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CDKN2A mRNA Over-expression Is Associated With CD8+ T Cell Exclusion and IDO1-Mediated Adaptive Immune Resistance in Gastric Adenocarcinoma

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Abstract

Background/Aim: Cellular senescence, mediated by CDKN2A-encoded $p16^{INK4a}$, generates a senescence-associated secretory phenotype (SASP) that may promote immune evasion in solid tumors. Recent immunohistochemical studies have identified associations between $p16^{INK4a}$ over-expression and CD8+ T cell exclusion in gastric adenocarcinoma, but transcriptomic validation and mechanistic characterization remain limited.

Materials and Methods: We analyzed 386 gastric adenocarcinoma samples from The Cancer Genome Atlas (TCGA-STAD) cohort, stratifying patients by CDKN2A mRNA expression using z-score thresholds: Loss ($z < -1.0$; n=57), Wild-Type ($-1.0 \leq z \leq +1.0$; n=253), and Over-expression ($z > +1.0$; n=76). Immune cell infiltration was estimated with quanTIseq deconvolution. SASP factor expression (IDO1, TGFB1, NT5E) and correlations with immune populations were assessed using Kruskal-Wallis tests, pairwise Wilcoxon rank-sum tests, and Spearman correlation analyses.

Results: CDKN2A over-expression was significantly associated with CD8+ T cell depletion (p=0.024) and IDO1 up-regulation (p=0.015) compared to wild-type tumors, validating prior immunohistochemical findings. However, TGFB1 (p=0.56) and NT5E (p=0.75) showed no significant differential expression. Paradoxically, IDO1 correlated positively with CD8+ T cell infiltration, as did TGFB1, suggesting reactive up-regulation rather than primary exclusion. Overall survival did not differ significantly across expression groups (p=0.3), nor did stratification by chromosomal instability (CIN p=0.76) or microsatellite instability (MSI p=0.73) molecular subtypes reveal prognostic associations.

Conclusion: This transcriptomic analysis confirms the association between CDKN2A over-expression and an immunosuppressive microenvironment characterized by CD8+ T cell depletion and IDO1 up-regulation. The strong positive correlation between IDO1 and CD8+ T cells supports an adaptive immune resistance model, wherein IDO1 is induced *via* interferon-gamma signaling as a reactive checkpoint rather than functioning as a primary T cell exclusion factor. These findings suggest that CDKN2A-over-expressing gastric adenocarcinomas may benefit from combination immunotherapy strategies incorporating IDO1 inhibition.

Keywords: Gastric adenocarcinoma, CDKN2A, IDO1, tumor microenvironment, immune evasion.

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Introduction

Gastric adenocarcinoma remains a leading cause of cancer-related mortality worldwide (1). The tumor microenvironment (TME) plays a critical role in tumor progression and response to immunotherapy (2). Recently, cellular senescence has emerged as a key modulator of the TME (3). The cyclin-dependent kinase inhibitor $p16^{INK4a}$, encoded by the *CDKN2A* gene, is a primary driver and marker of senescence (4).

In various malignancies, *CDKN2A* over-expression has been paradoxically linked to tumor progression, theoretically driven by the senescence-associated secretory phenotype (SASP). The SASP comprises a complex array of cytokines, chemokines, and immunomodulatory factors that can establish an immunoevasive contexture. Previous hypotheses suggest that senescent tumor cells utilize SASP factors – specifically transforming growth factor beta (TGF-beta), CD73 (*NT5E*), and indoleamine 2,3-dioxygenase 1 (IDO1) – to suppress or exclude cytotoxic immune infiltrates.

Recent literature highlights the complex role of cellular senescence in the gastric tumor microenvironment, particularly concerning the aberrant expression of the $p16^{INK4a}$ protein. Wang *et al.* recently identified a distinct triple-classification staining pattern for $p16^{INK4a}$ in gastric cancer, stratifying tumors into Loss, Wild-Type, and Over-Expression subgroups (5). Crucially, while $p16^{INK4a}$ loss and wild-type tumors exhibit comparable clinical trajectories, $p16^{INK4a}$ over-expression serves as a significant prognostic biomarker for aggressive disease. Clinically, this over-expression correlates with advanced pathologic T stage (pT stage), diminished overall survival, and marked resistance to both adjuvant chemotherapy and immune checkpoint inhibitors. This aggressive phenotype is biologically underpinned by an immunoevasive contexture, characterized by the exclusion of antitumor infiltrates like CD8+ T cells and elevated levels of immunosuppressive factors such as TGF-beta, CD73, and IDO (5, 6).

This study aimed to validate these mechanistic claims using transcriptomic data from The Cancer Genome Atlas Stomach Adenocarcinoma (TCGA-STAD) cohort, with computational deconvolution to assess whether *CDKN2A* over-expression correlates with CD8+ T cell exclusion and specific SASP factor up-regulation in a large patient population.

Materials and Methods

Data acquisition and processing. Bulk RNA-sequencing data (HTSeq-Counts) and matching clinical annotations for patients with gastric adenocarcinoma were obtained from the TCGA-STAD dataset *via* the Genomic Data Commons (GDC) portal. Gene expression values were normalized using the Trimmed Mean of M-values (TMM) method and log2-transformed. Duplicate gene entries were collapsed by calculating the mathematical mean using the limma framework (version 3.58.1).

Patient stratification. Patients were stratified into cohorts based on *CDKN2A* mRNA Z-scores calculated relative to the entire cohort (n=386): Loss (n=57): Z-score <−1.0; Wild-Type (WT, n=253): Z-score between −1.0 and +1.0; Over-expression (OE, n=76): Z-score >+1.0.

Computational deconvolution. Estimation of absolute immune cell infiltration fractions was performed using the immunedeconv R package (version 2.1.0) (7). The quanTIseq algorithm (8) was selected for its validated ability to provide absolute cell fractions, allowing for direct comparison of CD8+ T cells, M1 Macrophages, and Neutrophils across different patient samples.

Statistical analysis. All analyses were conducted in R (version 4.3.2). Differences in immune cell fractions and SASP gene expression (*TGFB1*, *NT5E*, *IDO1*) across cohorts were assessed using the Kruskal-Wallis test. Pairwise comparisons between the OE and WT groups were performed using the Wilcoxon rank-sum test. The relationship between SASP expression and CD8+ T cell infiltration was analyzed using Spearman rank correlation. Survival distributions were estimated using

Table I. *Clinical and pathologic characteristics of the TCGA-STAD cohort stratified by CDKN2A mRNA expression status.*

Characteristic	Overall (N=386)	Wild-type (WT) (n=253)	Loss (n=57)	Over-expression (OE) (n=76)
Age at diagnosis	65.1 (10.5)	65.6 (10.3)	61.9 (12.1)	66.0 (9.9)
Sex				
Female	137 (35%)	91 (36%)	17 (30%)	29 (38%)
Male	249 (65%)	162 (64%)	40 (70%)	47 (62%)
Pathologic stage (TNM)				
Stage I / IA / IB	52 (13%)	31 (12%)	12 (21%)	9 (12%)
Stage II / IIA / IIB	120 (31%)	80 (32%)	15 (26%)	25 (33%)
Stage III / IIIA / IIIB / IIIC	163 (42%)	104 (41%)	22 (39%)	37 (49%)
Stage IV	37 (10%)	26 (11%)	7 (13%)	4 (5%)
Unknown	14	12	1	1
ICD-O-3 Morphology				
8140/3 (Adenocarcinoma)	131 (34%)	89 (35%)	16 (28%)	26 (34%)
8144/3 (Intestinal type)	80 (21%)	50 (20%)	11 (19%)	19 (25%)
8145/3 (Diffuse type)	63 (16%)	49 (19%)	8 (14%)	6 (8%)
Other histologies	112 (29%)	65 (26%)	22 (39%)	25 (33%)

A total of 386 patient samples from The Cancer Genome Atlas Stomach Adenocarcinoma (TCGA-STAD) dataset were identified with complete transcriptomic and clinical annotations. Patients were classified into three cohorts based on normalized *CDKN2A* mRNA expression levels: Wild-type (WT, n=253), Loss (n=57), and Over-expression (OE, n=76). Statistical significance across cohorts was determined using Kruskal-Wallis rank sum tests for continuous variables and Pearson's Chi-squared tests for categorical variables. The cohorts were well-balanced regarding mean age at diagnosis (65.1 years) and sex distribution (65% male), consistent with demographic patterns reported in previous gastric cancer studies. Notably, the *CDKN2A* OE subgroup was associated with a higher frequency of advanced pathologic Stage III disease (49%) compared to the WT cohort (41%), reinforcing the association between $p16^{INK4a}$ high phenotypes and advanced pT stage progression. Histological classification using ICD-O-3 morphology codes confirmed a predominant adenocarcinoma profile across all cohorts.

the Kaplan–Meier method and compared *via* the log-rank test using the survival (v3.5-7) and survminer (v0.4.9) packages. A p-value <0.05 was considered statistically significant.

Results

Patient characteristics and cohort stratification. The study analyzed a total of 386 patients from the TCGA-STAD cohort with complete transcriptomic and clinical annotations. Patients were stratified based on CDKN2A mRNA expression levels into three distinct groups: WT (n=253), Loss (n=57), and OE (n=76). The mean age at diagnosis for the entire cohort was 65.1 years (SD=10.5), and the population was predominantly male (65%). No statistically significant differences were observed across the three CDKN2A cohorts regarding age or sex, ensuring these demographic variables did not confound subsequent immune analyses. Notably, the CDKN2A OE subgroup was associated with more advanced disease, with 49% of patients presenting with Pathologic Stage III (IIIA, IIIB, or IIIC) compared to 41% in the WT group. This distribution aligns with reported phenotypes where $p16^{INK4a}$ high expression correlates with advanced pT stage progression. A tumor pT stage refers to the pathological classification of the primary tumor based on direct examination of tissue removed during surgery. The "p" stands for pathologic, and "T" stands for tumor, evaluating the size and depth of invasion into nearby tissues. pT stage is more precise than clinical staging and guides post-surgery treatment (Table I).

CDKN2A over-expression predicts CD8+ T cell exclusion. To determine the impact of CDKN2A status on the tumor microenvironment (TME), quanTIseq estimated immune fractions were compared across the stratified cohorts. Tumors with CDKN2A over-expression exhibited a statistically significant depletion of infiltrating CD8+ T cells compared to the Wild-Type cohort. Conversely, no significant differences were observed in the infiltration of

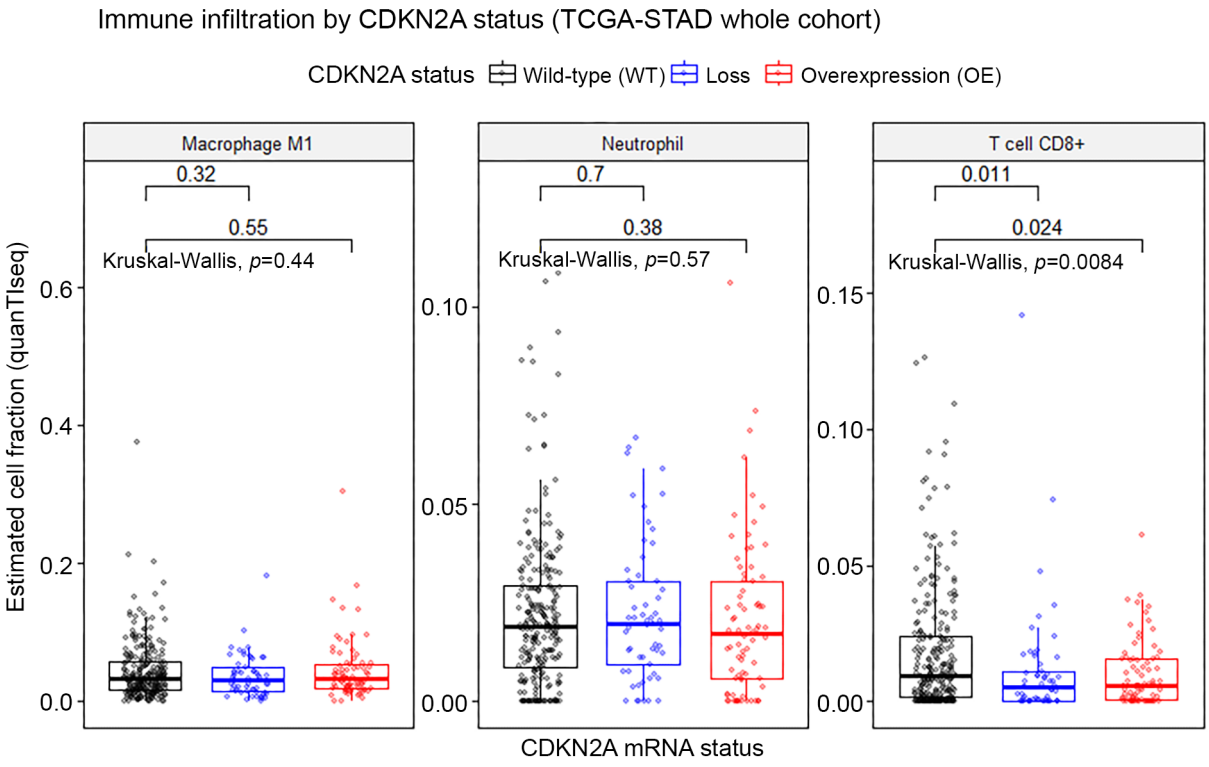

Figure 1. *Immune cell infiltration across CDKN2A mRNA expression cohorts in gastric adenocarcinoma. Computational deconvolution using the quanTIseq algorithm was applied to the TCGA-STAD whole cohort (n=386) to estimate absolute fractions of infiltrating immune cell populations. Tumors were stratified by CDKN2A mRNA status into Wild-type (WT), Loss, and Over-expression (OE) subgroups (Left/Center). No statistically significant differences are observed in the infiltration of M1 macrophages (p=0.44) or neutrophils (p=0.57) across the three cohorts, contrasting with previously reported immunohistochemical findings. (Right) CDKN2A over-expression is associated with a statistically significant depletion of infiltrating cytotoxic CD8+ T cells compared to the WT cohort (pairwise p=0.024; global Kruskal-Wallis p=0.0084). These data validate p16^{INK4a} over-expression as a transcriptomic biomarker for CD8+ T cell exclusion in the gastric tumor microenvironment (upper: Loss vs. WT; lower: OE vs. WT).*

M1 macrophages (p=0.44) or neutrophils (p=0.57) across the cohorts. These findings transcriptomically validate p16^{INK4a} over-expression as a specific biomarker for a CD8+ T cell-depleted TME in gastric adenocarcinoma (Figure 1).

While *CDKN2A* over-expression was associated with statistically significant CD8+ T cell depletion (p=0.024), the magnitude of this effect was characterized as negligible to small [Cliff's delta=-0.14; 95% confidence interval (CI)=-0.27, -0.01]. This modest transcriptomic effect size, contrasting with the prognostic disparities seen at the protein level, likely reflects the inherent decoupling between *CDKN2A* mRNA abundance and functional p16^{INK4a} protein activity in the gastric tumor microenvironment.

SASP factor up-regulation and adaptive immune resistance. Expression levels of proposed SASP mediators were evaluated to assess their mechanistic role in immune evasion. IDO1 demonstrated significant up-regulation in the CDKN2A OE cohort compared to WT, whereas NT5E (CD73) and TGFB1 showed no significant expression differences (Figure 2).

Direct correlation analysis further revealed that IDO1 expression maintained a strong, highly significant positive correlation with CD8+ T cell infiltration (R=0.64, p=2.2×10^{-16}) (Figure 3).

Similarly, TGFB1 expression exhibited a significant positive correlation with CD8+ T cell fractions (R=0.36, p=4.1×10^{-13}). These positive correlations contradict

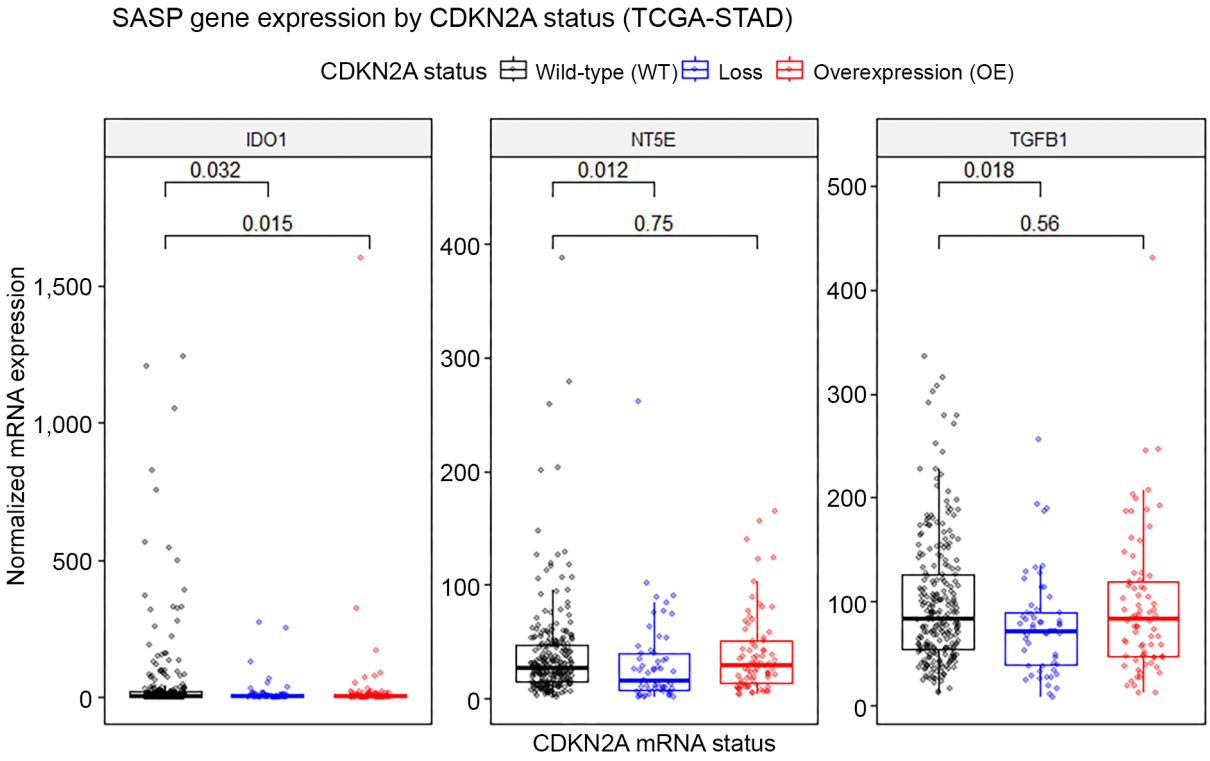

Figure 2. *Senescence-associated secretory phenotype (SASP) gene expression profiles by CDKN2A status. Normalized mRNA expression levels for key immunomodulatory factors were compared across Wild-type (WT), Loss, and Over-expression (OE) cohorts in the TCGA-STAD dataset. (Left) IDO1 demonstrates a statistically significant up-regulation in the CDKN2A OE cohort compared to the WT group (p=0.015), supporting its role as a potential mediator of the immunoevasive phenotype reported in literature. (Center/Right) Expression levels of NT5E (CD73) and TGFB1 showed no statistically significant differences between the OE and WT cohorts (p=0.75 and p=0.56, respectively), suggesting that these specific SASP factors may not be primary drivers of CDKN2A-associated immune exclusion at the transcriptomic level in this cohort (upper: Loss vs. WT; lower: OE vs. WT).*

primary exclusion models and instead suggest a mechanism of adaptive immune resistance, where these factors are reactively up-regulated in response to existing T cell presence rather than serving as the primary drivers of physical T cell exclusion (Figure 4).

Prognostic value of *CDKN2A* mRNA status survival outcomes were evaluated across the stratified *CDKN2A* cohorts (n=386) using Kaplan–Meier estimates and the log-rank test. While the OE group exhibited an early trend toward inferior overall survival, particularly between 24 and 48 months, the differences across the three groups did not reach statistical significance in the whole TCGA-STAD transcriptomic cohort (p=0.3). This contrasts with the highly significant survival disparities observed in the ZSHS IHC-based cohort (p=0.004) (5) and may reflect the inherent heterogeneity of bulk transcriptomic data compared to localized protein expression. Notably, the Loss cohort showed a trend toward superior survival outcomes in the first five years of follow-up compared to both the WT and OE groups (Figure 5).

Molecular subtype survival. Subtype-stratified survival analysis was performed to determine if the prognostic significance of *CDKN2A* is context-dependent. In both the chromosomal instability (CIN n=124, p=0.76) and microsatellite instability (MSI n=53, p=0.73) subtypes, no statistically significant differences in overall survival were observed across the WT, Loss, and OE cohorts. These

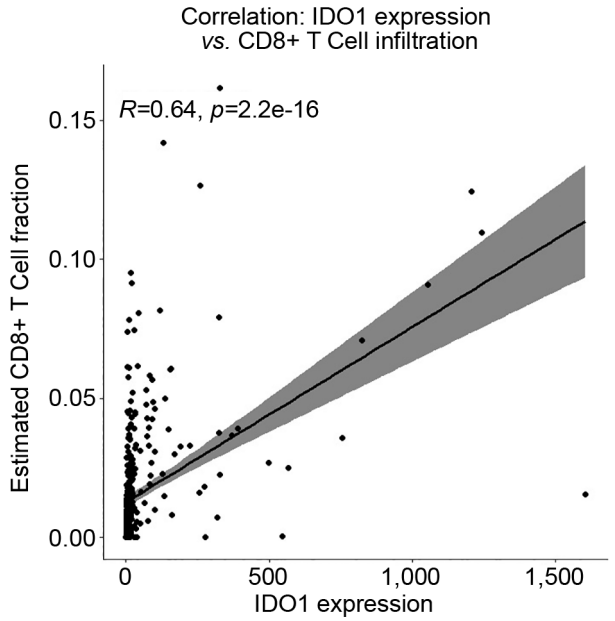

Figure 3. *Correlation between IDO1 expression and cytotoxic T cell infiltration. Spearman rank correlation analysis was performed to evaluate the relationship between IDO1 mRNA expression and estimated CD8+ T cell fractions derived from quanTIseq deconvolution. A strong, highly significant positive correlation was observed (R=0.64, p=2.2×10^{-16}). This relationship suggests that IDO1 expression in gastric adenocarcinoma may function as a mechanism of adaptive immune resistance – whereby IDO1 is up-regulated in response to existing T cell infiltration – rather than serving as a primary factor for T cell exclusion from the tumor microenvironment.*

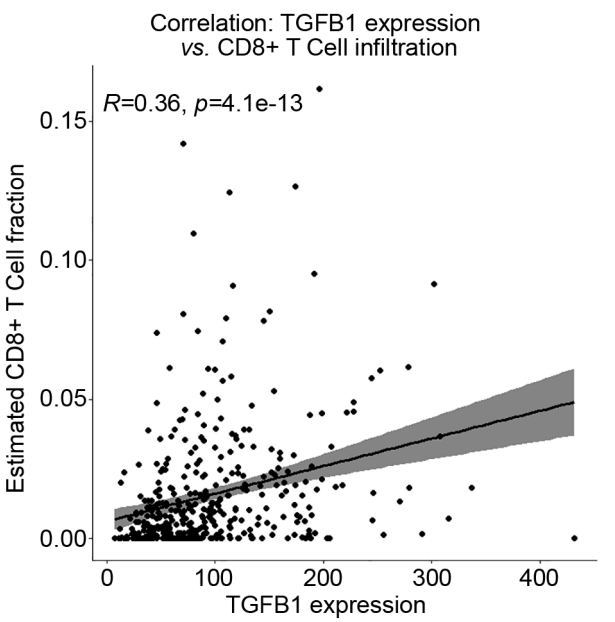

Figure 4. *Transcriptomic correlation between TGFB1 expression and CD8+ T cell infiltration in gastric adenocarcinoma. Spearman rank correlation analysis was utilized to assess the relationship between normalized TGFB1 mRNA expression and the absolute fraction of infiltrating CD8+ T cells as estimated by the quanTIseq algorithm. The analysis revealed a moderate and highly significant positive correlation (R=0.36, p=4.1×10^{-13}), suggesting that elevated TGFB1 expression does not universally drive the physical exclusion of cytotoxic T cells from the tumor bulk. These findings highlight a discrepancy between transcriptomic associations in the TCGA cohort and previously proposed protein-level exclusionary mechanisms.*

transcriptomic findings contrast with the protein-level immunohistochemistry (IHC) results reported by Wang *et al*. and suggest that *CDKN2A* mRNA levels may lack sufficient prognostic resolution compared to localized protein quantification.

Discussion

The complex interplay between cellular senescence and tumor immunity represents a critical frontier in gastric cancer research. This computational analysis of the TCGA-STAD cohort (n=386) confirms that *CDKN2A* mRNA over-expression is a statistically significant transcriptomic biomarker for a CD8+ T cell-depleted tumor microenvironment. These results provide independent validation of the clinical observations reported by Wang *et al*., who established that the p16^{INK4a} high phenotype correlates with advanced pathologic stage and an "immunoevasive contexture".

However, our findings reveal a notable divergence regarding the specific mediators of this evasion. While Wang *et al.* utilized IHC to demonstrate significantly higher protein expression of TGF-beta and CD73 in p16^{INK4a} high tumors, our transcriptomic analysis found no significant differences in *TGFB1* or *NT5E* mRNA levels across the *CDKN2A* cohorts.

Our extensive subtype-stratified analysis (CIN and MSI) failed to replicate the significant survival disparities reported by Wang *et al.* While we confirmed the biological immune contexture (CD8+ T cell depletion and IDO1 up-regulation), the lack of survival significance in CIN and MSI subtypes (p=0.76 and p=0.73, respectively) underscores a

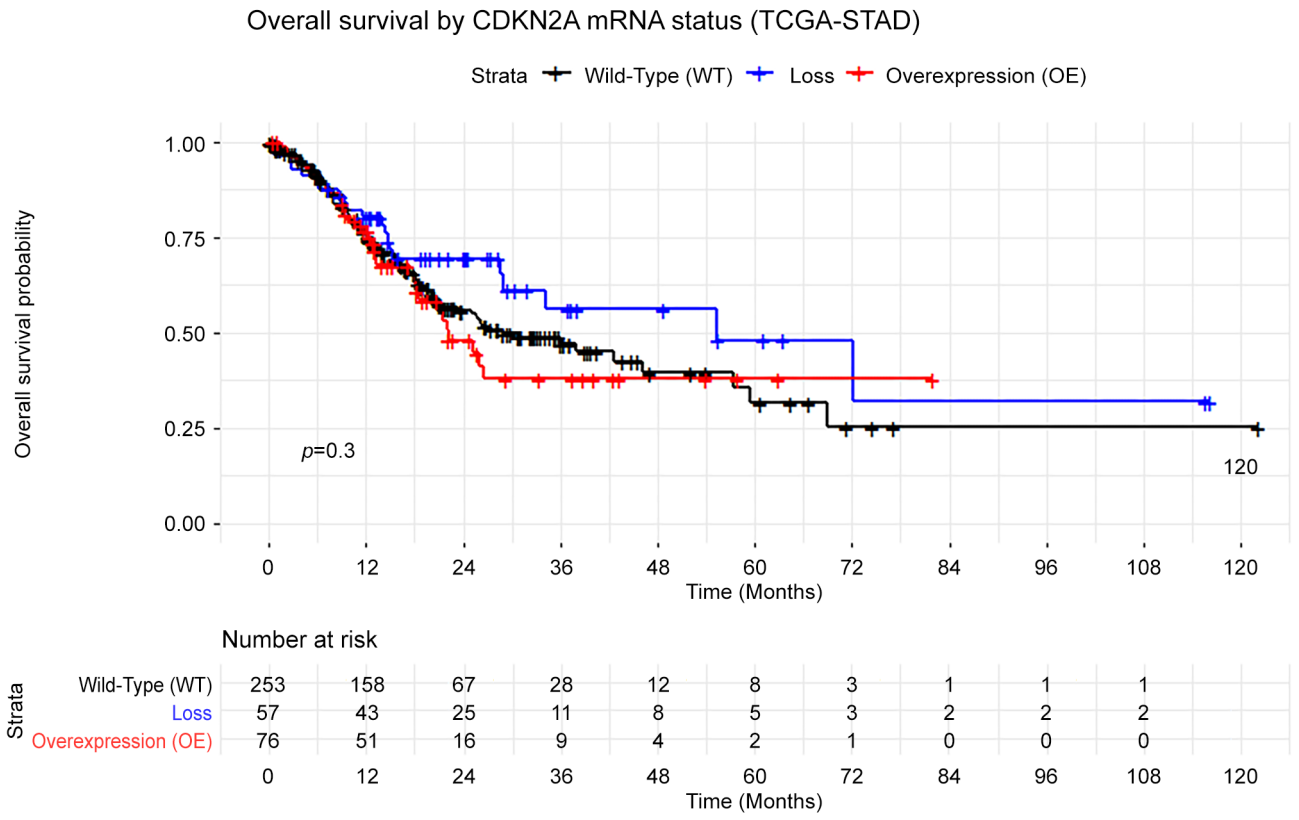

Figure 5. *Overall survival analysis of the TCGA-STAD cohort stratified by CDKN2A mRNA status. Kaplan–Meier curves demonstrate overall survival (OS) for patients with CDKN2A Wild-type (black), Loss (blue), and Over-expression (red) transcript levels. No statistically significant difference in OS is observed across the three groups in the unselected gastric cancer cohort (p=0.3, log-rank test).*

profound decoupling between *CDKN2A* transcript abundance and clinical outcomes. This divergence suggests that the aggressive clinical trajectory of $p16^{INK4a}$ high tumors is likely driven by post-translational protein stability, spatial immune exclusion, or enzymatic SASP activity that is not captured by bulk RNA-sequencing. Consequently, while *CDKN2A* mRNA is a marker for immune infiltration status, protein-level IHC remains the gold standard for clinical prognosis in gastric adenocarcinoma.

This discordance likely reflects the inherent decoupling between mRNA transcripts and functional protein levels. Factors such as TGF-beta undergo extensive post-translational regulation, and the enzymatic activity of CD73 (encoded by *NT5E*) is not always mirrored by transcript abundance. Furthermore, the IHC evidence provided by Wang *et al.* captures spatial localization that bulk RNA-sequencing averages across the tumor biopsy. These results suggest that while *CDKN2A* over-expression remains an indicator of a "cold" tumor, the specific SASP exclusionary mechanism may be driven by proteomic or metabolic shifts rather than a generalized up-regulation of SASP-related transcripts.

IDO1 and adaptive immune resistance. A critical finding of this study is the significant up-regulation of *IDO1* in the *CDKN2A* over-expressed cohort (p=0.015), which aligns with the protein-level increases observed by Wang *et al.* (p=0.026). However, the strong, highly significant positive correlation between *IDO1* expression and CD8+ T cell infiltration (R=0.64) challenges the model of *IDO1* as a primary exclusionary factor.

Instead, this dynamic is indicative of adaptive immune resistance. In this paradigm, initial infiltration by CD8+ T cells leads to the secretion of interferon-gamma (IFN-gamma), which in turn drives the reactive up-regulation of *IDO1* as a feedback inhibitory mechanism by the tumor and surrounding stroma.

Therefore, in *CDKN2A*-over-expressing gastric cancers, *IDO1* acts as a potent reactive immune checkpoint rather than a factor that physically bars T cells from the tumor microenvironment. This distinction is clinically important, as it suggests that the poor immunotherapy response observed by Wang *et al*. in $p16^{INK4a}$ high patients may be partially reversible through the strategic use of IDO1 inhibitors in combination with existing checkpoint blockade.

This mechanistic refinement has therapeutic implications. Wang *et al.* demonstrated that $p16^{INK4a}$ OE tumors respond poorly to immune checkpoint inhibitors, particularly in PD-L1 CPS ≥1 and CIN subsets. Our data suggest that IDO1-mediated adaptive resistance may contribute to this phenomenon. Consequently, *CDKN2A*-over-expressing gastric adenocarcinomas might benefit from combination immunotherapy strategies incorporating IDO1 inhibitors (*e.g*., epacadostat, linrodostat) alongside PD-1/PD-L1 blockade (9). While early-phase IDO1 inhibitor trials have yielded mixed results (10), patient selection based on *CDKN2A* status and IDO1 expression may identify a more responsive subset.

Study limitations. While this study provides computational validation of *CDKN2A* as a transcriptomic biomarker, several limitations must be acknowledged:

Transcriptomic vs. proteomic divergence: This analysis relied exclusively on bulk RNA-sequencing data from the TCGA-STAD cohort. In contrast, Wang *et al.* primarily utilized IHC to define $p16^{INK4a}$ status and immune cell densities. The lack of correlation observed here for M1 macrophages and neutrophils may reflect the inherent "decoupling" between mRNA expression and functional protein levels, or differences in spatial localization that bulk sequencing cannot capture.

Deconvolution constraints: Although the quanTIseq algorithm is highly validated for quantifying absolute immune fractions, it remains a mathematical estimation based on standardized gene signatures. These estimates may be influenced by the "purity" of the tumor samples or the presence of non-malignant stromal cells that also express SASP-related transcripts.

Retrospective nature and cohort bias: The TCGA-STAD dataset is a retrospective repository representing a diverse global population. The specific clinical outcomes and immune phenotypes reported by Wang *et al*. were derived from localized cohorts in Shanghai and Seoul. Variations in patient ethnicity, dietary factors, and *H. pylori* prevalence across these cohorts may contribute to the differing immune landscapes.

Bulk vs. single-cell resolution: Bulk RNA-seq averages the signal across the entire tumor biopsy. Consequently, we cannot definitively distinguish whether *IDO1* or *TGFB1* transcripts are originating from the senescent tumor cells themselves (as a true SASP) or from infiltrating myeloid and stromal cells in the surrounding niche.

Lack of functional validation: This study is purely observational and computational. While the strong positive correlation between *IDO1* and CD8+ T cells suggests a mechanism of adaptive immune resistance, *in vitro* functional assays or multiplexed spatial profiling would be required to confirm this interaction.

Conclusion

The computational deconvolution and transcriptomic analysis of the TCGA-STAD cohort (n=386) provides validation of CDKN2A mRNA over-expression as a significant biomarker for a CD8+ T cell-depleted tumor microenvironment in gastric adenocarcinoma. These findings align with the clinical and pathological observations reported by Wang *et al*., confirming that the $p16^{INK4a}$ high phenotype identifies a subset of patients with aggressive disease and an immunoevasive contexture.

However, our data suggests a more nuanced mechanistic landscape than a generalized, secretory

exclusion model. The lack of transcript-level up-regulation for TGFB1 and NT5E suggests that the immunoevasive properties of these specific factors in CDKN2A-over-expressing tumors may be driven by post-translational regulation or spatial sequestration rather than a simple increase in SASP-related mRNA.

Furthermore, the strong positive correlation between IDO1 and CD8+ T cell infiltration indicates that IDO1 serves as a marker of adaptive immune resistance. In this paradigm, IDO1 is reactively up-regulated in response to cytotoxic T cell activity, functioning as a localized immune checkpoint rather than a primary barrier to T cell entry. These results refine the biological understanding of senescence in the gastric microenvironment and highlight IDO1 inhibition as a potential therapeutic strategy to overcome immunotherapy resistance in CDKN2A-over-expressing gastric cancers.

Conflicts of Interest

The Authors declare that they have no competing interests in relation to this study.

Authors' Contributions

Steven Lehrer conceptualized the study, performed data acquisition and statistical analyses, interpreted the results, and drafted the manuscript. Peter Rheinstein contributed to study design, provided critical revisions of the manuscript for important intellectual content, and assisted in the interpretation of findings. Both Authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work. This work was supported in part through the computational and data resources and staff expertise provided by Scientific Computing and Data at the Icahn School of Medicine at Mount Sinai.

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Artificial Intelligence (AI) Disclosure

During the preparation of this manuscript, a large language model was used solely for language editing and stylistic improvements in select paragraphs. No sections involving the generation, analysis, or interpretation of research data were produced by generative AI. All scientific content was created and verified by the authors. Furthermore, no figures or visual data were generated or modified using generative AI or machine learning–based image enhancement tools.

References

1 Abengozar R, Sharma A, Sharma R: Gastric cancer: lessons learned from high-incidence geographic regions. J Gastrointest Oncol 12(Suppl 2): S350-S360, 2021. DOI: 10.21037/jgo-2019-gi-05

2 Jiao F, Wang Z, Yuan J, Shi F, Zhang S: The tumor microenvironment shapes gastric cancer progression by coordinating immune suppression and metabolic reprogramming. Front Immunol 17: 1787060, 2026. DOI: 10.3389/fimmu.2026.1787060

3 Song X, Liu X, Guo Q, Xu H, Cao L: Unraveling the nexus between cellular senescence and malignant transformation: a paradigm shift in cancer research. Cancer Biol Med 21(7): 541-546, 2024. DOI: 10.20892/j.issn.2095-3941.2024.0157

4 Safwan-Zaiter H, Wagner N, Wagner KD: P16INK4A-more than a senescence marker. Life (Basel) 12(9): 1332, 2022. DOI: 10.3390/life12091332

5 Wang J, Gu Y, Zhang Z, Ling Z, Lin C, Liu H, Li R, He H, Shao F, Xu J: Poor clinical outcomes and immunoevasive contexture in gastric cancer patients bearing p16 high phenotype. Cancer 132(6): e70363, 2026. DOI: 10.1002/cncr.70363

6 Munn DH, Mellor AL: IDO in the tumor microenvironment: inflammation, counter-regulation, and tolerance. Trends Immunol 37(3): 193-207, 2016. DOI: 10.1016/j.it.2016.01.002

7 Sturm G, Finotello F, List M: Immunedeconv: an R package for unified access to computational methods for estimating immune cell fractions from bulk RNA-sequencing data. Methods Mol Biol 2120: 223-232, 2020. DOI: 10.1007/978-1-0716-0327-7_16

8 Finotello F, Mayer C, Plattner C, Laschober G, Rieder D, Hackl H, Krogsdam A, Loncova Z, Posch W, Wilflingseder D, Sopper S, Ijsselsteijn M, Brouwer TP, Johnson D, Xu Y, Wang Y, Sanders ME, Estrada MV, Ericsson-Gonzalez P, Charoentong P, Balko J, de Miranda NFDCC, Trajanoski Z: Molecular and pharmacological modulators of the tumor immune contexture revealed by deconvolution of RNA-seq data.

Genome Med 11(1): 34, 2019. DOI: 10.1186/s13073-019-0638-6

9 Spranger S, Koblish HK, Horton B, Scherle PA, Newton R, Gajewski TF: Mechanism of tumor rejection with doublets of CTLA-4, PD-1/PD-L1, or IDO blockade involves restored IL-2 production and proliferation of CD8(+) T cells directly within the tumor microenvironment. J Immunother Cancer 2: 3, 2014. DOI: 10.1186/2051-1426-2-3

10 Long GV, Dummer R, Hamid O, Gajewski TF, Caglevic C, Dalle S, Arance A, Carlino MS, Grob JJ, Kim TM, Demidov L, Robert C, Larkin J, Anderson JR, Maleski J, Jones M, Diede SJ, Mitchell TC: Epacadostat plus pembrolizumab *versus* placebo plus pembrolizumab in patients with unresectable or metastatic melanoma (ECHO-301/KEYNOTE-252): a phase 3, randomised, double-blind study. Lancet Oncol 20(8): 1083-1097, 2019. DOI: 10.1016/s1470-2045(19)30274-8