Molecular Cancer

CORRESPONDENCE

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SELP$^+$ TEC:CD8$^+$ T cell crosstalk associates with improved radiotherapy efficacy in cervical cancer

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Abstract

P-selectin (SELP) expression in tumor cells has been implicated in promoting tumor progression and treatment resistance across various cancers. However, our prior study identified SELP expression in a specific subpopulation of endothelial cells within cervical cancer (CC) and potentially linked to anti-cancer immune response. The precise mechanisms by which SELP influences anti-cancer immunity and its involvement in radiotherapy response in CC, however, remain elusive. To address these gaps, this study analyzed tumor tissue samples from 205 CC patients undergoing radiotherapy, scRNA-seq data from 42,159 cells of eight patients, and bulk RNA-sequencing data from 187 radiotherapy-treated patients. The results revealed that elevated SELP expression in tumor endothelial cells (TECs) was significantly correlated with improved survival outcomes in patients treated with radiotherapy. The *SELP^{high}* group exhibited a prominent enrichment of immune-related pathways, coupled with a diminished enrichment in epithelial cell proliferation and angiogenesis pathways. Notably, this group demonstrated increased infiltration of CD8$^+$ T cells and enhanced expression of chemokine receptors, including ACKR1. Furthermore, our data suggest that SELP$^+$ TECs engage in crosstalk with CD8$^+$ T cells via the ACKR1-CCL5 axis, which is associated with improved radiotherapy efficacy. In conclusion, these findings underscore the pivotal role of SELP$^+$ TEC:CD8$^+$ T cell interactions through the ACKR1-CCL5 pathway in enhancing radiotherapy response in CC. Targeting this crosstalk may offer novel therapeutic strategies to mitigate treatment resistance and improve patient survival.

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Introduction

Cervical cancer (CC) ranks as the fourth most prevalent malignancy among women and represents a significant contributor to global cancer-related mortality [1]. While radiotherapy has been shown to improve outcomes in CC patients, responses to treatment vary, with approximately 30% of patients with advanced disease developing resistance [2–4]. Thus, identifying novel therapeutic targets and prognostic biomarkers to enhance radiotherapy efficacy is imperative. P-selectin (SELP), a vascular cell adhesion molecule, is expressed on the surface of tumor endothelial cells (TECs) [5]. TEC-derived SELP has been implicated in promoting tumor metastasis [6], and SELP expression in tumor cells has been linked to tumor progression and treatment resistance [7, 8]. Our prior investigation into the initiation and progression of squamous cell carcinoma identified *SELP* expression in a specific subpopulation of endothelial cells, which was associated with the interferon-gamma signaling and antigen processing and presentation pathways [9]. While these findings suggest that SELP plays a critical role in modulating cancer immunity, its precise mechanisms in promoting anti-cancer immunity and influencing radiotherapy responses in CC remain unclear. To address these questions, this study included tumor tissue samples from 205 CC patients undergoing radiotherapy, scRNA-seq data from 42,159 cells derived from eight patients, and bulk RNA-sequencing data from 187 patients treated with radiotherapy. The comprehensive study protocol is detailed in the Supplementary Materials.

Results

Clinical data from 205 patients with CC who underwent radiotherapy were collected and analyzed. Of these, 180 patients received concurrent chemotherapy, while 25 patients did not due to health conditions preventing chemotherapy tolerance, advanced age, or personal refusal (Fig. 1A). The results revealed that SELP was predominantly expressed in TEC (Fig. 1B). High SELP expression was significantly correlated with improved local recurrence-free survival (LRFS), overall survival (OS), and progression-free survival (PFS) ($P < 0.05$ for all; Fig. 1C, Supplementary Fig. S2A). Multivariate analysis using the Cox proportional hazards model confirmed that elevated SELP expression was an independent predictor of enhanced LRFS, OS, and PFS in CC patients treated with radiotherapy (LRFS: hazard ratio [HR] = 0.28, $P = 0.029$; OS: HR = 0.38, $P = 0.002$; PFS: HR = 0.28, $P < 0.001$; Fig. 1D, Supplementary Fig. S2B). Furthermore, pathological type, tumor cell differentiation, FIGO stage, and treatment strategy were identified as significant predictors of survival in CC patients (Fig. 1D, Supplementary Fig. S2B). These findings collectively indicate that SELP is predominantly expressed in TECs and that its high expression is positively associated with improved outcomes in patients with CC undergoing radiotherapy.

To validate the critical role of *SELP* in immunity and radiotherapy response in CC, bulk RNA-sequencing data from 187 CC patients undergoing radiotherapy were extracted and analyzed from the TCGA database. The results demonstrated that high *SELP* expression was associated with a favorable prognosis (Fig. 1E). The $SELP^{high}$ group exhibited upregulation of *KCNE1* and *SCGB3A2* (Fig. 1F). GO enrichment analysis revealed that the $SELP^{high}$ group showed significant enrichment in processes related to cell–cell adhesion regulation, leukocyte migration, immune response activation, positive regulation of lymphocyte activation, and T cell activation. In contrast, processes related to the regulation of epithelial cell proliferation were less enriched (Fig. 1G). To further explore the immune landscape, the relationship between SELP expression and immune cell infiltration was examined. The $SELP^{high}$ tumors exhibited significantly higher infiltration of $CD8^+$ T cells ($P = 0.012$) and $CD68^+$ macrophages ($P = 0.03$) compared to $SELP^{low}$ tumors, while no significant difference in $CD56^+$ NK cell infiltration was observed between the two groups ($P = 0.42$, Supplementary Fig. S3A). These findings were corroborated by deconvolution analysis of TCGA data, which confirmed a higher proportion of $CD8^+$ T cells and macrophages in $SELP^{high}$ tumors, with no significant difference in NK cells (Supplementary Fig. S3B). Previous research has highlighted a strong correlation between radiotherapy response and angiogenesis or hypoxia [10].

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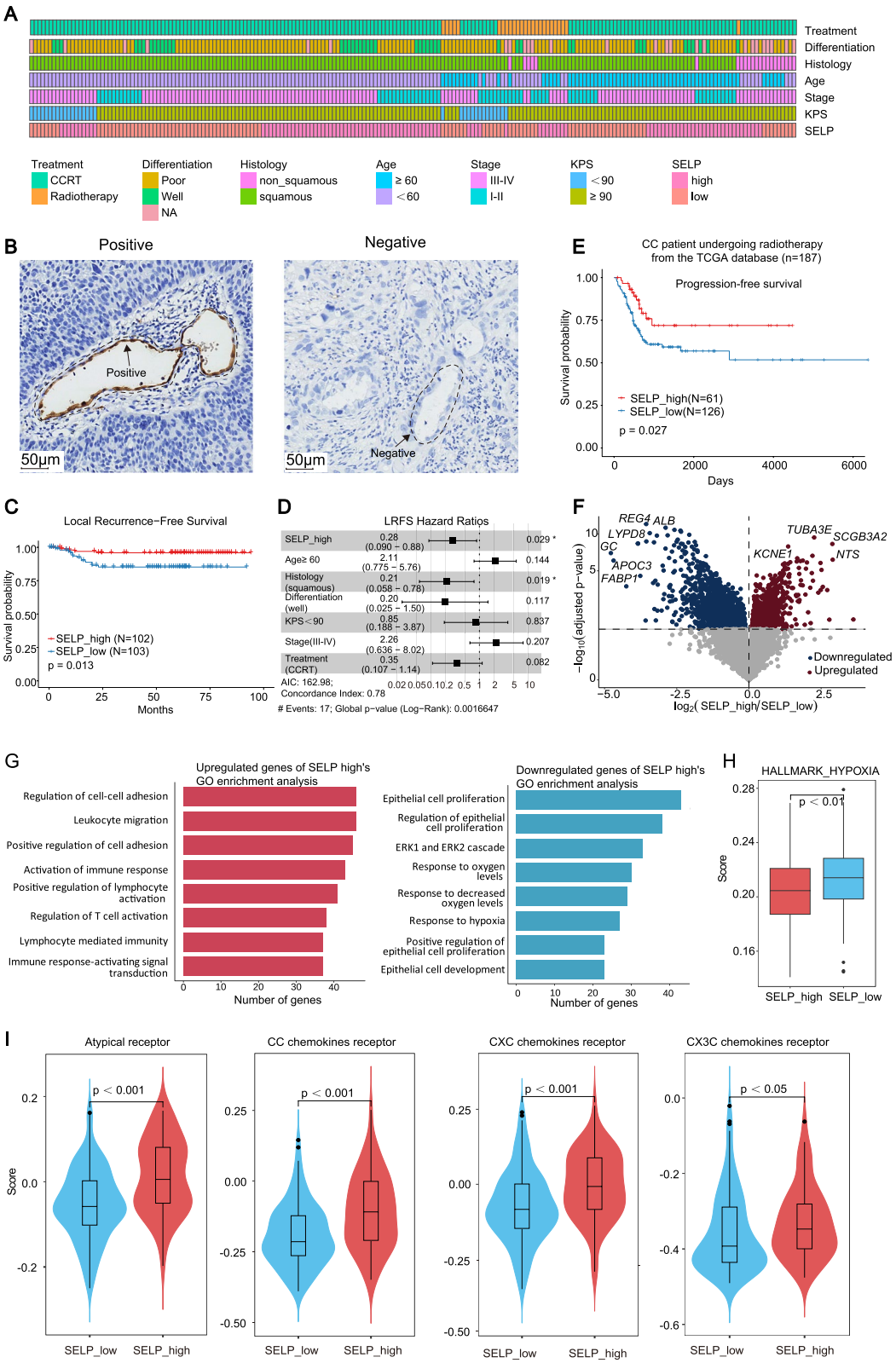
Fig. 1 Association of $SELP^+$ TEC with enhanced radiotherapy efficacy and immune activation in patients with CC. **A** Clinical characteristics of 205 patients with CC. **B** Representative immunohistochemical images of SELP expression in TECs. **C** Kaplan–Meier survival curves showing local recurrence-free survival in CC patients stratified by SELP expression levels. **D** Multivariate Cox proportional hazards analysis assessing the relationship between clinical characteristics and local recurrence-free survival in CC patients. **E** Kaplan–Meier survival curve demonstrating PFS of CC patients treated with radiotherapy in the $SELP^{high}$ and $SELP^{low}$ groups (with optimal cutoff value derived from the TCGA dataset). *P*-values from the two-sided log-rank test are shown. **F** Volcano plot illustrating differentially expressed genes between the $SELP^{high}$ and $SELP^{low}$ groups, with the most significant genes highlighted. **G** GO terms enriched in the $SELP^{high}$ group. **H** Box plots comparing gene set scores between the $SELP^{high}$ and $SELP^{low}$ groups. **I** Violin plots displaying the expression levels of atypical chemokine receptor genes in CC patients



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The lower level of hypoxia observed in the *SELP*^{high} group was associated with improved radiotherapy efficacy (Fig. 1G, H). Additionally, the *SELP*^{high} group exhibited elevated expression of chemokine receptors critical for the recruitment of CD8$^+$ T cells, including members of the atypical, CC, CXC3, and CXC chemokine receptor families (Fig. 1I). These results suggest that SELP plays a pivotal role in enhancing anti-tumor immunity and improving radiotherapy outcomes in CC, potentially by influencing chemokine-mediated T cell infiltration and activation.

To investigate the potential role of SELP in TECs, scRNA-seq data derived from 42,159 cells obtained from eight CC patients were analyzed. Seven distinct cell populations were identified in the dataset (Supplementary Fig. S4). Based on the expression of lineage-specific markers, these populations were categorized into seven major clusters: B cells (*MS4A1*), TECs (*VWF*), epithelial cells (*EPCAM*, *KRT19*), cancer-associated fibroblasts (*PDGFRB*, *LUM*, *MYH11*), myeloid cells (*CD68*, *CD14*), NK/T cells (*CD3D*, *NKG7*), and plasma cells (*MZB1*).

TECs were subsequently classified as *SELP*$^+$ or *SELP*$^-$ based on their *SELP* expression levels (Fig. 2A). Multiplex immunofluorescence staining confirmed the distinct clusters identified (Fig. 2B). The *SELP*$^+$ TECs exhibited differential expression of genes such as *ACKR1*, *SELE*, *C7*, and *IL1RI*, while the *SELP*$^-$ TECs expressed genes including *ESM1*, *BTNL9*, *HEY1*, and *FCN3* (Fig. 2C). Consistent with bulk RNA-sequencing analysis, SELP$^+$ TECs showed enhanced enrichment in processes related to leukocyte migration, leukocyte-mediated immunity, positive regulation of cell–cell adhesion, and cytokine-mediated signaling pathways (Fig. 2D, Supplementary Fig. S5A). These processes were linked to a favorable prognosis in CC patients undergoing radiotherapy (Supplementary Fig. S6). In contrast, *SELP*$^+$ TECs exhibited reduced enrichment in processes associated with epithelial cell proliferation, endothelial cell migration, endothelium development, and sprouting angiogenesis (Fig. 2D). Additionally, *SELP*$^+$ TECs displayed higher expression levels of atypical chemokine receptors (Supplementary Fig. S5B). To further validate these findings, single-cell endothelial data from additional tumor types, including clear cell renal cell carcinoma, lung adenocarcinoma, and head and neck squamous cell carcinoma, were examined. In these datasets, *SELP*$^+$ TECs consistently demonstrated immune activation characteristics (Supplementary Fig. S7). Moreover, *SELP*$^+$ endothelial cells in normal cervical tissue exhibited similar features (Supplementary Fig. S8A-8C). Notably, *SELP*^{high} cervical cancer samples displayed an even higher degree of immune activation compared to *SELP*^{high} cells in normal cervical tissue (Supplementary Fig. S8D). These results suggest that *SELP*$^+$ TECs exhibit enhanced immune-related features and increased chemokine receptor expression, which are correlated with a favorable prognosis and improved outcomes in CC patients undergoing radiotherapy. Taken together, these findings underscore the critical role of SELP in enhancing anti-tumor immunity and radiotherapy efficacy in CC.

Building on the aforementioned results, it was hypothesized that *SELP*$^+$ TECs may enhance anti-tumor immunity by facilitating lymphocyte infiltration. To test this hypothesis, interactions between NK/T cells and TECs were examined. Based on transcriptomic profiling, NK/T cells were classified into seven distinct subclusters: LAG3_CD8_T, CD4_Naive, GZMK_CD8_T, NK, Treg, GINS2_CD8_T, and proliferating_T (Supplementary Fig. S9A-C). CD4_Naive cells exhibited characteristics of a naïve state, while LAG3_CD8_T cells displayed features of immune exhaustion, consistent with an exhausted phenotype. The GZMK_CD8_T cluster showed strong cytotoxic activity, TCR signaling, and effector function activation, highlighting its active role in anti-tumor immunity. NK cells demonstrated pronounced involvement in cytokine and chemokine receptor signaling, suggesting a role in immune cell recruitment and communication. The GINS2_CD8_T and Proliferating_T

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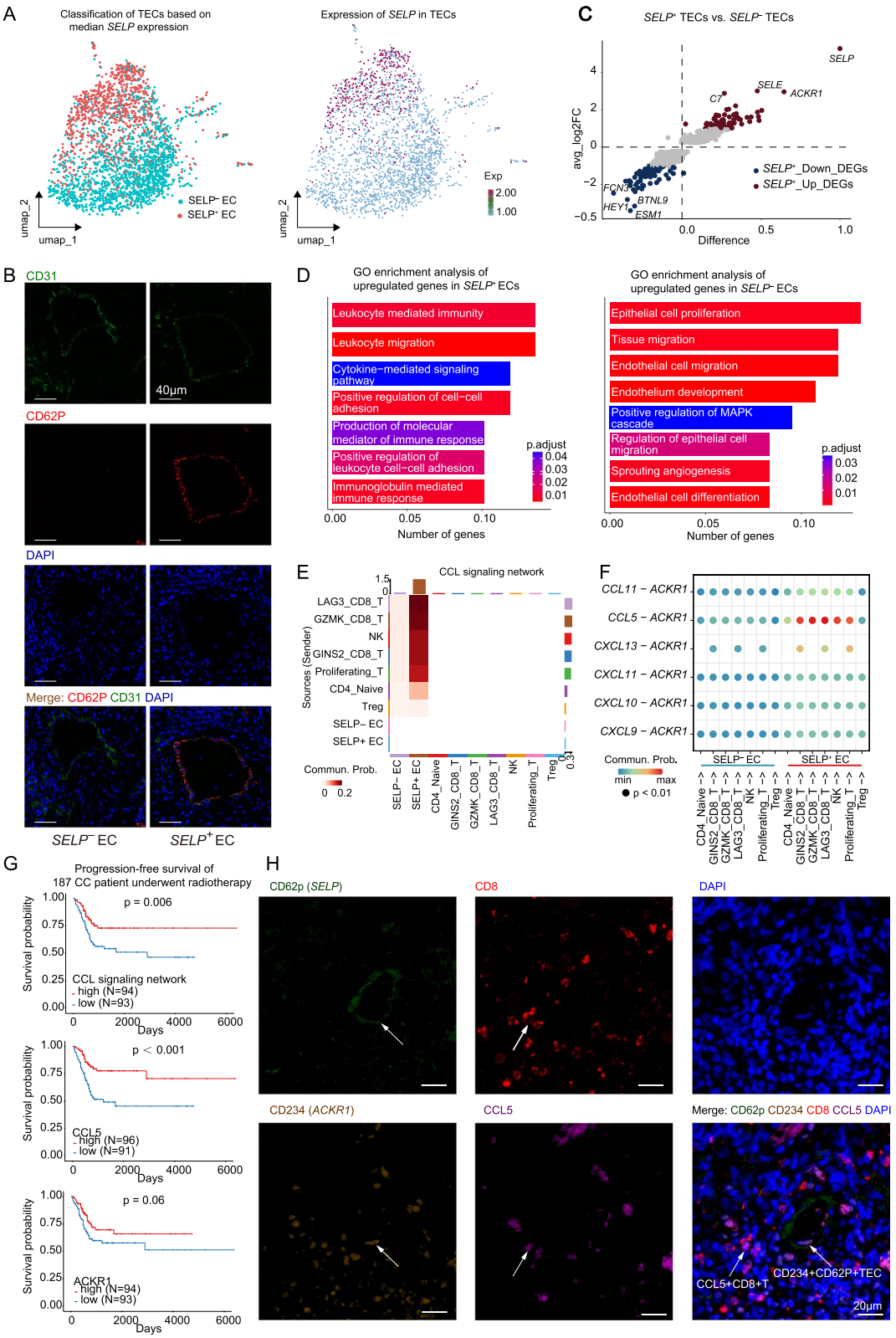
Fig. 2 Correlation of SELP$^+$ TEC:CD8$^+$ T cell crosstalk with improved radiotherapy outcomes and enhanced immune responses in patients with CC. **A** UMAP plots showing the expression of SELP in 2,569 TECs, color-coded by *SELP* expression levels, stratified by the median SELP expression value. **B** Representative images of immunofluorescence staining for CD62P in TECs within tumor tissue. **C** Volcano plot depicting differentially expressed genes between *SELP*$^+$ TECs and *SELP*$^-$ TECs. **D** GO terms enriched in *SELP*$^+$ TECs and *SELP*$^-$ TECs. **E** Heatmap illustrating intercellular communication between TECs and NK/T cell subclusters via the CCL signaling pathway. Color intensity reflects the probability of communication. **F** Bubble plots showing specific ligand–receptor interactions from the CCL signaling pathway involved in TEC–NK/T cell crosstalk. Bubble size indicates *P*-values, and color intensity reflects the interaction probability. **G** Kaplan–Meier survival curve demonstrating PFS in CC patients treated with radiotherapy, stratified by CCL signaling pathway score, CCL5 expression, and ACKR1 expression in the TCGA dataset. **H** Immunofluorescence staining revealing the interaction between CD62P$^+$ endothelial cells (green for CD62P) and CD8$^+$ T cells (red) via the *ACKR1-CCL5* axis. CCL5 is shown in purple, *ACKR1* (CD234) in orange, and nuclei in blue (DAPI staining). The merged image illustrates the colocalization of these markers within the tissue (scale bar = 40 μm). TECs, tumor endothelial cells; OS, overall survival; PFS, progression-free survival; CC, cervical cancer; UMAP, uniform manifold approximation and projection



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clusters were marked by heightened metabolic activity, reflecting intense cell cycle progression and elevated energy demands.

To investigate how *SELP*$^+$ TECs contribute to CD8$^+$ T cell infiltration, we analyzed interactions between TECs and NK/T cells using CellChat. Notably, signaling networks involving CCLs emerged as key mediators of TEC-NK/T cell communication, with *SELP*$^+$ TECs exhibiting stronger interaction intensities (Fig. 2E). Further analysis of ligand-receptor pairs revealed that the *ACKR1-CCL5* interaction was notably more active in *SELP*$^+$ TECs than in *SELP*$^-$ TECs, particularly in the context of CD8$^+$ T cell interactions (Fig. 2F). The CCL signaling network, along with *CCL5* and *ACKR1*, was found to be associated with favorable PFS in patients with CC treated with radiotherapy (Fig. 2G). Validation via multiplex immunofluorescence staining confirmed the colocalization of SELP$^+$CD234$^+$ TECs with CCL5$^+$CD8$^+$ T cells in the tumor vasculature (Fig. 2H). ACKR1, as a receptor of CCL5, may facilitate the TECs-mediated recruitment and infiltration of CCL5-secreting CD8$^+$ T cells into the tumor microenvironment [11]. Meanwhile, *SELP*$^+$ TECs exhibited an up-regulation of pathways related to leukocyte cell adhesion and regulation of cellular extravasation (Supplementary Fig. S10A), suggesting enhanced capabilities for immune cell recruitment. Additionally, lower cytoskeleton organization scores of *SELP*$^+$ TECs (Supplementary Fig. S10B) indicated reduced cytoskeletal stability, which is often associated with increased endothelial permeability. Further spatial transcriptomics analysis validated that *SELP*$^+$ TECs enriched regions were negatively correlated with cytoskeleton organization and positively correlated with cellular extravasation scores (Supplementary Fig. S10C). In summary, SELP$^+$ TECs bind CCL5-secreting CD8$^+$ T cells through ACKR1, and their enhanced leukocyte adhesion properties, along with increased endothelial permeability, may contribute to the recruitment and extravasation of CD8$^+$ T cells.

Discussion

SELP is primarily recognized as an adhesion molecule expressed on endothelial cells [5]. Previous studies have closely linked SELP to tumor metastasis, progression, and resistance to treatment [6–8]. In this investigation, the role of SELP in cancer immunity and radiotherapy efficacy in CC was explored. Our results demonstrated a positive correlation between SELP expression and improved radiotherapy outcomes in CC. Notably, *SELP*$^+$ TECs exhibited significant upregulation of pathways associated with tumor immune activation, immune cell migration, adhesion, and genes related to the atypical chemokine receptor family. Furthermore, *SELP*$^+$ TECs displayed elevated expression of the atypical chemokine receptor gene *ACKR1*, a molecule known to regulate immune cell activation and migration [12]. *ACKR1* exhibited heterogeneity within tumors and served as a distinguishing marker for TECs [13]. In lung cancer, a subset of TECs characterized by the expression of *ACKR1* and *SELP* exhibited reduced antigen presentation and impaired leukocyte homing [14], a similar subset in thyroid cancer demonstrated characteristics favoring leukocyte recruitment and adhesion [15]. Given the elevated chemokine receptor expression in *SELP*$^+$ TECs and the enrichment of immune activation, adhesion, and immune cell migration pathways, it is hypothesized that SELP$^+$ TECs contribute to enhanced immune responses. To investigate the interactions between TECs and NK/T cells, ligand-receptor pair analysis revealed the *ACKR1-CCL5* axis as particularly active in facilitating crosstalk between *SELP*$^+$ TECs and CD8$^+$ T cells. We propose that *SELP*$^+$ TECs recruit immune cells through the ACKR1-CCL5 interaction, enabling the initial binding of CCL5-secreting CD8$^+$ T cells. Subsequently, the up-regulated adhesion pathways and increased endothelial permeability in *SELP*$^+$ TECs may enhance their ability to facilitate the infiltration of these immune cells into the tumor microenvironment. This was further corroborated by multiplex immunofluorescence, which confirmed the colocalization of SELP$^+$CD234$^+$ TECs with CCL5$^+$CD8$^+$ T cells. Additionally, *SELP*^{high} tumors exhibited significantly greater CD8$^+$ T cell infiltration compared to *SELP*^{low} tumors, further supporting the hypothesis that TECs expressing ACKR1 plays a role in modulating immune cell recruitment by attracting CCL5-secreting CD8$^+$ T cells. These findings underscore the potential of targeting SELP$^+$ TEC:CD8$^+$ T cell crosstalk to optimize radiotherapy strategies, potentially overcoming treatment resistance and improving patient survival. Despite significant findings, a few limitations of this study should be acknowledged. First, while the data suggested that crosstalk between SELP$^+$ TECs and CD8$^+$ T cells via the ACKR1-CCL5 axis played a crucial role in enhancing radiotherapy efficacy in CC, direct functional experiments to investigate the underlying mechanism by which this crosstalk contributes to immune activation and CD8$^+$ T cell recruitment were not conducted. Therefore, further research is needed to elucidate such mechanisms. Second, although the analysis of scRNA-seq data from 42,159 cells provided valuable insights into the expression pattern of *SELP* in TECs, a larger sample size would improve the robustness and generalizability of these findings. Future studies should validate and expand

these results in larger datasets to confirm their applicability across broader populations.

Conclusion

In conclusion, this study highlights the pivotal role of $SELP^+$ TEC:$CD8^+$ T cell crosstalk via the ACKR1-CCL5 axis in enhancing radiotherapy efficacy in CC. Comprehensive analyses, including clinical data, bulk RNA sequencing, and single-cell RNA-seq, revealed that high *SELP* expression correlates with increased immune activation, reduced tumor hypoxia, and improved radiotherapy outcomes in CC patients. The interaction between $SELP^+$ TECs and $CD8^+$ T cells, mediated by the ACKR1-CCL5 pathway, underscores SELP as a crucial regulator of immune cell recruitment and activation within the tumor microenvironment. Consequently, targeting the $SELP^+$ TEC:$CD8^+$ T cell crosstalk holds potential as a strategy to optimize radiotherapy, mitigate treatment resistance, and improve survival in CC patients.

Abbreviations

CC	Cervical cancer
TECs	Tumor endothelial cells
LRFS	Local recurrence-free survival
OS	Overall survival
PFS	Progression-free survival
HR	Hazard ratio
CCL5	CC motif chemokine ligand 5

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12943-025-02244-7.

Supplementary Material 1.

Acknowledgements

The authors have nothing to report.

Authors' contributions

C.L., Q.Y.H. and J.B.Y. conceived the project, designed the study, and interpreted the results. Q.Y.H. and R.H. contributed to sample collection and clinical data collection. W.H.Y. and F.H.W. performed the data analysis and prepared the figures. Q.Y.H., Q.W., X.H.L., T.Y.L., and S.Q.Y. wrote the manuscript. Q.A. and W.X.Z checked and embellished the figures. C.L., J.B.Y, and Q.Y.H. jointly supervised this work. All authors reviewed and approved the final manuscript.

Funding

This work was supported by the following grants: National Natural Science Foundation of China (82403773), Postdoctoral Fellowship Program of CPSF (GZB20230041, 2024M760140), Shandong Provincial Natural Science Foundation (ZR2021QH006), National Natural Science Foundation of China (Grant No. 82272753), Shandong Provincial Natural Science Foundation (ZR2021LZL002), Bethune Cancer Radiotherapy Translational Medicine Research Fund (flzh202103), and The Key Research and Development Program of Shandong (Major Science & Technology Innovation Project) (2021SFGC05012021).

Data availability

Data is provided within the manuscript or supplementary information files.

Declarations

Ethics approval and consent to participate

The present study was approved by Shandong Cancer Hospital and Institute (Jinan, China). All patients provided written informed consent.

Consent for publication

All the authors have read and approved the final manuscript for publication.

Competing interests

The authors declare no competing interests.

Received: 28 August 2024 Accepted: 20 January 2025
Published online: 03 February 2025

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