

Perioperative inflammation, anesthesia modulation and cellular signaling in lung cancer: an integrated transcriptomic and single-cell analysis

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Background: Patients undergoing lung cancer surgery experience significant systemic inflammatory responses and anesthetic interventions during the perioperative period, which can affect immune status and the tumor microenvironment. Different anesthetic techniques variably regulate inflammation, cytokine signaling, and tissue protection. It remains unclear, however, whether perioperative inflammatory signals leave identifiable molecular patterns at the tissue level. Furthermore, analyses integrating multi-layered data are currently lacking. We performed an integrated transcriptomic and single-cell analysis to identify shared molecular patterns linking perioperative inflammation, anesthetic modulation, and the lung cancer tumor microenvironment, and to localize these pathways to specific cellular communication axes.

Methods: Integrated analysis was performed across three levels using publicly available transcriptomic data: peripheral blood, myocardial tissue, and single-cell data from lung cancer. Peripheral blood data delineated acute inflammatory features, identified differentially expressed genes, and performed pathway enrichment to construct a risk score reflecting inflammatory burden. Paired myocardial tissue samples were compared to assess pathway alterations before and after anesthesia with propofol versus sevoflurane, evaluating the directional influence of the anesthetic regimen on inflammation-related regulation. Cell annotation and composition statistics were then performed on single-cell data from lung cancer and adjacent tissues. This analysis localized the cellular origins of major pathways and reconstructed cell communication networks from ligand-receptor interactions to identify signaling hub cells and key communication axes.

Results: Analysis of peripheral blood revealed enrichment in autophagy, protein processing, and inflammatory pathways. The risk score increased progressively across the Healthy, D1 sepsis, and D2 sepsis groups, reflecting the intensity of the acute inflammatory response. A comparison of anesthesia methods showed that samples from both groups exhibited enrichment in cytokine signaling and inflammatory pathways, though the specific genes involved, the degree of enrichment, and the regulatory patterns differed. In the single-cell data, T cells, natural killer (NK) cells, and macrophages constituted the major cell populations, with inflammatory and immune-related pathways active across multiple cell types. CellChat analysis revealed that macrophages/monocytes and epithelial/endothelial cells participated in dense communication networks characterized by antigen-presentation-related interactions [human leukocyte antigens (HLA) class I and II signaling with CD8A and CD4] and extracellular matrix-associated interactions (FN1- and collagen-based signaling through integrins, CD44, and syndecans), distinguishing tumor tissue from adjacent normal lung tissue. Signals related to MHC, FN1, and COLLAGEN were enhanced in tumor tissue, where multiple ligand-receptor pairs demonstrated high communication probabilities.

Conclusions: A continuous transcriptional link connects acute inflammation, anesthetic techniques, and the tumor microenvironment. Within lung cancer tissues, monocytes/macrophages, T cells, and epithelial cells primarily mediate the pathways regulated by inflammation and anesthesia, establishing a communication network via antigen presentation, cell adhesion, and matrix-related signaling. These results offer a molecular foundation for understanding how perioperative management relates to the lung cancer immune microenvironment.

Keywords: Lung cancer; perioperative inflammation; anesthesia; single-cell RNA sequencing; cell communication

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Introduction

Lung cancer remains a leading cause of global cancer incidence and mortality (1,2). For patients with early-to mid-stage non-small cell lung cancer (NSCLC), surgical resection continues to offer a primary curative intervention (3). While refinements in surgical technique and perioperative care have reduced perioperative mortality (4,5), postoperative recurrence and poor long-term survival persist as major clinical concerns (6). Emerging evidence indicates that tumor resection triggers not only a local intervention but also profound systemic effects, including inflammatory responses, immune remodeling, and physiological stress. These systemic alterations may subsequently influence long-term outcomes by affecting residual disease, circulating tumor cells, and micrometastatic foci (7). Perioperative anesthetic management constitutes a key element within this period (8,9). Various anesthetic

agents and techniques differentially modulate immune cell function, inflammatory pathways, and tissue injury responses. However, a systematic understanding of whether anesthetic modulation during the perioperative period correlates with specific transcriptomic pathway-level alterations in the tumor microenvironment of lung cancer patients is still lacking.

Under perioperative stress and critical illness, the body can mount an acute systemic inflammatory response akin to sepsis, marked by rapid immune cell activation, cytokine release, and the initiation of multiple inflammatory pathways in peripheral blood (10,11). Transcriptomic studies have identified in the peripheral blood of sepsis patients a set of molecular signatures linked to disease severity and prognosis (12). These signatures frequently implicate pathways involving cytokine-receptor interactions, innate immune receptors, metabolic stress, and protein processing (13). Such acute inflammatory risk profiles serve as an extreme model of perioperative inflammatory responses, helping to pinpoint a core set of pathways and gene sets that are highly sensitive to systemic inflammation. During major surgeries like cardiac surgery, myocardial tissue undergoes substantial transcriptional changes in response to ischemia, reperfusion, and inflammatory stimuli (14). The anti-inflammatory, antioxidant, and myocardial-protective effects of intravenous anesthetics such as propofol and volatile agents like sevoflurane are not uniform. However, most current investigations are confined to a single drug, a single time point, or a single tissue marker, lacking systematic transcriptomic pathway comparisons between different anesthetic approaches (15,16).

The tumor microenvironment in lung cancer comprises diverse cell types, including tumor cells, T cells, natural killer (NK) cells, macrophages, monocytes, neutrophils,

Highlight box

Key findings

- This study identifies shared inflammatory and immune signaling pathways linking perioperative inflammation, anesthesia modulation, and the lung cancer microenvironment.

What is known and what is new?

- Perioperative inflammation and anesthesia are known to affect immunity.
- This study newly maps their transcriptomic signatures onto specific cellular and communication networks in lung cancer tissue.

What is the implication, and what should change now?

- Perioperative management should consider its potential impact on tumor immune ecology, supporting the integration of immune and molecular endpoints in future cancer surgery research.

endothelial cells, and fibroblasts (17,18). These cells interact via cytokines, chemoattractants, co-stimulatory molecules, and extracellular matrix components, which collectively shape the local immune landscape and influence therapeutic outcomes (19-21). Single-cell transcriptomics now permits a cellular-resolution dissection of this microenvironment, enabling the discrimination of immune cell subsets, the identification of heterogeneous myeloid populations, and the inference of cell-cell communication through ligand-receptor analysis (22). Few studies have connected systemic inflammatory risk signals or the regulatory effects of anesthetic modalities on tissue pathways to specific cell types and communication networks within this microenvironment. It remains unclear whether perioperative inflammation-related molecular pathways, potentially modulated by anesthetic management, are consistently reflected in the transcriptomic landscape and cellular interactions of lung cancer tissue (23).

To test whether perioperative inflammation-associated transcriptomic pathways, potentially influenced by anesthetic modalities, are linked to specific cellular and molecular features of the lung cancer tumor microenvironment, we integrated multiple publicly available transcriptomic datasets. We hypothesized that core inflammatory pathways identified from acute systemic inflammatory states would overlap with anesthesia-modulated tissue transcriptomic pathways and would be preferentially mapped to specific immune and stromal cell populations and communication networks within the lung cancer microenvironment. Using peripheral blood transcriptomic data as a model of acute systemic inflammation, we identified core inflammatory risk pathways and gene signatures, constructing a risk score to characterize the intensity of the inflammatory response. A comparison of myocardial transcriptomes before and after anesthesia revealed the differential regulatory effects of propofol and sevoflurane on these pathways, illustrating how distinct anesthetic methods directionally alter inflammation-, cytokine-, and metabolism-related pathways. In single-cell transcriptomic data from lung cancer and adjacent tissues, we annotated major immune and structural cell types and analyzed their composition. The inflammatory risk and anesthetic modulation pathways were then mapped onto these specific cell populations. Using ligand-receptor information, we reconstructed cell-cell communication networks to identify key interacting pairs and signaling axes that may mediate these processes. This multi-level integrative analysis establishes molecular connections across systemic inflammation, anesthetic methods, and the lung

cancer tumor microenvironment, providing transcriptomic evidence for understanding how perioperative management may influence tumor microenvironment remodeling. Accordingly, the following analyses were designed to examine this concept stepwise, from systemic inflammatory signatures to tissue-level anesthetic modulation and finally to cell-type-specific communication networks. We present this article in accordance with the STREGA reporting checklist (available at <https://tlcr.amegroups.com/article/view/10.21037/tlcr-2026-1-0022/rc>).

Methods

Data source and preprocessing

All data were obtained from the public Gene Expression Omnibus (GEO, <https://www.ncbi.nlm.nih.gov/geo/>) database. Peripheral blood transcriptomic data originated from the GSE137340 dataset, which contains samples from healthy individuals and from sepsis patients at day 1 (D1) and day 2 (D2) of diagnosis. These data were generated on the GPL20301 platform. Myocardial tissue transcriptomic data were selected from the GSE4386 dataset of coronary artery bypass grafting (CABG) procedures, comprising paired pre- and post-operative samples from patients under either propofol or sevoflurane anesthesia on the GPL570 platform. Single-cell RNA sequencing (scRNA-seq) data were derived from lung tissue, encompassing both tumor and adjacent normal samples. The raw expression matrices and corresponding annotation files for all datasets were downloaded directly from GEO. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

Raw expression matrices for bulk transcriptomic data were downloaded, and platform annotation files were used to convert probe IDs to gene symbols. When multiple probes corresponded to a single gene, their average expression value represented that gene's expression level. Background correction and normalization were applied, and the bulk data were log₂-transformed. Genes with low expression were filtered out, requiring expression above a defined threshold in at least a subset of samples. For microarray data, normalization was performed using the RMA (Robust Multi-array Average) algorithm or comparable methods, and batch effects were assessed. For scRNA-seq data, raw count matrices were imported, and low-quality cells and lowly expressed genes were filtered based on criteria such as a minimum number of detected

genes per cell and a maximum threshold for mitochondrial gene content. Normalization was applied, and highly variable genes were selected for subsequent analysis. Integration methods corrected inter-sample differences to construct a unified expression space, forming the basis for downstream dimensionality reduction and clustering. All source data are publicly available, and no additional ethical approval was required. Download links and platform information are provided on the respective GEO data pages.

Differential analysis and pathway enrichment

Bulk transcriptome differential analyses were conducted in R. For the GSE137340 dataset, we constructed a design matrix with group as the independent variable and fitted linear models with the limma package to identify differentially expressed genes (DEGs). Significance testing employed moderated t-statistics, with P values adjusted for multiple comparisons via the Benjamini-Hochberg method. DEGs were filtered according to thresholds for absolute log2 fold change and adjusted P value. The paired pre- and post-operative design of the GSE4386 dataset required the inclusion of a pairing factor in its linear model. We performed separate pre- versus post-operative comparisons for the propofol and sevoflurane groups, generating independent DEG lists. Functional enrichment analyses were then performed on these DEGs. Kyoto Encyclopedia of Genes and Genomes (KEGG) over-representation analysis (ORA) using the hypergeometric test was applied separately to up- and downregulated gene sets. Significant pathways were selected based on gene set size and adjusted P value, with pathway gene sets obtained from the KEGG database and analyses executed using the clusterProfiler package. Gene Set Enrichment Analysis (GSEA) was performed on pre-ranked gene lists ordered by test statistics or regression coefficients. Utilizing the GSEA function in clusterProfiler with defined upper and lower gene set size limits, we obtained enrichment results through permutation testing and applied false discovery rate (FDR) correction. All enrichment analyses used a unified pathway background with names and identifiers sourced from the official KEGG database.

Single-cell data processing, annotation, and cellular composition

Single-cell transcriptomic analysis was conducted using the Seurat framework. Raw unique molecular identifier (UMI)

count matrices were imported and subjected to quality control for both cells and genes. Cells were filtered based on thresholds for the minimum number of detected genes and the maximum proportion of mitochondrial reads. The remaining cells were normalized, and highly variable genes were selected for downstream modeling. Dimensionality reduction was performed via principal component analysis (PCA). A nearest-neighbor graph was built from these principal components, and cell clusters were identified by graph-based clustering at a defined resolution. Two-dimensional embeddings for visualization were generated using Uniform Manifold Approximation and Projection (UMAP) with default parameters for neighborhood size and minimum distance. To integrate multiple samples, anchors were used to correct for batch effects, aligning all samples within a common low-dimensional space. Cell types were annotated according to established marker genes. For every cluster, the most highly expressed genes were compiled and cross-referenced with canonical markers from published literature to assign identities. This annotation was validated against multiple independent marker sets covering lymphocytes, myeloid cells, epithelial cells, endothelial cells, and smooth muscle cells. Finally, the absolute counts and relative proportions of each annotated cell type were quantified per sample and summarized in tables and bar charts.

Pathway localization and cell communication analysis

Based on the annotation results, expression matrices were extracted for each cell type. Differential expression analysis was conducted for each type, and the resulting gene sets were filtered using a uniform threshold for subsequent enrichment. KEGG enrichment analysis was then performed separately for each cell type using the clusterProfiler package, with gene set size ranges and adjusted P value thresholds configured to retain significant pathways. The final output included pathway names, counts of involved genes, and associated significance metrics.

Cell communication was analyzed with the CellChat tool using a ligand-receptor database. The analysis required annotated cell types and an expression matrix as input. Communication probabilities and interaction strengths between cell pairs were derived from ligand and receptor expression levels, with significance assessed via permutation testing. The results comprised the overall communication network, matrices of sending and receiving relationships, and pathway-specific summaries. For each cell pair, we quantified the number of interactions and their average

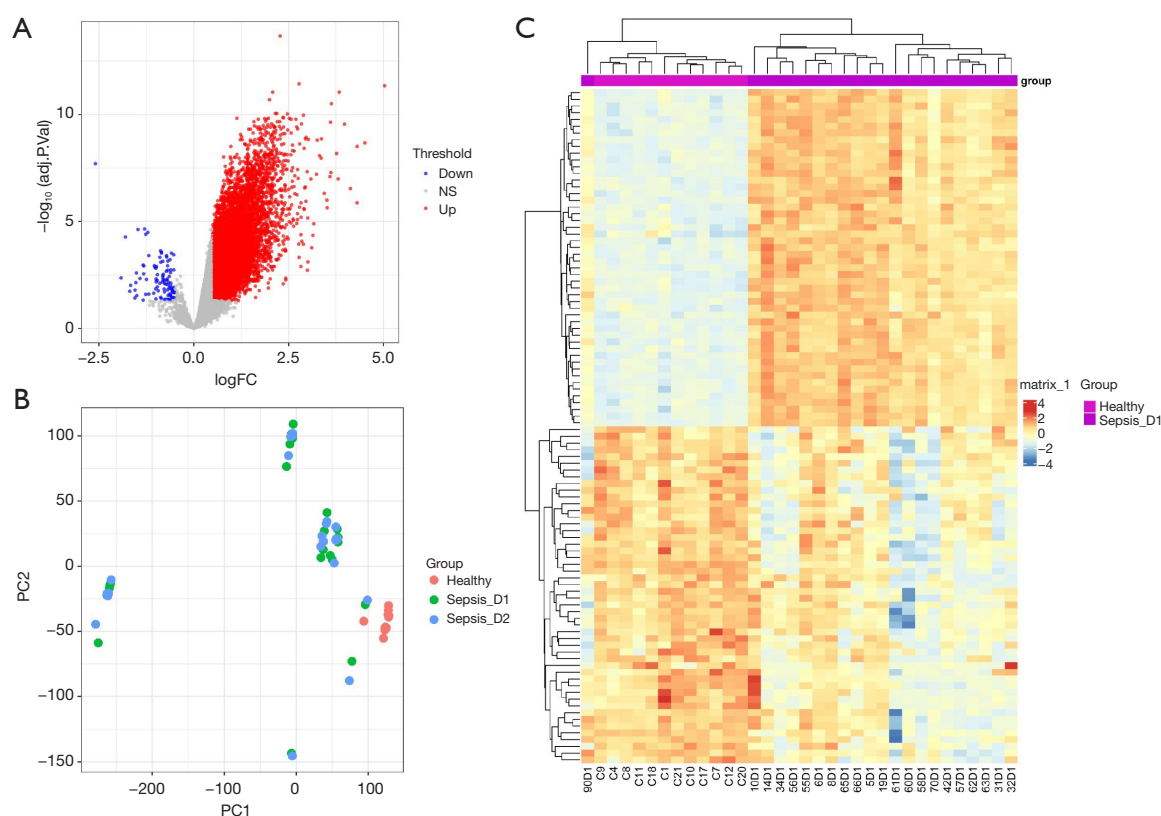


Figure 1 Overall sample distribution and expression patterns. (A) Differential gene expression distribution across groups. (B) Principal component analysis showing group separation. (C) Heatmap of high-variable genes indicating distinct expression patterns across Healthy and D1 groups. FC, fold change; NS, not significant.

strength, visualizing these data in heatmaps and network diagrams. At the pathway level, interactions were grouped into signaling families, including antigen presentation, cell adhesion, and matrix-associated signals to generate clustering matrices. Finally, we identified significant ligand-receptor pairs and presented them in bubble charts that detail the source cells, target cells, communication probabilities, and statistical significance.

Statistical analysis

All statistical analyses were performed using R. Continuous variables were compared between groups with either *t*-tests or non-parametric tests, depending on data distribution, while categorical variables were assessed using the chi-square test or Fisher's exact test. The Benjamini-Hochberg method controlled the false discovery rate for multiple comparisons. Enrichment, differential, and communication analyses were conducted as two-sided tests, with a uniform significance

threshold applied throughout. All figures were generated in R.

Results

Data quality control and sample distribution

Analysis of the publicly available transcriptomic dataset GSE137340 included peripheral blood samples from 23 D1 sepsis patients, 22 D2 sepsis patients, and 12 healthy controls. A volcano plot comparing the D1 sepsis and healthy control groups revealed DEGs (Figure 1A). Most DEGs were upregulated, producing a distinctly right-skewed distribution that indicates widespread transcriptional activation during early sepsis. Downregulated genes were fewer and primarily occupied the left low-expression region, while neutral genes clustered near the plot's center, yielding a clear differential expression pattern. PCA reduced the dimensionality of the gene expression matrix for all samples. In the space defined by the first two principal components (PC1 and PC2), the three sample types formed relatively

distinct clusters (*Figure 1B*). D1 sepsis samples were generally distant from the healthy controls, concentrating on the opposite side. D2 sepsis samples were positioned between the other two groups, though closer to the D1 group, which suggests a persistent inflammatory activation state at the D2 time point with a partial shift of some samples toward the healthy phenotype. The three groups exhibited clear boundaries in the principal component space, characterized by small within-group and large between-group variation.

Expression patterns were further examined at the gene level. A clustered heatmap of the top 50 differentially expressed genes provided a horizontal comparison between D1 sepsis and Healthy samples (*Figure 1C*). In the Healthy group, these genes generally showed low to moderate expression, while their expression was broadly elevated in the D1 sepsis group, forming large areas of high-expression color blocks. Hierarchical clustering divided the samples into two major clusters: one consisted almost entirely of Healthy samples, and the other was primarily composed of D1 sepsis samples. A few samples were located at the boundary but did not show significant intermixing. Gene clustering similarly revealed two stable modules, with the upper module containing genes significantly upregulated in D1 sepsis and the lower module comprising genes maintaining relatively low expression in Healthy samples. These results indicate stable and extensive differences in the peripheral blood transcriptome between sepsis patients and healthy controls within this dataset.

Differential expression and enrichment analysis

To characterize core transcriptomic features of acute systemic inflammation, we performed pathway enrichment analysis on the DEGs from the D1 sepsis versus Healthy comparison, focusing on functional modules linked to upregulated genes. GSEA revealed the prominent enrichment of several pathways involved in protein quality control and cellular autophagy, namely autophagy, lysosome, endoplasmic reticulum protein processing, and ubiquitin-mediated proteolysis (*Figure 2A*). These pathways showed a consistent upregulation trend in the D1 sepsis group, with high enrichment scores. Pathways related to cytokine-cytokine receptor interaction and Toll-like receptor signaling, which are central to inflammation regulation and cytokine signaling, also ranked near the top of the enrichment list and displayed high normalized enrichment score (NES) values. This pattern indicates

a synchronized activation of inflammation-related gene clusters under infectious conditions.

Further examination of the GSEA enrichment plot revealed significant enrichment in multiple neurodegenerative disease-related pathways, including prion disease, Huntington's disease, and Parkinson's disease (*Figure 2B*). These pathways do not represent the diseases themselves but indicate a common upregulation of genes involved in protein folding, misfolding, and aggregation during sepsis. This pattern was stable within the differentially expressed gene set, where a core group of genes repeatedly participated in multiple functional modules. The finding suggests that the pathway enrichment arises from relatively concentrated, rather than discrete, changes in gene expression. A representative GSEA enrichment curve illustrating the enrichment pattern of an individual pathway is shown in *Figure 2C*.

To further validate the directionality of pathway enrichment, we performed KEGG ORA on the differentially expressed genes and screened for significant entries (*Figure 3*). The enrichment list prominently featured pathways related to protein processing, lysosomal function, and metabolic regulation, including lysosome, protein processing in endoplasmic reticulum, and various metabolic pathways. Inflammation- and host defense-related pathways, such as antigen processing and presentation and the complement and coagulation cascades, were also significantly enriched. Significant infection-related pathways included *Staphylococcus aureus* infection and pathogenic *Escherichia coli* infection. These pathways share a common involvement in immune recognition, inflammatory response, and pathogen handling, indicating a broad activation of these mechanisms during sepsis. Integrating the GSEA and ORA results revealed three prominent enrichment themes: a significant enhancement of protein processing and quality control processes; a general upregulation of cellular degradation mechanisms like autophagy and lysosomal function; and a global elevation in the expression of inflammatory signaling, cytokine-receptor interactions, and infection defense systems. These pathways are interconnected through overlapping genes and functional relationships, forming a coherent profile that helps explain the D1 sepsis state.

Construction of risk score and intergroup trends

After constructing a risk score from differentially expressed genes, we compared the three sample groups: Healthy, D1

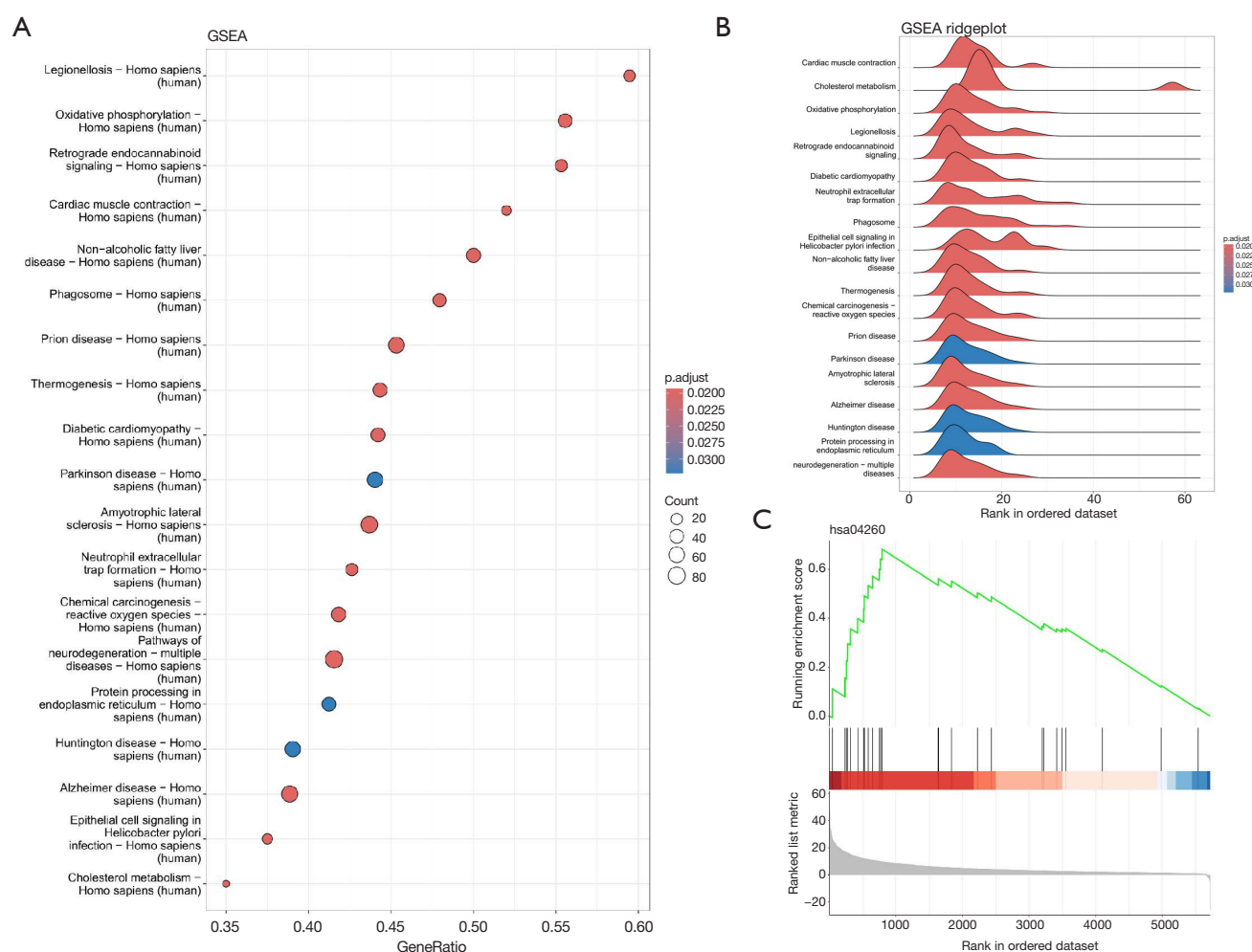


Figure 2 GSEA enrichment of differentially expressed genes. (A) Representative pathways. (B) GSEA enrichment plots. (C) Representative GSEA enrichment curve for the cardiac muscle contraction pathway. GSEA, Gene Set Enrichment Analysis.

sepsis, and D2 sepsis. The Healthy group exhibited the lowest overall risk scores, with a distribution concentrated in a low range and sample points densely clustered around the median (*Figure 4A*). In contrast, the D1 sepsis group showed generally elevated scores, with all sample points above the Healthy group's range and a pronounced upward shift in the median. The dispersion range also increased, with some samples reaching the highest interval. Risk scores for the D2 sepsis group were intermediate, higher than the Healthy group but slightly lower than the D1 group. Although the median decreased, most samples remained in a higher interval, indicating incomplete recovery. A mean trend plot further revealed a continuous pattern of change across the three groups (*Figure 4B*). The mean score was lowest in the Healthy group, rose significantly in the D1

group, and was slightly lower in the D2 group than in D1, while remaining above the Healthy level, forming a progressive trend from Healthy to D1 to D2. The error ranges around the means indicated greater score variability in the D1 and D2 groups compared to the Healthy group, consistent with the observed dispersion. This pattern demonstrates that the risk score reflects differences in sample status, markedly increasing from the normal to the acute inflammatory state and showing a partial decline during inflammatory remission.

Differential effects of anesthetic modalities on molecular responses in myocardial tissue

To assess whether inflammation-associated pathways

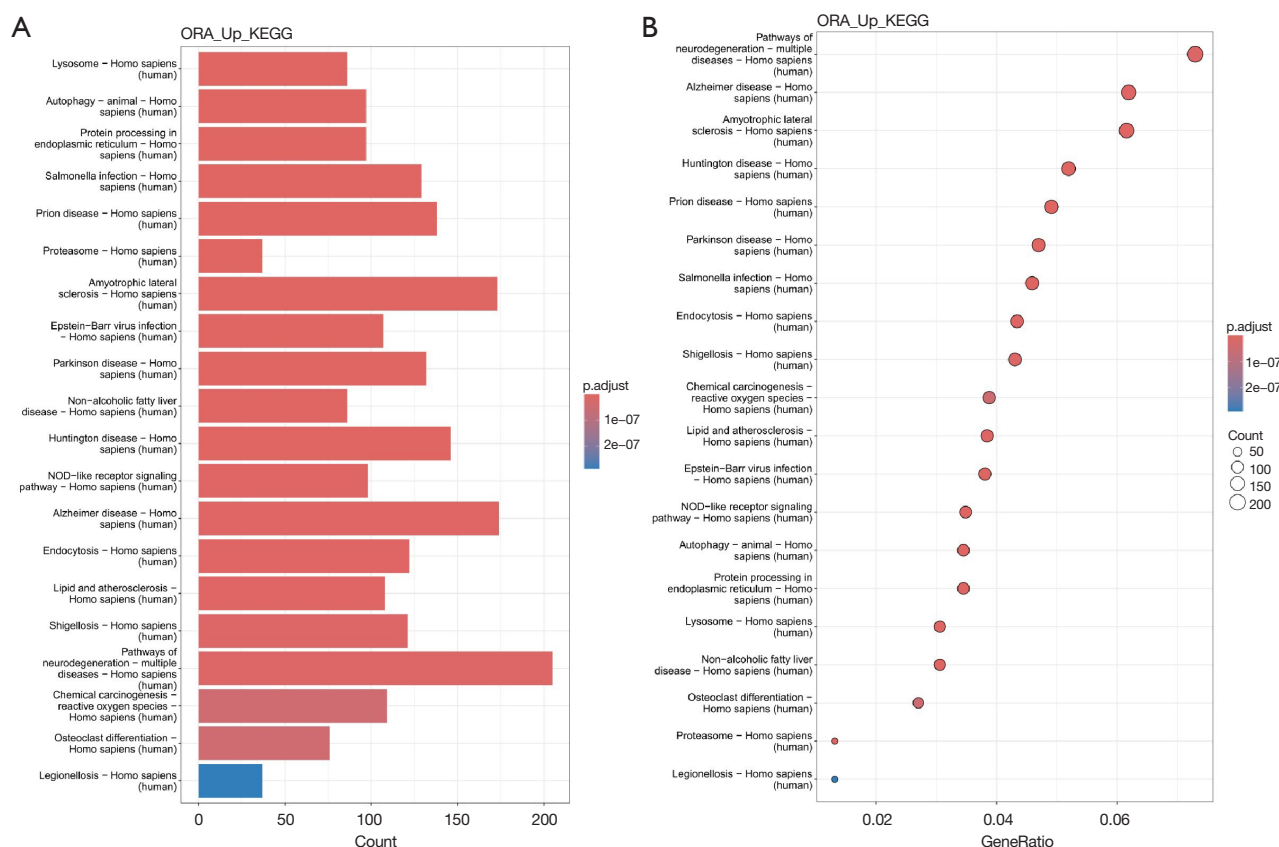


Figure 3 KEGG ORA of upregulated genes in D1 sepsis. (A) Bar plot of the top enriched KEGG pathways ranked by gene count. (B) Dot plot of the same pathways showing gene ratio, gene count, and adjusted P value. KEGG, Kyoto Encyclopedia of Genes and Genomes; ORA, over-representation analysis.

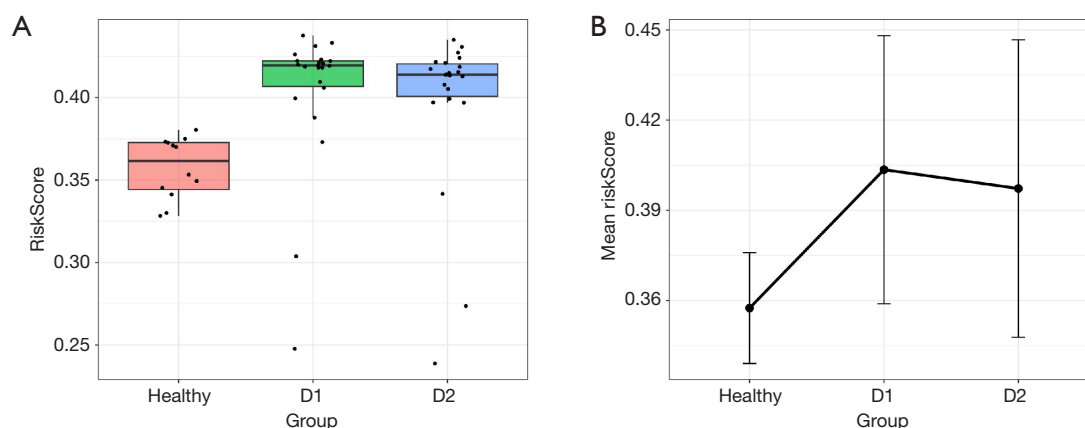


Figure 4 Risk score distribution and trends across groups. (A) Risk score differences among Healthy, D1 sepsis, and D2 sepsis. (B) Mean value trend.

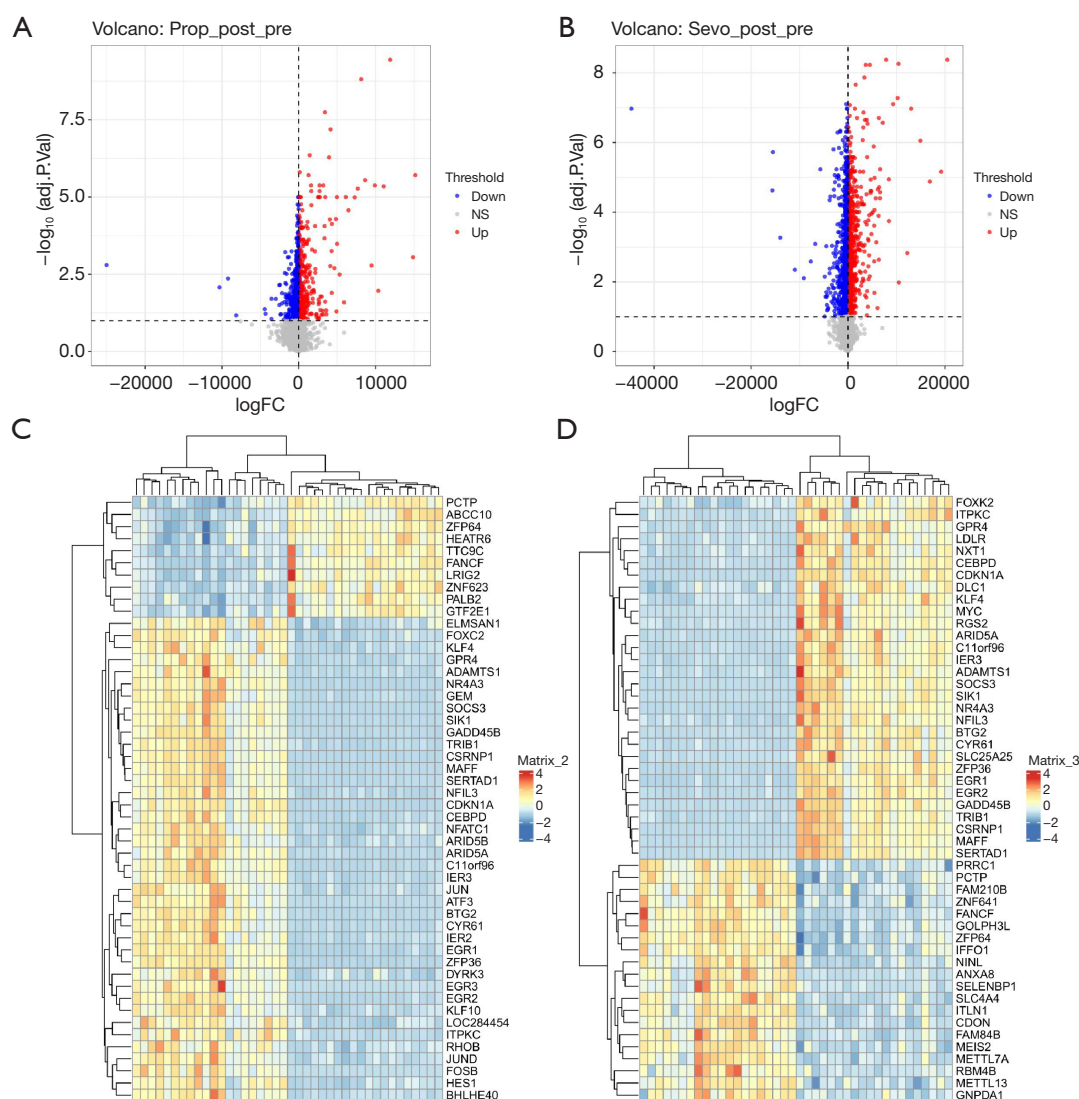


Figure 5 Differential expression patterns before and after anesthesia. (A) Volcano plot for propofol (post *vs.* pre). (B) Volcano plot for sevoflurane (post *vs.* pre). (C) Heatmap of representative genes in the Propofol group. (D) Heatmap of representative genes in the Sevoflurane group. FC, fold change; NS, not significant.

identified in the sepsis analysis are modulated at the tissue level by anesthetic techniques, transcriptional profiles of myocardial tissue in the GSE4386 dataset from a CABG study were compared between preoperative and postoperative states for patients receiving either propofol or sevoflurane anesthesia. The volcano plot for the propofol group (postoperative versus preoperative) showed that surgery and anesthesia altered the expression of numerous genes, with a slight predominance of upregulated over downregulated genes. This pattern indicates substantial transcriptional reprogramming in myocardial tissue

under the combined effects of propofol and surgical stress (Figure 5A). Similarly, the sevoflurane group comparison revealed broad changes in gene expression postoperatively, with a relatively even distribution of upregulated and downregulated genes. The overall scale of change was comparable to the propofol group, though the specific genes affected and their magnitudes of change differed (Figure 5B). A heatmap was constructed using the most differentially expressed genes. For the propofol group, representative genes formed two distinct expression patterns that clearly separated preoperative from postoperative samples, with

one set showing consistently high postoperative expression and another showing overall reduction. Cluster analysis demonstrated good aggregation of samples within each condition (Figure 5C). The sevoflurane group heatmap displayed upregulation and downregulation patterns for a different gene set, which also effectively distinguished the preoperative and postoperative states (Figure 5D). These results suggest that both anesthetic regimens induce large-scale remodeling of myocardial gene expression, but the specific genes and expression patterns involved are distinct.

GSEA evaluated pathway-level changes between postoperative and preoperative states. In the propofol group, multiple inflammation- and cytokine-related pathways were enriched postoperatively, such as the IL-17 signaling pathway, cytokine-cytokine receptor interaction, TNF signaling pathway, NF- κ B signaling pathway, and MAPK signaling pathway. The NES values for these pathways were primarily positive and all achieved statistical significance (Figure 6A). The enrichment plot for the *Staphylococcus aureus* infection pathway displayed an overall downward shift, with corresponding genes enriched toward lower-ranked positions postoperatively, indicating a reduction in the expression of genes involved in bacterial infection response (Figure 6B). In contrast, the enrichment plot for the IL-17 signaling pathway exhibited a pronounced upward trend, with key associated genes clustered at the leading edge, reflecting an overall postoperative enhancement in the expression of genes within this pathway (Figure 6C). Under propofol anesthesia, gene sets linked to cytokine signal transduction and inflammatory regulation in myocardial tissue showed an overall activation trend, while gene sets related to specific bacterial infection responses and ribosomes were relatively suppressed.

GSEA of the sevoflurane group further implicated multiple inflammation- and immune-related pathways in the postoperative transcriptional response (Figure 6D). Pathways including cytokine-cytokine receptor interaction, TNF signaling, and IL-17 signaling also exhibited positive NES. Their enrichment strength and rank order, however, differed from those observed in the propofol group. Pathways such as *Staphylococcus aureus* infection and ribosome showed negative NES values, with generally descending enrichment curves that indicated an overall postoperative reduction in the expression of their constituent genes. For example, the enrichment curve for cytokine-cytokine receptor interaction displayed a pronounced upward shift, with the majority of its core enrichment genes ranking near the top, suggesting this pathway's activity was enhanced

following sevoflurane anesthesia and surgery (Figure 6E). Integrating the results from both anesthetic groups indicates that both regimens activate a suite of inflammatory and cytokine signaling pathways while suppressing those related to ribosomal function and bacterial infection response in myocardial tissue. The differential enrichment strength of specific pathways and variations in their core gene sets, however, imply that the two anesthetics exert distinct molecular regulatory patterns (Figure 6F).

Cellular composition and distribution of major cell types at the single-cell level

UMAP was applied to the integrated single-cell transcriptomic dataset to visualize the global distribution of all cells in a low-dimensional space. When colored by sample ID, the cells were intermingled, with no sample forming an isolated block, indicating controlled batch effects and a satisfactory overall integration (Figure 7A). Cells from Group A (adjacent) and Group T (tumor) showed an interdigitated distribution with substantial overlap, differing only in their proportions within a few peripheral clusters (Figure 7B). Unsupervised clustering resolved 27 distinct clusters, each occupying a relatively independent region in the UMAP plot (Figure 7C). These clusters were annotated as major cell types, including T cells, NK cells, macrophages, monocytes, neutrophils, endothelial cells, epithelial cells, smooth muscle cells, and B cells based on canonical marker gene expression (Figure 7D). Spatially, T cells and NK cells populated the two largest contiguous areas. Macrophages, monocytes, and neutrophils were primarily located in clusters near the bottom and left side, while endothelial and smooth muscle cells were mostly concentrated in peripheral clusters. Epithelial cells and B cells occupied relatively smaller regions, with clear boundaries between cell types and good internal continuity within each type.

The cellular composition of each sample was quantified and statistically compared. T cells represented the predominant population across all samples, followed by NK cells and macrophages. Neutrophils and monocytes were present at moderate levels, whereas endothelial cells, epithelial cells, smooth muscle cells, and B cells were observed in relatively low proportions (Figure 8A). While variations in cellular proportions existed between samples, such as markedly elevated NK cells in some and relatively high macrophages in others, the overall compositional pattern remained consistent. To visualize these differences

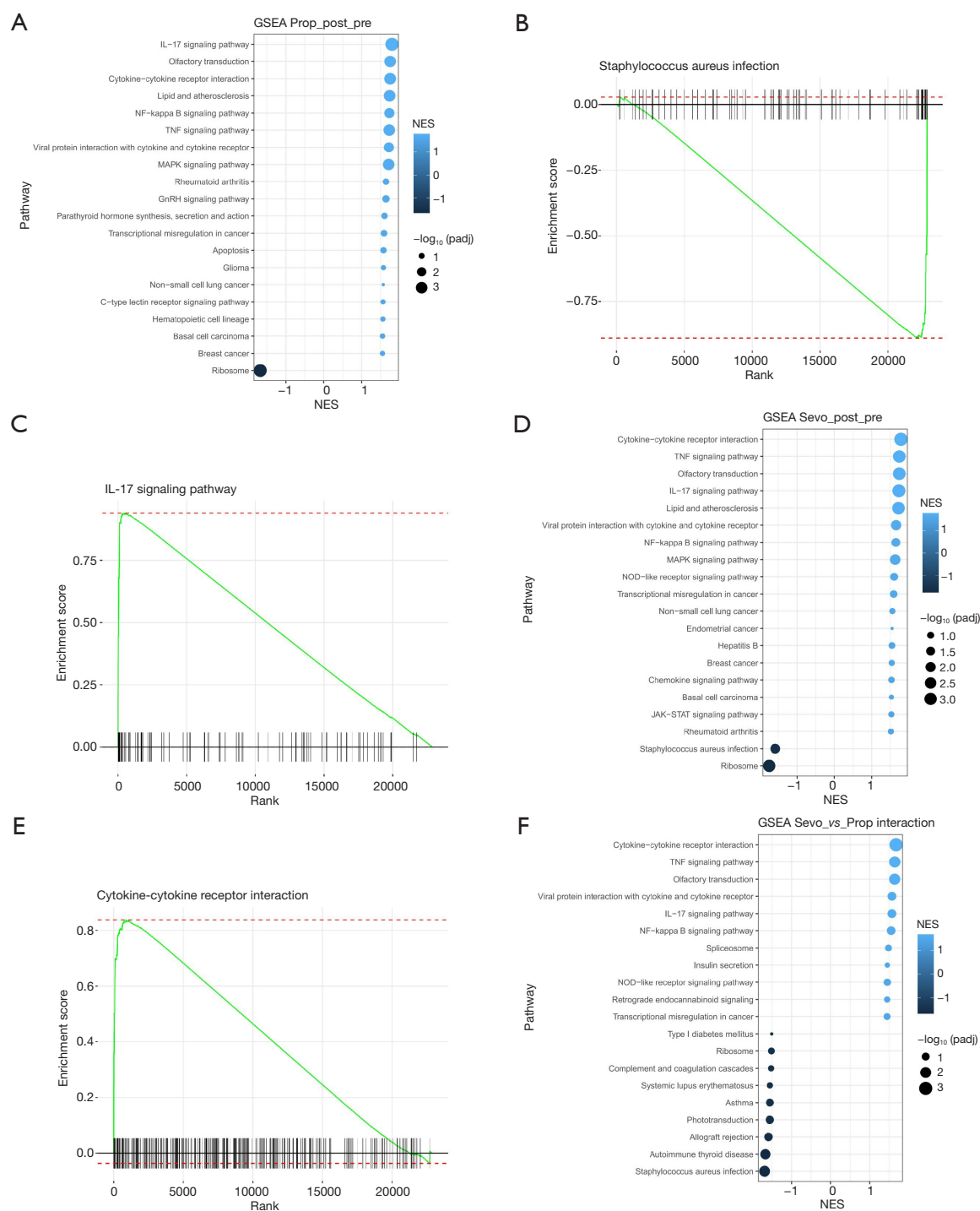


Figure 6 GSEA pathway enrichment before and after anesthesia. (A) KEGG pathways enriched in the propofol group (post *vs.* pre). (B) Enrichment plot for the *Staphylococcus aureus* infection pathway in the propofol group. (C) Enrichment plot for the IL-17 signaling pathway in the propofol group. (D) KEGG pathways enriched in the sevoflurane group (post *vs.* pre). (E) Enrichment plot for the cytokine-cytokine receptor interaction pathway in the sevoflurane group. (F) Differential GSEA enrichment comparison between the sevoflurane and propofol groups. GSEA, Gene Set Enrichment Analysis; KEGG, Kyoto Encyclopedia of Genes and Genomes; NES, normalized enrichment score.

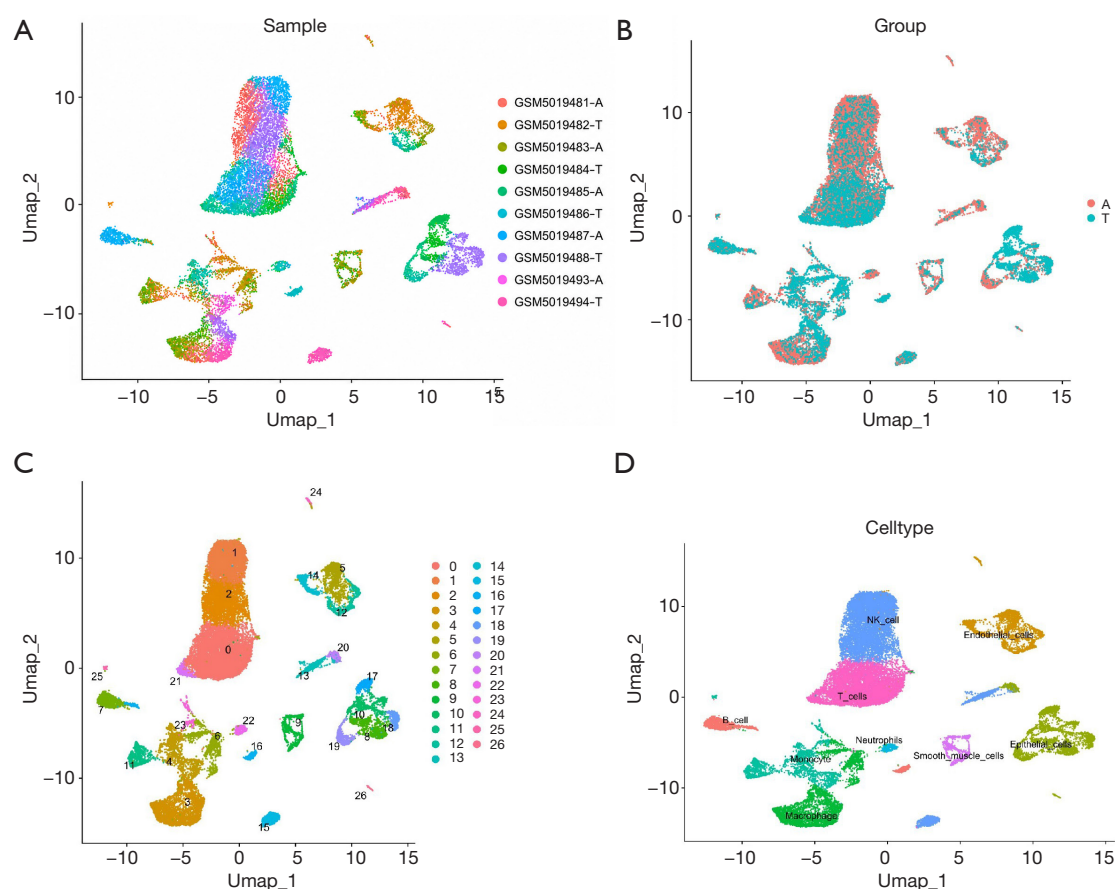


Figure 7 Single-cell distribution and cell type annotation. (A) UMAP colored by sample ID. (B) UMAP colored by group (A vs. T). (C) Unsupervised clusters. (D) Annotated cell types. A, adjacent; T, tumor; UMAP, Uniform Manifold Approximation and Projection.

more intuitively, a heatmap was generated with cell types as rows and samples as columns (*Figure 8B*). In this heatmap, the rows for T cells and NK cells displayed darker shades in most samples, while the macrophage row showed isolated high-value blocks. Rows corresponding to endothelial cells, epithelial cells, and B cells were generally light, reflecting their minor contribution to the overall composition. These results indicate that the samples were predominantly composed of lymphocytes and myeloid cells, with other cell types being quantitatively minor.

Enrichment distribution of pathways across different cell types

Based on annotated cell types, we performed KEGG enrichment analysis on the differentially expressed genes from each major cluster. The results are summarized in a pathway-cell type map (*Figure 9*), where the x-axis denotes

the nine cell types and the y-axis shows the enriched KEGG pathways. Bubble size represents the number of genes involved in a given pathway, while color intensity corresponds to the adjusted significance level. Overall, the five immune cell types, macrophages, monocytes, neutrophils, T cells, and NK cells, exhibited the highest number and most densely distributed enriched pathways. Endothelial and epithelial cells followed, whereas smooth muscle cells and B cells showed relatively fewer pathways and lower significance. The multi-row continuous distributions of cell types along the y-axis indicate that most pathways were not restricted to a single cell type but were concurrently enriched across multiple immune subsets.

From a specific pathway distribution perspective, pathways involving inflammatory factors and immune receptors were concurrently observed in T cells, NK cells, macrophages, monocytes, and neutrophils. For example, pathways including cytokine-cytokine receptor

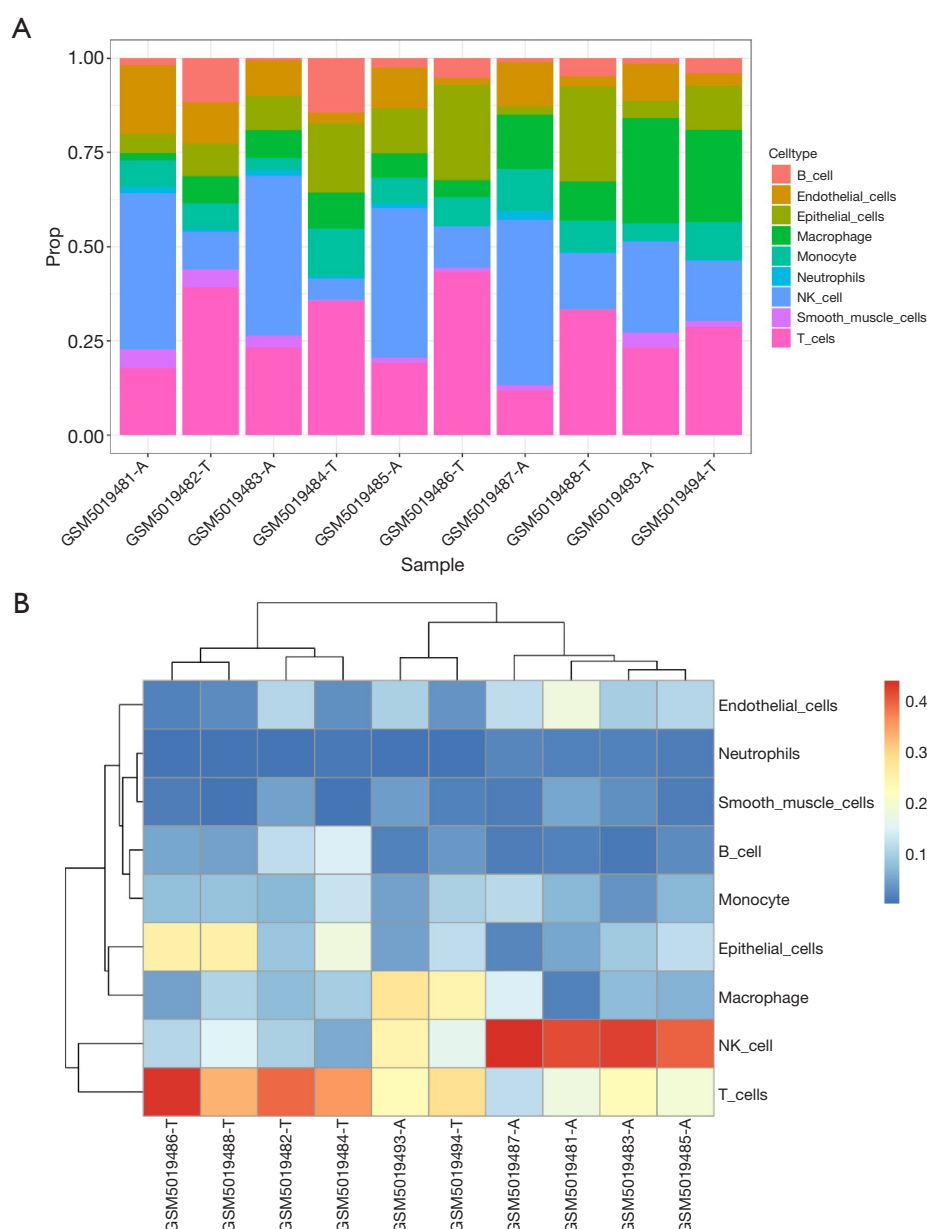


Figure 8 Cell composition and proportion heatmap across samples. (A) Stacked bar plot of cell type proportions. (B) Heatmap of relative proportions for each cell type across samples.

interaction, chemokine signaling, NF- κ B signaling, JAK-STAT signaling, and Toll-like receptor signaling were all significantly enriched in these cell types, indicating their collective involvement in inflammatory signal transduction and cytokine network regulation. Pathways associated with pathogen response, such as various KEGG entries for bacterial and viral infections, showed a more concentrated and pronounced enrichment pattern in macrophages,

neutrophils, and monocytes; although fewer in number, these pathways were still widely distributed in T cells and NK cells. Pathways related to metabolism and oxidative stress, such as those for lipid metabolism, carbohydrate metabolism, and reactive oxygen species, were more densely enriched in macrophages and neutrophils, suggesting a greater degree of gene involvement in metabolic reprogramming and reactive oxygen species handling within

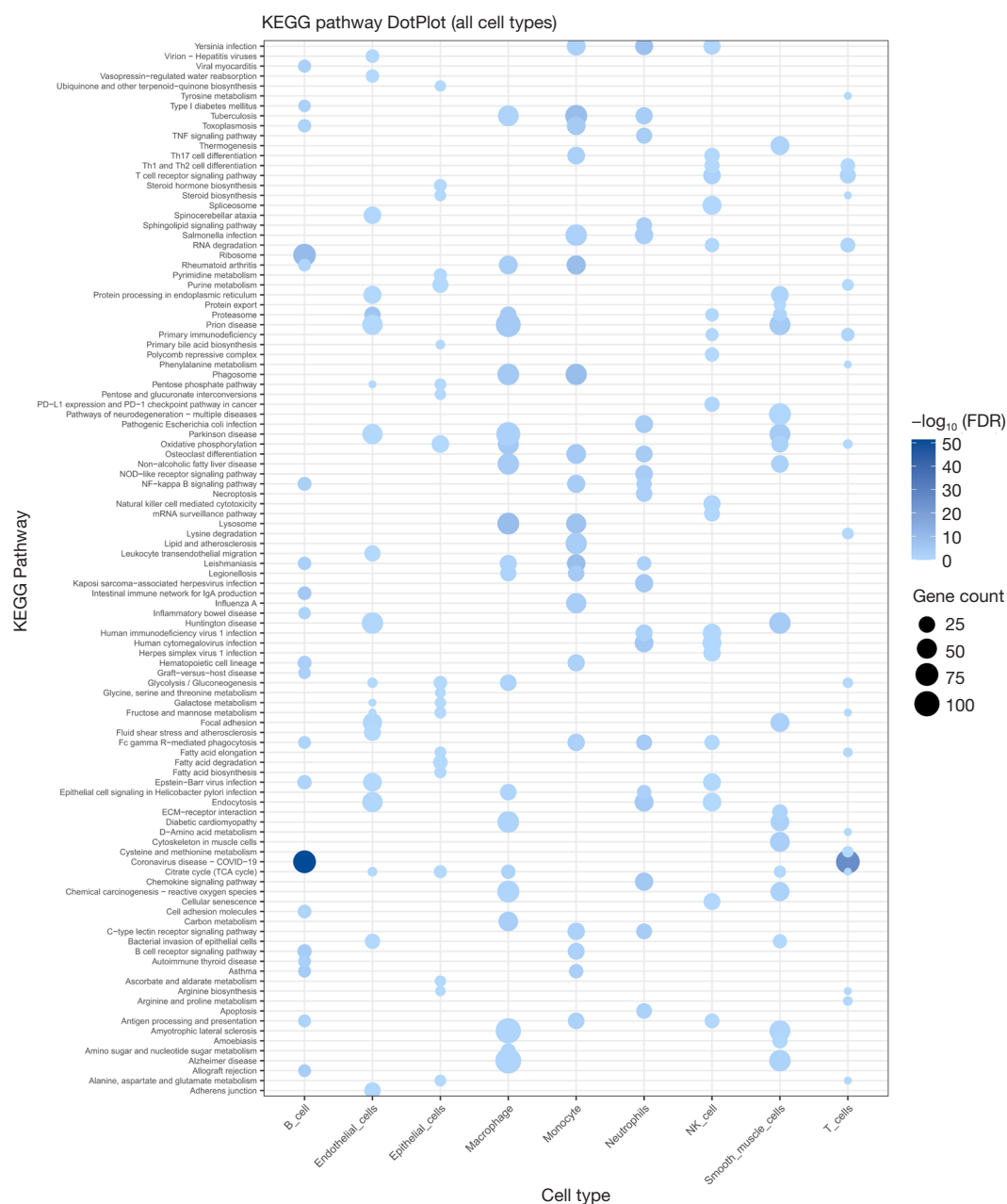


Figure 9 KEGG pathway enrichment across cell types. FDR, false discovery rate; KEGG, Kyoto Encyclopedia of Genes and Genomes.

these two cell types. Endothelial and epithelial cells were primarily enriched in pathways related to vascular function, cell adhesion, and barrier integrity, with some involvement in inflammatory signaling pathways, though the significance and gene counts were lower than in typical immune cell populations. B cells and smooth muscle cells were generally less represented, exhibiting only sporadic significant enrichment in a limited number of pathways.

Immune cell communication network and key signaling axes

To localize the inflammation- and anesthesia-associated pathway signals to specific cellular interactions, a communication network among the nine major cell types in the lung cancer microenvironment was constructed from ligand-receptor interaction data. In both the adjacent tissue

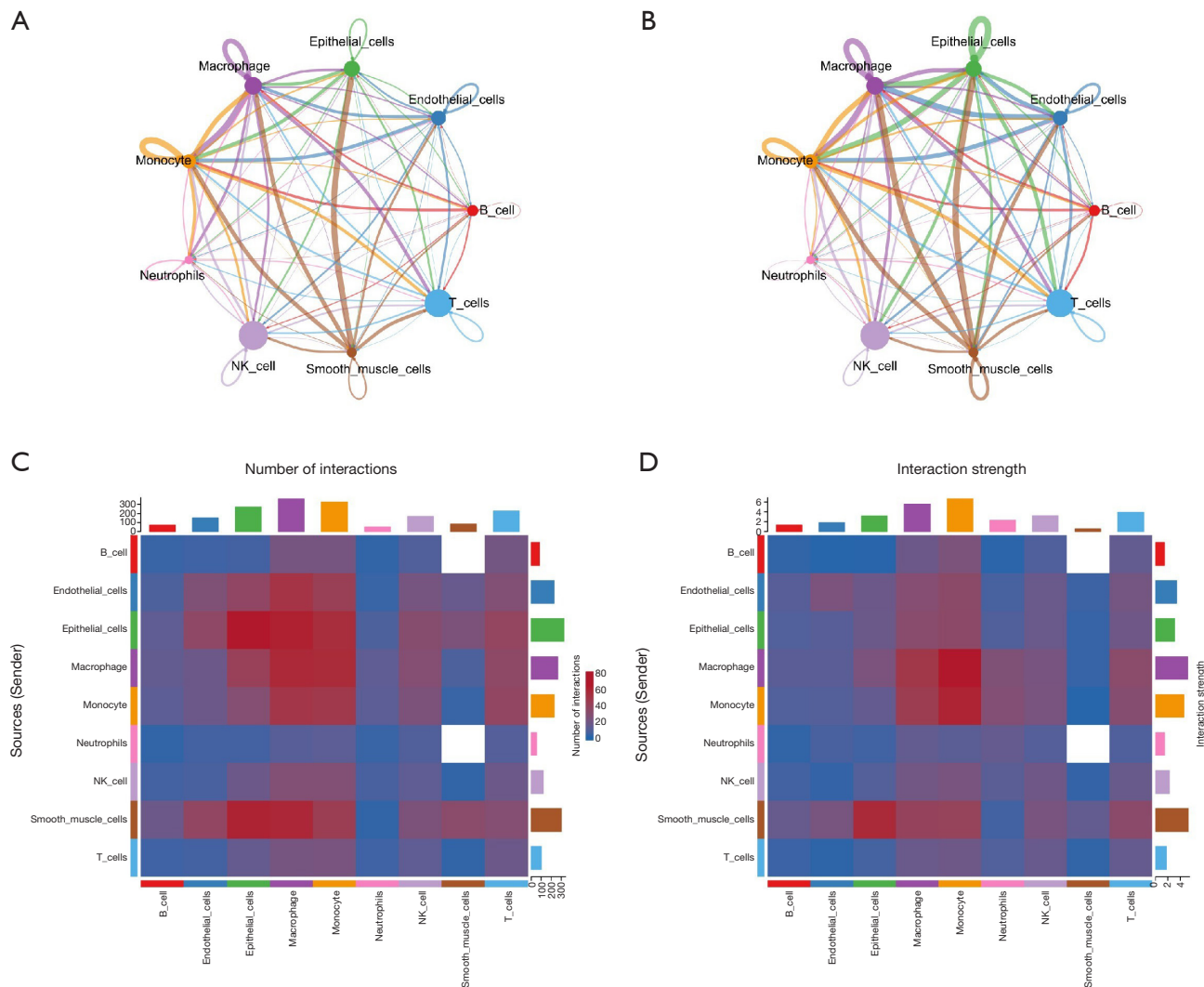


Figure 10 Cell-cell communication patterns. (A,B) Overall interaction networks in adjacent tissue and tumor tissue. (C) Heatmap of interaction number between sending and receiving cell types. (D) Heatmap of interaction strength. The marginal bar plots along the top of each heatmap summarize the total number of interactions (C) or total interaction strength (D) for each sending cell type; those along the right summarize values for each receiving cell type.

and tumor groups, all cell types exhibited multi-directional connectivity, though with distinct differences in connection density and strength (Figure 10A,10B). In both contexts, the interactions involving macrophages and monocytes with T cells, epithelial cells, and endothelial cells were the most concentrated, comprising both outgoing and incoming links. Neutrophils and NK cells participated in fewer connections but still interacted with multiple cell types, whereas smooth muscle cells occupied a more peripheral position in the network. Comparing the two networks showed that overall connectivity was denser in the tumor group. Moreover,

the connection strength between macrophages/monocytes and epithelial cells was elevated, suggesting more active communication between these inflammation-related cells and epithelial cells within the tumor microenvironment.

Quantitative comparison of communication levels across all cell pairs was achieved by aggregating all ligand-receptor pairs according to their cellular sources and targets. When macrophages and monocytes acted as signal senders, their connection counts with epithelial cells, endothelial cells, and T cells were highest, followed by those with NK cells and neutrophils. As receivers, epithelial cells, endothelial cells,

and T cells received signals from multiple immune cell types, with total connection numbers substantially exceeding those of B cells and smooth muscle cells (*Figure 10C*). High-intensity red blocks formed in directions such as macrophage-to-epithelial cells, macrophage-to-endothelial cells, monocyte-to-epithelial cells, and T cell-to-macrophage, while most grid points associated with B cells and smooth muscle cells remained at low values (*Figure 10D*). In lung cancer tissues, monocytes and macrophages exhibited enhanced outgoing and incoming communication through antigen-presentation pathways (HLA class I and II interactions with CD8A and CD4) and matrix-adhesion pathways (FN1- and collagen-based signaling), forming structured communication modules with epithelial and endothelial cells rather than merely acting as generic hubs, whereas other cell types occupied more auxiliary or peripheral positions.

At the pathway family level, all communication events were clustered and summarized by signal pathway category, revealing the relative intensity distribution of different cell types across major signaling axes (*Figure 11A,11B*). MHC-I and MHC-II signals were primarily concentrated between antigen-presenting cells and T cells. FN1 and COLLAGEN-related signals showed moderate activity between macrophages/monocytes and endothelial cells/smooth muscle cells, whereas pathways such as ICAM, APP, and RESISTIN exhibited relatively low overall intensities (*Figure 11A*). In the tumor group, the relative intensities of signaling axes including MHC-I/MHC-II, FN1, COLLAGEN, and ICAM were significantly heightened between macrophages/monocytes and epithelial cells/endothelial cells. Concurrently, MHC-class signals associated with NK cells and T cells were also elevated. Furthermore, new high-intensity blocks for certain APP- and ANNEXIN-related signals appeared between several cell pairs (*Figure 11B*). This concurrent enhancement of signaling axes involved in antigen presentation, cell adhesion, and matrix remodeling across multiple cell types aligns with the observed enrichment of inflammatory and immune pathways in immune and epithelial cells.

At the specific ligand-receptor level, significantly enriched communication events were extracted to generate a bubble plot (*Figure 11C*). Ligands from the HLA family formed an extensive network with various receptors, primarily distributed among macrophages, monocytes, and T cells. FN1-related ligand-receptor pairs (FN1-ITGA/ITGB) and multiple COLLAGEN-integrin combinations were concentrated in communication pathways linking macrophages and monocytes to epithelial cells, endothelial

cells, and smooth muscle cells, where they exhibited high significance. Several ICAM-related pairs, along with a limited number of APP- and ANNEXIN-related pairs, formed distinct clusters between specific cell pairs. These ligand-receptor combinations showed high statistical significance and communication probability, forming a primary signaling foundation between immune and structural cells in the lung cancer microenvironment.

Discussion

Perioperative management is a critical determinant of outcomes in lung cancer treatment (24). Although surgical resection eliminates the primary tumor, intraoperative tissue injury, anesthetic agents, and the surgical stress response provoke widespread immune and inflammatory reactions that influence both postoperative recovery and long-term prognosis (25). The perioperative period involves more than transient physiological changes; it can induce lasting effects on residual tumor cells and potential metastases by altering immune cell function, cytokine networks, and the tissue microenvironment. Integrating transcriptomic data from peripheral blood, anesthetized myocardial tissue, and lung cancer single-cell datasets revealed a sustained relationship between acute inflammation, anesthetic modulation, and the tumor microenvironment, with shared pathway-level features recurring across the three analytical layers. This indicates that perioperative stimuli produce not only systemic effects but also generate distinct molecular signatures at the tissue level (26,27). The integrated analysis demonstrated that several key pathways, including autophagy, protein processing, cytokine signaling, and stroma-associated pathways, were consistently active across all three dimensions. These results offer novel evidence connecting perioperative biological responses to the tumor immune ecosystem.

At the peripheral blood level, a clear expression gradient was observed among the Healthy, D1 sepsis, and D2 sepsis groups (28). Pathways including autophagy, lysosome function, and protein processing were significantly enhanced under acute inflammatory conditions, alongside the activation of cytokine-cytokine receptor interactions, Toll-like receptor signaling, and antigen processing and presentation (29). These alterations reflect not only a direct inflammatory response but also indicate that cells are under sustained stress, requiring adjustments to protein quality control and metabolic load. The risk score increased progressively across the three groups, indicating that the

expression patterns are directional and can distinguish differing inflammatory intensities. As an extreme model of perioperative stress, these findings establish a reference baseline for subsequent observations of pathway alterations within tissues, confirming that systemic inflammatory signals carry distinct molecular signatures.

At the tissue level under anesthesia, both regimens induced significant transcriptional changes between the pre- and postoperative states (27). Propofol and sevoflurane each activated inflammatory and cytokine signaling pathways, while suppressing pathways linked to ribosomes and specific infections. The combined surgical and anesthetic intervention perturbed the balance between inflammation and metabolism (14). The two anesthetics differed in their enrichment intensity and the particular gene sets affected, revealing distinct regulatory profiles. These differences represented variations in the direction and degree of regulation rather than absolute opposites, which may help explain clinical observations linking anesthetic choice to immune status, organ injury, and recovery speed. Although myocardial and lung cancer tissues are not identical, these findings imply that anesthetic agents exert systemic regulatory effects, potentially influencing diverse tissues via modulation of the cytokine network (30).

At the single-cell level in lung cancer, T cells and NK cells are the predominant populations, followed by macrophages and monocytes, which reflects active immune infiltration within the tumor microenvironment (31). Pathway enrichment analysis shows that inflammatory and immune signaling pathways are present across multiple immune cell types, while stromal and cell adhesion signals are more concentrated in epithelial cells, endothelial cells, and smooth muscle cells. This pattern suggests that inflammatory signals are not confined to a specific cell type but are co-transmitted between immune and structural cells. Communication analysis further demonstrates that macrophages and monocytes engage in structured interaction programs with epithelial, endothelial, and T cells, dominated by antigen presentation-related HLA signaling and extracellular matrix-integrin communication axes, highlighting specific molecular routes through which immune and structural compartments are interconnected in lung adenocarcinoma tissue. The overall communication intensity is higher in tumor tissue than in adjacent tissue, indicating that the tumor microenvironment is sensitive to systemic immune stimulation and mounts an amplified local response.

When the enriched pathways identified at the systemic and tissue levels are examined together with the single-

cell communication patterns, several shared molecular features become apparent. Inflammatory pathway enrichment observed in peripheral blood and myocardial tissue primarily involves cytokine signaling, innate immune activation, and protein processing programs. At the single-cell level, these pathway-level signals correspond to specific interaction axes rather than diffuse transcriptional changes. Antigen presentation-related signaling, mediated by HLA class I and class II ligand-receptor pairs, represents one such axis and is predominantly observed in interactions between myeloid cells and T cells. A second axis involves extracellular matrix and adhesion-related signaling, in which FN1 and multiple collagen ligands interact with integrins, CD44, and syndecan receptors, mainly linking macrophages or monocytes with epithelial and endothelial cells. These axes provide a molecular framework through which systemic inflammatory or perioperative stress-associated signals may be translated into coordinated immune-structural cell interactions within the tumor microenvironment.

Pathway and communication axis analyses identified antigen presentation, FN1, and COLLAGEN-related signaling as recurrent core structures. HLA class ligands and receptors established dense connections across multiple cell types, whereas FN1-integrin and COLLAGEN-integrin interactions were primarily localized between macrophages/monocytes and epithelial or endothelial cells. These signaling patterns correspond to those implicated in peripheral inflammation and anesthetic regulation, implying that the perioperative state may impart molecular imprints in tissues via the same axes. In the tumor group, signaling was broadly intensified, positioning these axes as potential key regulatory nodes and offering a mechanistic rationale for how the perioperative state modulates the tumor immune microenvironment.

Several retrospective clinical studies have examined whether anesthetic technique influences long-term outcomes after lung cancer surgery, with inconsistent results. In a large single-center cohort of patients undergoing curative resection for NSCLC, the choice of propofol-based total intravenous anesthesia (TIVA) versus volatile agent anesthesia was not associated with significant differences in overall survival or recurrence-free survival after propensity score adjustment (32). A similar retrospective analysis from a different cohort also found no statistically significant impact of anesthetic technique on cancer-specific survival or overall survival in NSCLC patients (33). Conversely, other observational data suggest potential associations between TIVA and better long-term outcomes; for example, in early-

stage (I/II) NSCLC, propofol-based TIVA was associated with improved recurrence-free and overall survival compared with inhalation anesthesia (34). Meta-analyses and broader retrospective reviews also report heterogeneous findings regarding anesthetic technique and long-term oncologic outcomes, with some analyses indicating a trend favoring propofol in overall mortality but without consistent effects on cancer-free survival (35).

These discrepancies likely reflect differences in study populations, tumor stages, perioperative management, and analytic methods. Importantly, most available evidence is observational in nature, limiting causal inference and raising the possibility of residual confounding. Prospective randomized trials focusing specifically on NSCLC, such as the multicenter GAS TIVA trial comparing recurrence-free survival between propofol- and inhalational anesthesia groups, are currently underway and may provide more robust data on this question (36). Within this context, the present study does not directly assess clinical survival outcomes; rather, it provides transcriptomic and cellular evidence that perioperative inflammation and anesthetic modulation converge on immune and stromal signaling pathways within lung cancer tissue, offering a mechanistic framework that may help interpret and guide future clinical investigations.

This study has several limitations. All data were sourced from public databases and lack validation with clinical samples. Changes in myocardial tissue may result from the cardiac surgical procedure itself, complicating efforts to separate the effects of anesthetic agents from those of surgical stimulation. The lung cancer single-cell data did not consider postoperative timing, preventing direct validation of how anesthesia or acute inflammation immediately alters cellular composition and communication. Future work should integrate blood samples, tissue specimens, and defined anesthetic protocols to test whether the identified pathways and signaling axes correlate with postoperative recurrence, immunosuppression, or survival. Protein-level assays, histopathological imaging, or spatial transcriptomics could further delineate the spatial distribution of these signals within tissues. Despite these limitations, our multi-layer analysis reveals connections between perioperative inflammation, anesthetic methods, and immune signaling in lung cancer tissue, highlighting recurrent pathway themes that link peripheral inflammation, tissue responses under anesthesia, and tumor microenvironment communication. Autophagy-related protein processing, cytokine networks, and stromal signaling appear as consistent themes linking

peripheral and tissue-level observations. Macrophages, monocytes, and epithelial cells form the principal cellular communication hubs and represent plausible regulatory targets. These results establish a framework for investigating how intraoperative anesthesia influences the tumor microenvironment and guide subsequent research into the effects of perioperative interventions on tumor immune responses and long-term outcomes.

Conclusions

This study integrated peripheral blood transcriptomic data, anesthesia-related tissue data, and single-cell data from lung cancer, revealing a continuum of molecular associations linking perioperative inflammation, anesthesia methods, and the tumor microenvironment. Peripheral inflammation was characterized by enhanced activity in autophagy, lysosomal, and protein processing pathways, alongside activated cytokine signaling. At the tissue level, both propofol and sevoflurane anesthesia induced the enrichment of inflammation- and cytokine-related pathways while suppressing ribosome-related pathways and certain infection responses, with distinct regulatory patterns observed between the two agents. Single-cell analysis demonstrated intensive intercellular communication between immune and structural cells within tumor tissues, where antigen presentation and FN1- and COLLAGEN-related signaling emerged as major connecting axes. The overall signaling intensity was higher in tumor tissues than in adjacent normal tissues. These findings indicate that the perioperative state influences not only the systemic inflammatory burden but may also establish identifiable molecular patterns within tumor tissues, providing a basis for understanding how anesthetic management relates to the immune status of lung cancer tissue.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments.

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