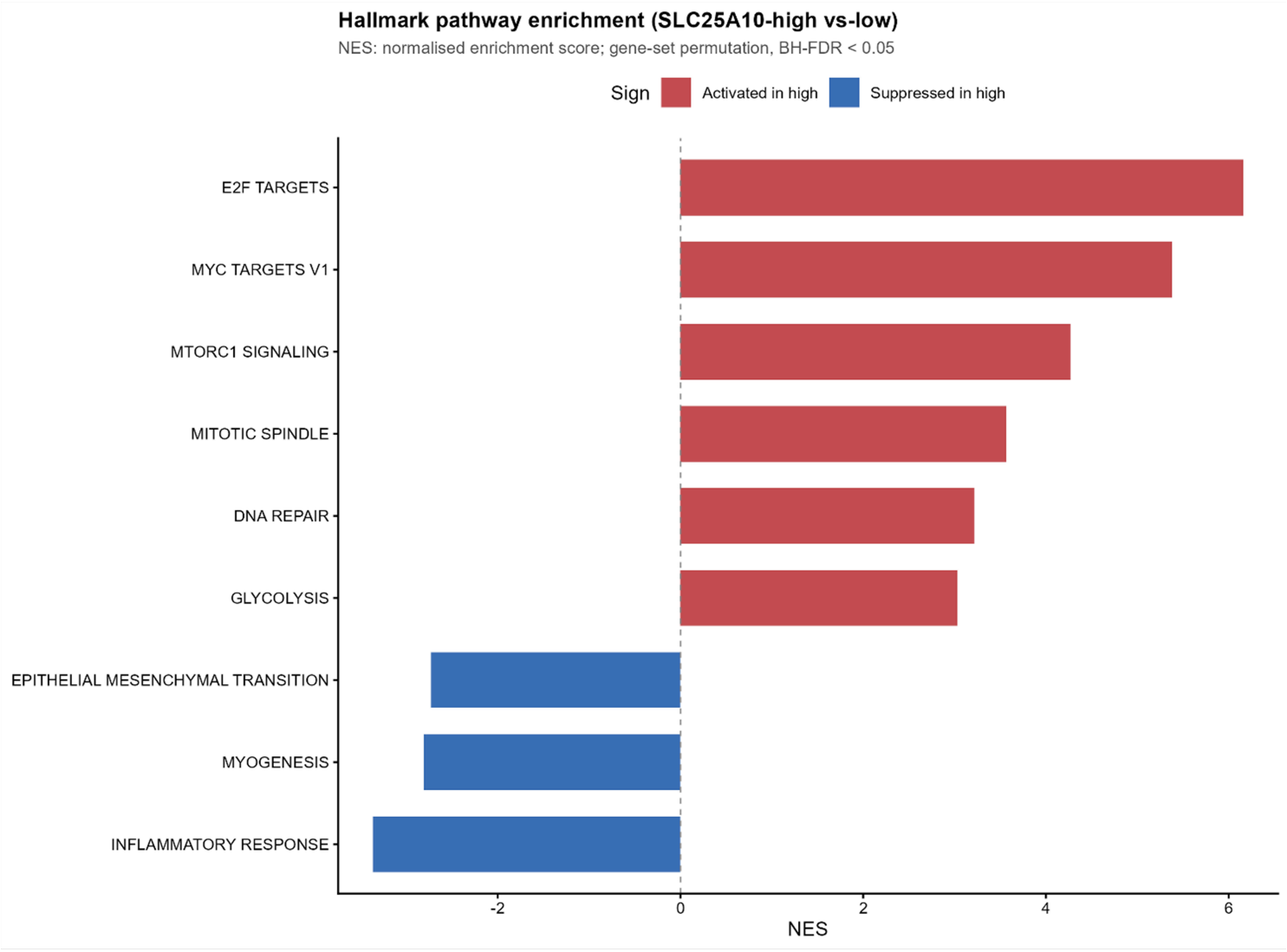


Figure 4

Gene set enrichment analysis of MSigDB Hallmark pathways associated with SLC25A10 expression in STAD. Patients were stratified into SLC25A10-high and SLC25A10-low groups (n=206 each) at the median; genes were ranked by the difference in mean expression between groups and enrichment scores computed against the 50 Hallmark gene sets with gene-set permutation. Twenty-six pathways reached FDR<0.05; the figure shows a single horizontal bar chart of the nine most significant, with the six most strongly activated in SLC25A10-high tumors in red (E2F targets, MYC targets V1, mTORC1 signaling, mitotic spindle, DNA repair, glycolysis) and the three most strongly suppressed in blue (epithelial mesenchymal transition, myogenesis, inflammatory response). Bars extend rightward for positive and leftward for negative normalized enrichment scores (NES); the dashed vertical line marks NES=0. FDR, false discovery rate

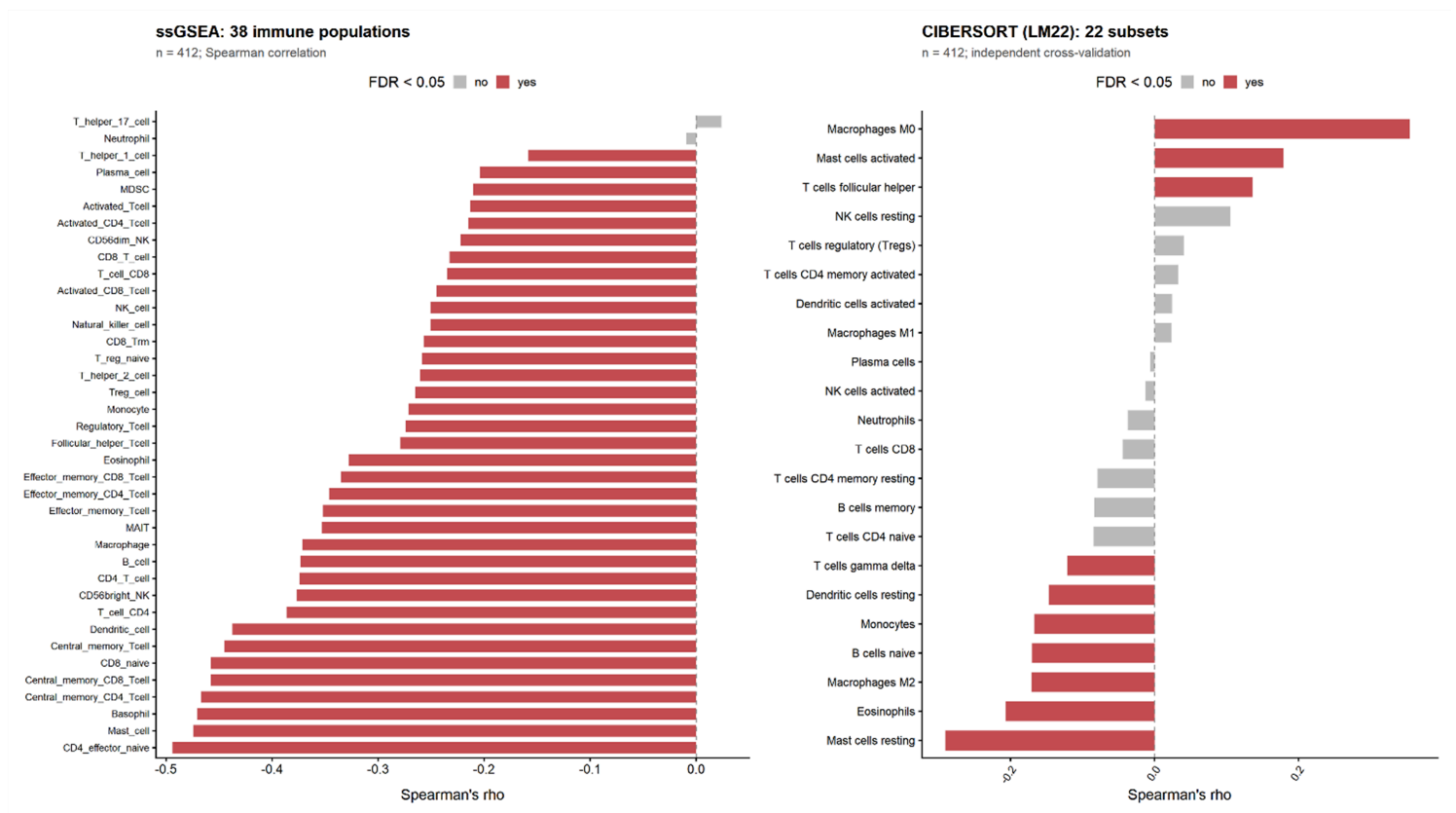


Figure 5

Association between SLC25A10 expression and the immune microenvironment in TCGA-STAD. The figure comprises two panels. Left: single-sample gene set enrichment analysis (ssGSEA) of 38 immune populations in 412 tumors, ranked by Spearman correlation with SLC25A10 expression; red bars denote FDR<0.05 after Benjamini-Hochberg correction. Thirty-six of 38 populations were significantly negative, strongest for CD4 effector naive cells ($\rho=-0.494$, FDR= 3.7×10^{-25}), mast cells ($\rho=-0.474$) and basophils ($\rho=-0.471$); Th17 cells ($\rho=0.024$) and neutrophils did not reach significance. Right: independent cross-validation by CIBERSORT deconvolution with the LM22 signature matrix (22 subsets), again ranked by Spearman rho with red bars denoting FDR<0.05. Ten subsets were significant, the dominant association being increased M0 macrophages ($\rho=0.355$, FDR= 2.6×10^{-12}), with decreases in resting mast cells ($\rho=-0.291$), macrophages M2 ($\rho=-0.171$), naive B cells ($\rho=-0.170$) and eosinophils ($\rho=-0.206$). The two panels share a substantial number of genes, so their agreement is partial; only naive B cells and resting dendritic cells agree in direction and significance. FDR, false discovery rate

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