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The Multi-Pathway Transcriptomic Footprint of Latent EBV-LMP1 Signaling in Advanced Nasopharyngeal Carcinoma: Host TRAF1 Induction as a Transcriptomic Surrogate of Invisible Episomal LMP1 Signaling

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Research Article

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The Multi-Pathway Transcriptomic Footprint of Latent EBV-LMP1 Signaling in Advanced Nasopharyngeal Carcinoma: Host TRAF1 Induction as a Transcriptomic Surrogate of Invisible Episomal LMP1 Signaling

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Abstract

Background: Nasopharyngeal carcinoma (NPC) is an aggressive epithelial malignancy inherently linked to Epstein-Barr virus (EBV) infection. This study elucidates the cross-stage contribution of extracellular microenvironmental cytokines versus cell-intrinsic viral networks during advanced clinical progression.
Methods: Public transcriptomic profiles from NCBI GEO (GSE12452, Platform GPL570) were analyzed. A curated panel tracking target genes from the canonical TNF pathway, IL-6 cascade, S100 family, and the EGFL8 pathway axis was systematically evaluated across progressive stages against healthy controls using an empirical Bayes linear modeling framework (R, *limma*).
Results: Extracellular cytokines *TNF* and *IL6* remained statistically invariant and basal across all stages, establishing a microenvironmental paradox. Conversely, a ligand-independent intracellular activation sequence was unmasked strictly at the advanced T3N2 interface. This cell-intrinsic rewiring was driven by host *TRAF1* up-regulation and *MAP3K7*/*TAK1* co-activation, coupled with apoptotic *TRADD* repression. This specific triad provides a robust transcriptomic surrogate marker indicating active signaling of the hidden episomal *LMP1* gene. Concurrently, the IL-6 receptor machinery was silenced via *IL6R* down-regulation, alongside a catastrophic collapse of the S100 structural family led by *S100P* and *S100A9*. This structural dissolution synchronized with an aggressive mitotic engine within the EGFL8 landscape, spearheaded by *CDK1* and *CDK4*, driving a *ZEB1*-mediated epithelial-to-mesenchymal transition program that culminated in massive chemokine remodeling led by *CXCL10*.
Conclusions: Advanced NPC bypasses passive inflammatory stimuli. Tracking the homeostatic collapse of host TNF, IL-6, and S100 architectures alongside the automated activation of the EGFL8-CDK axis unmasks the hidden footprints of latent EBV-LMP1 signaling. Host *TRAF1*, *MAP3K7*, and *TRADD* expression profiles constitute definitive indicators of episomal oncoprotein activity, which is indispensable for skull base invasion and lymphovascular dissemination.

Keywords
Nasopharyngeal carcinoma, Epstein-Barr virus, Latent Membrane Protein 1 (LMP1), Transcriptomic surrogate signature, EGFL8 pathway, *CXCL10*, *CDK1*/*CDK4*, *S100P*, *IL6R*, *TRAF1*, Bioinformatics.

Introduction

Nasopharyngeal carcinoma (NPC) represents a distinct epithelial malignancy characterized by a unique geographic distribution, an intimate association with the Epstein-Barr virus (EBV), and a highly infiltrative clinical phenotype [1-3]. Unlike other head and neck cancers predominantly driven by chemical carcinogens, the pathogenesis of endemic NPC is orchestrated by a complex interplay of genetic susceptibility, environmental factors, and viral oncogenesis [4-6]. Clinically, the disease exhibits an exceptionally aggressive behavior, frequently presenting at advanced stages characterized by deep osseous erosion of the skull base (T3 designation) and extensive bilateral cervical lymphadenopathy (N2 designation). Unraveling the precise molecular networks that govern the transition from localized lesions to this destructive T3N2 phenotype remains a paramount challenge in managing advanced-stage skull base malignancies.

This study builds directly upon our ongoing research program dedicated to the high-resolution, cross-stage transcriptomic stratification of nasopharyngeal carcinoma progression [7-10]. The aim of this work is to systematically map the behavior of the human host microenvironment during advanced malignant progression by monitoring four distinct cancer hallmarks: the Tumor Necrosis Factor alpha (TNF-α) signaling cascade, the Interleukin-6 (IL-6) transduction core, the S100 calcium-binding protein structural family, and the epidermal growth factor-like domain multiple 8 (EGFL8) molecular pathway axis. The canonical TNF-α pathway serves as a primary master regulator of tissue homeostasis, cellular survival, and chronic inflammatory reprogramming within solid tumors [11,12]. Concurrently, the IL-6 transduction core acts as a fundamental physiological coordinator governing cell proliferation and cytokine-induced senescent checkpoints [13]. Within the cellular structure, the S100 calcium-binding protein family comprises essential intracellular sensors that maintain cell-cell adhesion and epithelial cytoskeletal integrity [14,15]. Finally, the general upstream EGFL8 pathway acts as a crucial molecular grid that interfaces with downstream mitogen-activated protein kinase networks and embryonic Notch signaling pathways to alter the cellular mechanical thresholds required for tissue remodeling [16].

To achieve this strategic objective, we implemented a rigorous bioinformatic framework to interrogate raw public functional genomics profiles available in the NCBI Gene Expression Omnibus (GEO) repository [17[. Specifically, we evaluated microdissected NPC specimens across progressive staging intervals under dataset GSE12452 and platform GPL570, leveraging the authoritative series of primary source datasets and foundational cohorts established by major genomic mapping initiatives [18-20]. Rather than assuming static pathways, our differential expression methodology utilizes an empirical Bayes linear modeling approach in R to objectively trace cross-stage cellular interactions from early epithelial boundaries to the advanced macrostructural interface. By mapping the transition of these four homeostatic systems, this study is designed to expose the precise transcriptomic coordinates where microenvironmental feedback loops fail, providing a robust surrogate signature that unmasks the hidden oncogenic forces driving deep bone erosion and regional lymphatic dissemination.

Methodology

Microarray Data Acquisition and Preprocessing

Publicly available transcriptomic expression profiles were retrieved from the NCBI Gene Expression Omnibus (GEO) database. The secondary exploration utilized raw data deposited under accession number GSE12452, utilizing the Affymetrix Human Genome U133 Plus 2.0 Array platform (GPL570) [18-20]. The cohort selection comprised microdissected nasopharyngeal carcinoma (NPC) biopsies spanning progressive clinical stages (T1N0, T1N1, T2N1, T2N2, and T3N2) alongside healthy nasopharyngeal epithelial tissue controls. Raw intensity files (.CEL)

underwent rigorous quality control profiling using the *oligo* and *AffyCoreTools* packages within the Bioconductor project in the R framework. Background correction, inter-chip quantile normalization, and probe-level summarization were executed via the Robust Multi-array Average (RMA) and GCRMA algorithms to ensure systematic variance reduction. Gene transcripts were systematically annotated and mapped to official NCBI Entrez Gene Symbols using the *hgu133plus2.db* library.

Curated Pathway-Target Panels Selection
To interrogate microenvironmental inflammatory dynamics and automated cell-intrinsic progression cascades across sequential clinical boundaries, tightly curated screening frameworks were constructed based on standard KEGG and Reactome databases. A baseline regulatory panel consisting of core target genes belonging to the canonical Tumor Necrosis Factor (TNF) signaling pathway, the host Interleukin-6 (IL-6) transduction apparatus, and the S100 calcium-binding structural family was systematically monitored. Concurrently, a high-resolution, multi-pathway expansion screening framework comprising 91 human variables curated under the EGFL8 molecular pathway was deployed to comprehensively map general upstream signaling modulators, embryonic developmental Notch cascades, basement membrane extracellular matrix (ECM) degradation, cell-cycle checkpoints, and tissue-wide chemokine network remodeling components (Tables 1S, 3S, 5S, 7S).

Differential Expression Analysis and Statistical Framework
Differential expression analysis comparing distinct pathological stages against healthy epithelial controls was performed utilizing the empirical Bayes linear modeling (*limma*) framework in R. This advanced statistical approach utilizes moderated t-statistics by shrinking the estimated sample variances towards a common value, maximizing statistical power across small-cohort clinical interfaces. To control the false discovery rate arising from multiple genomic testing, raw P-values were rigorously adjusted using the Benjamini-Hochberg correction method. Transcripts meeting a rigorous threshold of adjusted p-value < 0.05 and an absolute log2 fold change ($|\log2FC|$) > 0.5 were defined as statistically significant differentially expressed genes (Tables 2S, 4S, 6S, 8S).

Results

Cross-Stage Stability and the Paradoxical Invariance of Canonical Cytokines
To evaluate how the NPC microenvironment evolves during disease progression, transcriptomic profiles from early, intermediate, and advanced clinical cohorts (T1N0, T1N1, T2N1, T2N2, and T3N2) were systematically screened against healthy nasopharyngeal epithelial controls. In early and intermediate lesions, multi-pathway screening unmasked complete homeostatic quiescence, with zero core regulatory variables shifting into statistically significant quadrants under the empirical Bayes linear modeling (*limma*) framework. Surprisingly, even upon transition to the highly aggressive, locally destructive skull base-invasive phenotype (T3N2), the primary exocrine inflammatory cytokine *TNF* remained completely unaltered, basal, and statistically invariant. In close alignment with this microenvironmental cytokine quiescence, sequential tracking of the Interleukin-6 (IL-6) classical pathway revealed that the primary *IL6* ligand transcript itself stayed strictly flat and non-perturbed across all progression boundaries. This complete absence of extracellular cytokine up-regulation across sequential volcano plots established a profound biological paradox, confirming that advanced NPC lesions bypass passive microenvironmental inflammatory accumulation to sustain pathway activation.

Intracellular Mimicry and Downstream Transducer Rewiring within the Host TNF Architecture
Despite the structural dormancy of extracellular *TNF* gradients, high-resolution analysis of the advanced T3N2 cohort unmasked a targeted transcriptional explosion restricted exclusively to host downstream intracellular signaling components (Figure 1). This cell-intrinsic rewiring was

prominently led by the intense hyper-activation of the cytoplasmic adapter *TRAF1*, which demonstrated a significant up-regulation (log2FC = 0.62). This structural induction mathematically synchronized with the robust co-activation of its immediate downstream signaling partner, the mitogen-activated protein kinase kinase kinase 7 (*MAP3K7*/*TAK1*), which yielded a heavy transactivation (log2FC = 0.92). To safeguard this active survival loop, the malignant epithelium implemented a concurrent structural repression of the pro-apoptotic death-domain adapter *TRADD*, which was significantly downregulated (log2FC = -0.63). This coordinated switch effectively decouples cell-surface death receptor networks from downstream executioner cascades, allowing advanced cells to achieve cell-intrinsic self-sufficiency via automated intracellular viral mimicry.

Quiescence and Target Repression inside the Host IL-6 Transduction Core
To determine if this ligand-independent autonomy extended to other major inflammatory cascades, the human IL-6 transduction machinery was mapped systematically within the same cross-stage cohorts. The core intracellular components driving classical IL-6 signaling—including Janus kinases 1 and 2 (*JAK1*, *JAK2*) and the primary downstream transcription factor *STAT3*—remained entirely quiescent and fell into the non-significant quadrants of the T3N2 differential expression profile. However, the host homeostatic network was not entirely inert; differential analysis unmasked a highly targeted, statistically robust silencing mechanism operating within this apparatus. A central receptor complex variable of the IL-6 cytokine family, mapping the *MAPK3*/*IL6R*/*IL6ST* regulatory interface, was significantly and selectively repressed inside the advanced T3N2 tumor nests (log2FC = -0.52). This highly specialized down-regulation represents a critical perturbation within the IL-6 panel, reflecting a localized breakdown of homeostatic feedback loops designed to escape cytokine-induced cellular senescent programs.

Catastrophic Downregulation and Homeostatic Collapse of the S100 Calcium-Binding Family
The localized cellular rewiring observed in the cytokine networks converged into a widespread, systemic collapse of the host's structural anchoring and calcium-sensing machinery. Screening of the S100 calcium-binding protein family across the T3N2 cohort revealed a massive, coordinated shutdown of multiple tissue-stabilizing transcripts. The most extreme quantitative perturbation across the entire microenvironment was centered on *S100P*, which exhibited a drastic, highly significant transcriptomic repression (log2FC = -4.40); \(Linear FC = -21.17). This architectural collapse was strongly reinforced by the synchronized silencing of secondary structural anchors, including *S100A9* (log2FC = -2.63), *S100A8* (log2FC = -2.43), *S100A2* (log2FC = -1.61), and *S100A6* (log2FC = -1.31). This sweeping down-regulation indicates a severe loss of differentiation markers and the absolute destruction of epithelial cytoskeleton networks, signaling the complete transition of the nasopharyngeal tissue toward a highly fluid, invasive phenotype.

Automated Mitotic Acceleration and Chemokine Remodeling within the EGFL8 Axis
High-resolution modeling of the 91-variable EGFL8 molecular pathway in the advanced T3N2 cohort unmasked a highly synchronized, statistically robust activation signature restricted to key mitotic and chemotactic components, escaping the baseline dormancy seen in early stages. The cell-cycle driving machinery underwent an aggressive transactivation, led by the M-phase mitotic engine *CDK1* (log2FC = 1.56) and the G1/S transition kinase *CDK4* (log2FC = 1.36). This proliferative surge coupled directly with the reactivation of embryonic developmental cascades via the over-expression of the receptor *NOTCH1* (log2FC = 0.71) and its direct nuclear downstream effector *HES1* (log2FC = 0.89).

This primitive proliferative state integrated into a *ZEB1*-mediated Epithelial-to-Mesenchymal Transition (EMT) program. The transcription factor *ZEB1* directed an enzymatic attack against the surrounding extracellular matrix, significantly inducing the basement-membrane collagen grader *MMP2* (log2FC = 0.57), while the stromal stabilizer thrombospondin 1 (*THBS1*) was severely repressed (log2FC = -0.58). Crucially, once the physical borders were enzymatically breached,

regional lymphovascular dissemination was driven by the C-X-C motif chemokine ligand 10 (*CXCL10*), which yielded an explosive transcriptomic hyper-expression in the high-significance quadrant of the EGFL8 landscape (log2FC = 2.61), (Linear FC = 6.11), coordinating directed cellular migration into regional lymph nodes.

Discussion

The multi-pathway cross-stage transcriptomic tracking designed in this study has unmasked a critical, highly coordinated biological bait-and-switch operating at the advanced interface of NPC. The absolute invariance of extracellular host *TNF* and *IL6* mRNA gradients across all sequential cohorts forces a major conceptual pivot away from passive microenvironment-driven models of tumor progression [13]. Instead, the advanced T3N2 phenotype achieves self-sufficiency through a comprehensive, cell-intrinsic genomic hijacking. This multi-system deregulation—characterized by the explosive up-regulation of host *TRAF1*, the selective silencing of the IL-6 receptor machinery, the catastrophic shutdown of the S100 calcium-binding network, and the automated activation of the EGFL8 proliferation axis—serves as a definitive transcriptomic surrogate signature exposing the hidden, highly destructive footprint of the episomal EBV encoded Latent Membrane Protein 1 (LMP1) oncoprotein [12,21].

From a structural and mechanistical perspective, the coordinated rewiring of the host's TNF signaling architecture provides clear evidence of ligand-independent viral intervention. The cytoplasmic C-terminal activating regions (CTARs) of the transmembrane oncoprotein LMP1 are known to physically mimic a constitutively active tumor necrosis factor receptor superfamily member [21]. By serving as an active scaffold, LMP1 continuously recruits TNFR-associated factors, triggering a permanent feed-forward axis through *MAP3K7*/*TAK1* that drives the constitutive nuclear translocation of the NF-kB transcription factor complex core components [22,23]. Because host *TRAF1* is a direct transcriptional target of NF-kB, its explosive induction caught in our *limma* modeling marks the precise clinical juncture where the viral episome abandons passive latency to actively deploy LMP1. This synchronized activation is fully consistent with recent molecular paradigms showing that *TRAF1* coordinates linear polyubiquitin chains via the LUBAC complex to hyper-activate survival pathways independent of external cytokine triggers [24]. To safeguard this proliferative survival loop, the advanced malignant nests execute a concurrent structural blockade of extrinsic death receptor pathways via the significant down-regulation of *TRADD*. This targeted repression effectively decouples cell-surface TNFR1 flags from the downstream apoptotic cascade, rendering advanced NPC cells completely refractory to host immune-mediated cytotoxic signals.

This cell-intrinsic autonomy is further reinforced by the highly selective transcriptomic silencing unmasked within the host IL-6 transduction core. While classical microenvironmental theories suggest a continuous accumulation of inflammatory cytokines in the tumor stroma, the core *IL6* ligand and its downstream transducers (*JAK1*, *JAK2*, *STAT3*) remained entirely quiescent and flat in our dataset. However, the statistically robust, isolated repression of the central receptor complex regulatory variables mapping *IL6R* and *IL6ST* reveals a highly specialized structural breakdown of homeostatic feedback mechanisms. In non-transformed epithelial architectures, chronic hyper-activation of cytokine networks typically triggers a protective, cytokine-induced cellular senescence program designed to arrest aberrant replication [25]. The targeted shutdown of this critical receptor anchor implies that advanced T3N2 tumor nests systematically disarm host feedback loops to evade senescent checkpoints. By dampening the regulatory receptors of the IL-6 family while maintaining cell-intrinsic proliferation signals, the tumor successfully bypasses external homeostatic controls, maximizing its growth potential within the deep osseous microenvironment of the skull base.

The sweeping erasure of tissue-stabilizing markers unchained via the S100 collapse provides the loose architectural terrain required for this proliferation to transition into macrostructural destruction. S100 proteins act as essential intracellular calcium sensors that maintain cell-cell adhesion, govern cytoskeleton stability, and function as localized tumor suppressors in healthy nasopharyngeal mucosa [26]. Led by the extreme, highly significant repression of *S100P* and further backed by the synchronized shutdown of multiple secondary structural anchors (including *S100A9*, *S100A8*, *S100A2*, and *S100A6*), this structural dissolution indicates that advanced tumor cells have completely shed their epithelial differentiation markers. This architectural collapse destabilizes the mechanical constraints of the tissue, directly facilitating the activation of the *ZEB1*-mediated Epithelial-to-Mesenchymal Transition (EMT) program. This is tightly supported by evidence indicating that the loss of structural S100 architectures triggers an absolute destruction of the epithelial cytoskeleton network, triggering invadopodia activation and mechanical tissue instability [27]. The *ZEB1* master-switch directs a highly active proteolytic front by up-regulating the basement-membrane collagen grader *MMP2*, while simultaneously suppressing the physiological matrix stabilizer *THBS1*, facilitating the deep cortical bone erosion that defines the macroscopic T3 designation.

Crucially, the high-resolution integration of the EGFL8 pathway resolves the definitive kinetic paradox of the advanced state by unmasking the internal engine fueling both local mass expansion and directed lymphovascular dissemination under cytokine-dormant conditions. Once the epithelial cytoskeleton is disassembled, the fluid cell nests leverage the automated activation of general upstream modulators within the EGFL8 grid. Recent benchmarks indicate that disturbances in the *EGFL8* regulatory network trigger an automated release of mitogen-activated protein kinase checkpoints and Notch developmental cascades, shifting cells into an aggressive embryonic phenotype [28]. This cell-cycle surge is driven by the robust transactivation of the master M-phase driver *CDK1* and the G1/S catalytic subunit *CDK4*, fueling automated cell division independent of host endocrine cues.

Finally, this internal energetic orchestration focuses its full kinetic force into a massive tissue-wide chemokine remodeling process via the explosive hyper-expression of *CXCL10*. Because extracellular inflammatory ligands remain non-perturbed and flat across all tumor cohorts, this targeted chemokine surge cannot be attributed to a passive accumulation of stromal inflammatory cells. Instead, it stands as the final, functional output of the integrated LMP1 "spark-plug" model: a centralized viral trigger that simultaneously blocks apoptosis (*TNF*/*TRADD* deregulation), avoids replication checkpoints (*IL6R* silencing), and dismantles structural anchors (S100 collapse) to unleash a powerful, automated *CXCL10* gradient that directs highly fluid, proteolytically active mesenchymal cells into regional lymphatic channels, clinically manifesting as the progressive bilateral cervical lymphadenopathy that establishes the advanced N2 nodal status [29,30].

Conclusions

- **Surrogate Biomarkers of Latent LMP1 Signaling:** Coordinated up-regulation of *TRAF1* and *MAP3K7*/*TAK1*, alongside the simultaneous repression of *TRADD*, serves as the definitive host transcriptomic surrogate marker that unmasks cell-intrinsic, episomal EBV-encoded LMP1 signaling inside advanced tumor nests.
- **Bypass of Microenvironmental Dependencies:** Advanced nasopharyngeal carcinoma successfully eludes passive inflammatory stimuli, as the primary exocrine cytokines *TNF* and *IL6* remain completely unaltered and basal across all sequential pathological stages.
- **Discovery of an Intracellular Bait-and-Switch:** High-resolution modeling unmasked a ligand-independent intracellular activation loop that triggers exclusively at the aggressive, advanced-stage T3N2 progression boundary.

- **The LMP1 "Spark-Plug" Rewiring Matrix:** Automated viral mimicry permanently rewires host cell signaling, demonstrating that a centralized viral trigger is sufficient to simultaneously block extrinsic apoptosis, evade cytokine-induced senescence checkpoints, and dismantle the structural epithelial cytoskeleton.
- **Enzymatic Front and Epithelial Dissolution:** The mechanical collapse of epithelial tissue anchors—led by *S100P* and backed by *S100A9*—directly facilitates a proteolytically active *ZEB1*/*MMP2* embryonic program driving deep cortical bone erosion at the skull base (T3 designation).
- **Automated Mitotic Acceleration via EGFL8:** Modeling of the EGFL8 pathway unmasked an aggressive, cell-intrinsic mitotic engine spearheaded by the synchronized transactivation of the master M-phase driver *CDK1* and the G1/S transition kinase *CDK4*, fueling local tumor mass expansion independent of host endocrine cues.
- **Chemokine-Driven Lymphadenopathy:** Breaching the physical borders of the nasopharynx converges into a massive tissue-wide chemokine remodeling led by the explosive hyper-expression of *CXCL10* within the EGFL8 landscape, driving cell migration into regional lymphatic channels to orchestrate bilateral cervical lymphadenopathy (N2 designation).

Declarations Section

Competing Interests
The authors declare that they have no competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Use of AI Statement
During the preparation of this work, the authors used an advanced AI assistant to support data analysis pipelines in R, refine the grammatical structure of the English manuscript, and ensure compliance with formatting guidelines. The authors maintain full responsibility for the academic integrity and final validation of the scientific content.

Supplementary Material

Curated Pathway Panels (Tables 1S, 3S, 5S, 7S) and Empirical Bayes Linear Modeling (R-limma) Output for the Host Pathway Architectures (T3N2 Interface vs Healthy Controls) (Tables 2S, 4S, 6S, 8S)

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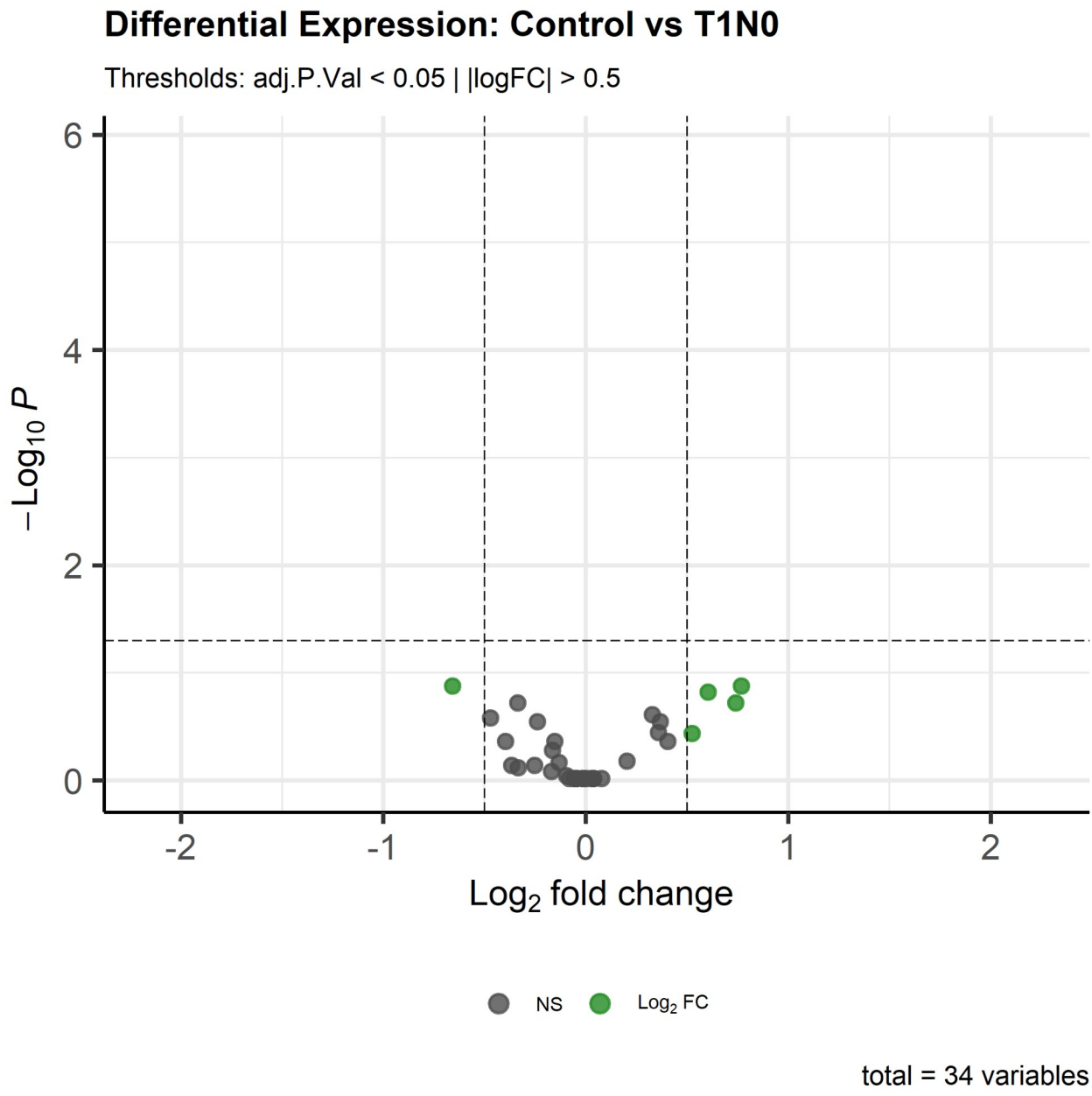
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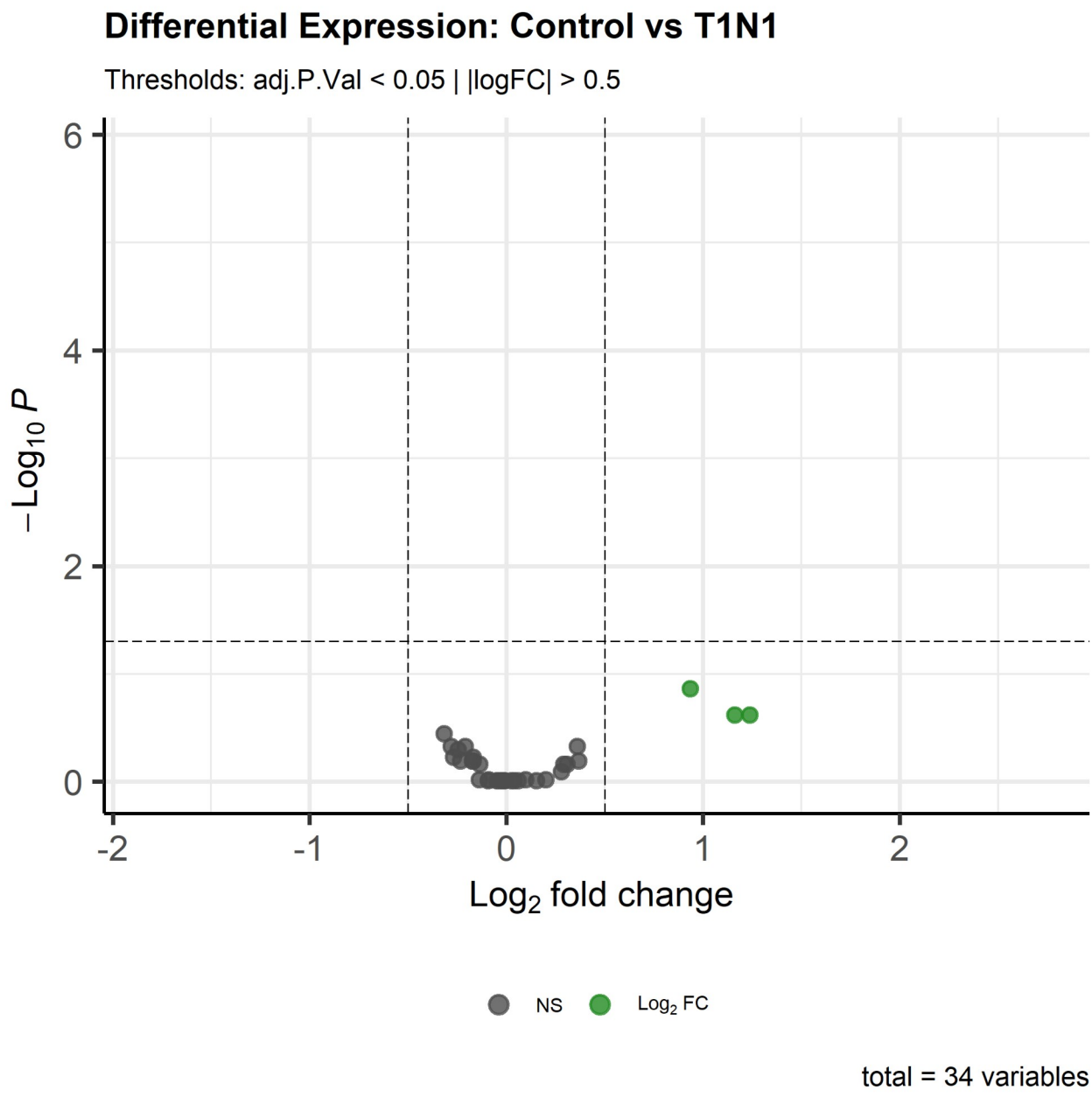
Figure 1. Cross-Stage Sequential Transcriptomic Profiling of the Curated TNF Signaling Panel in Nasopharyngeal Carcinoma Progression.

A



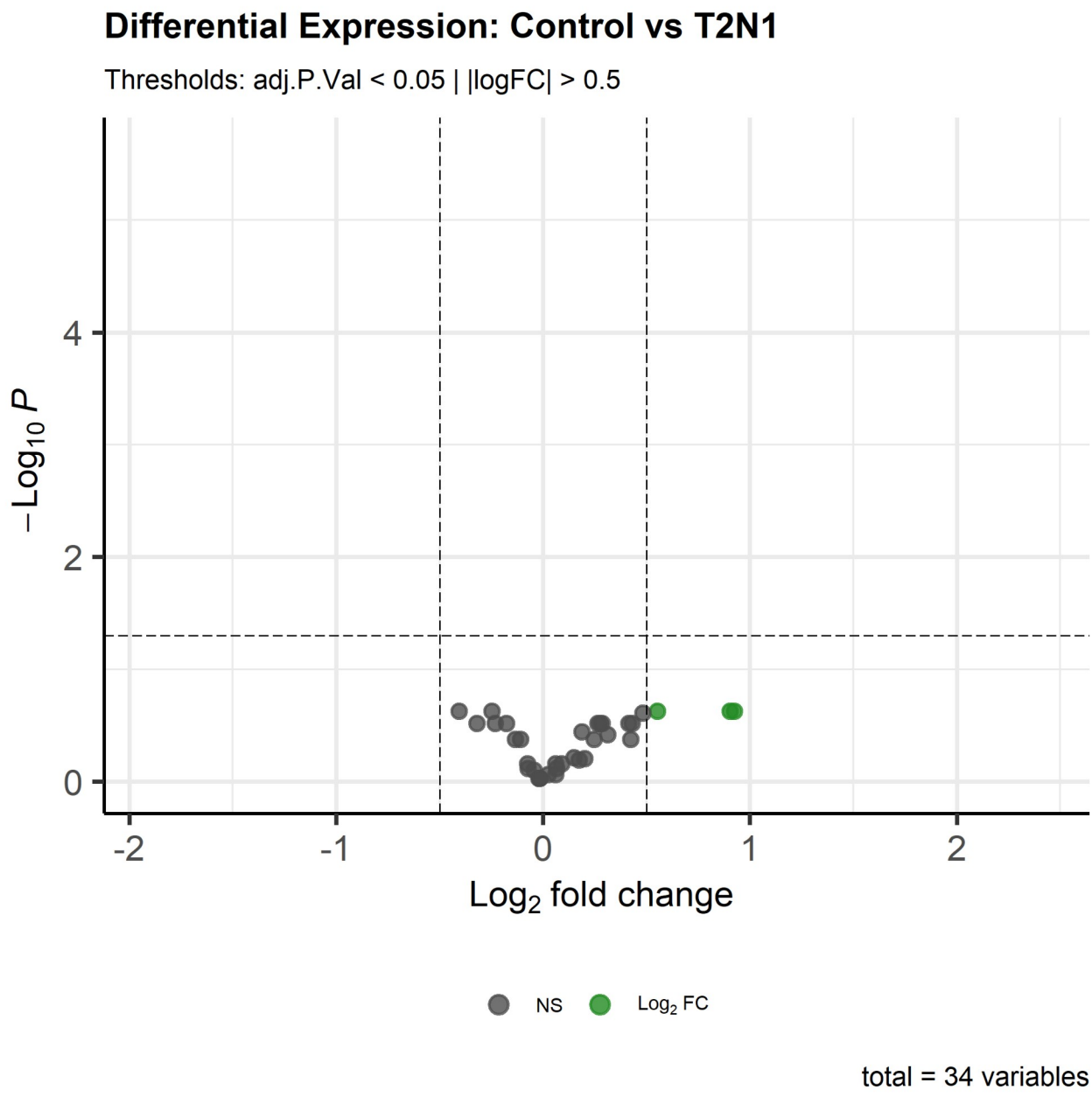
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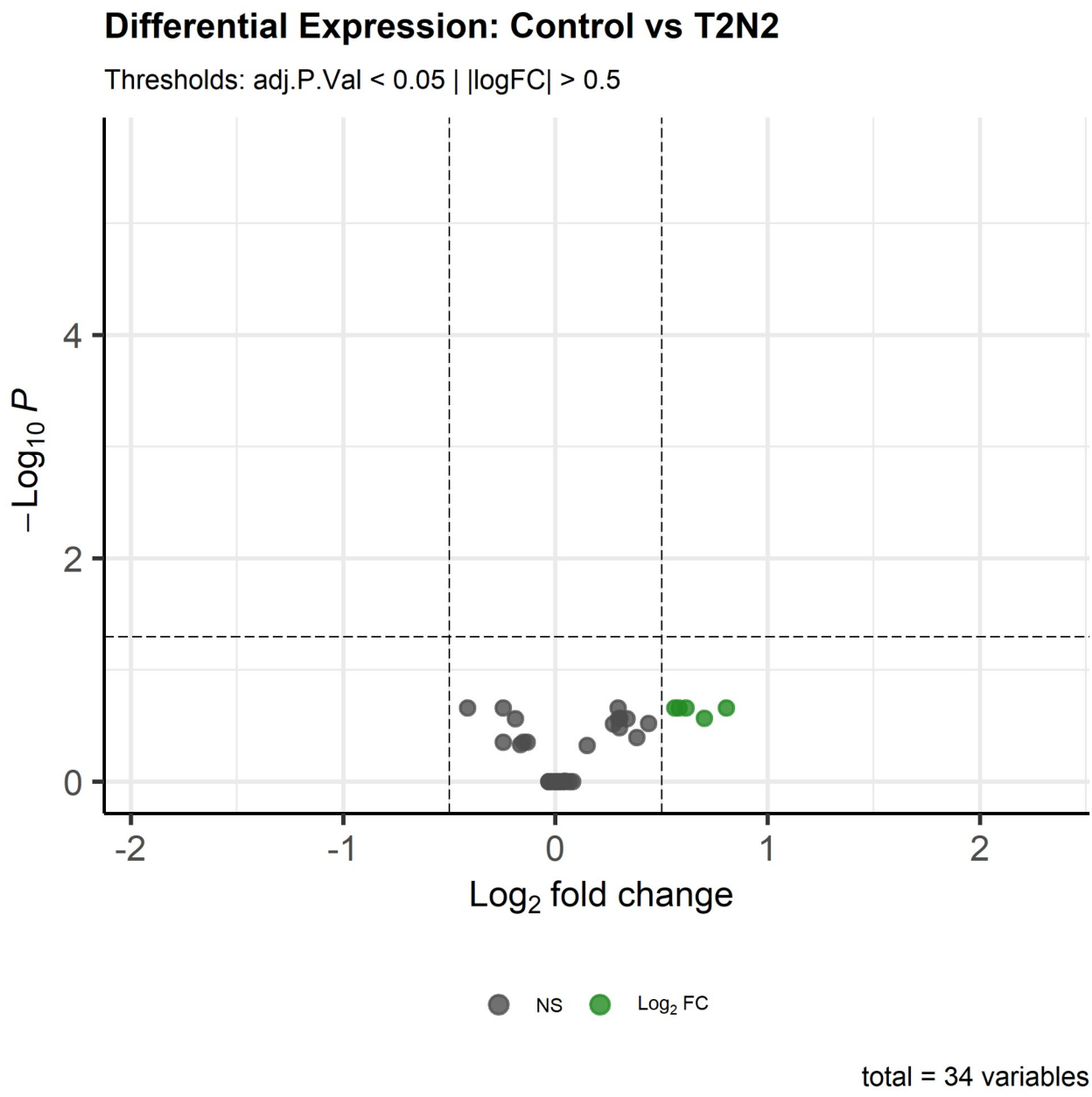
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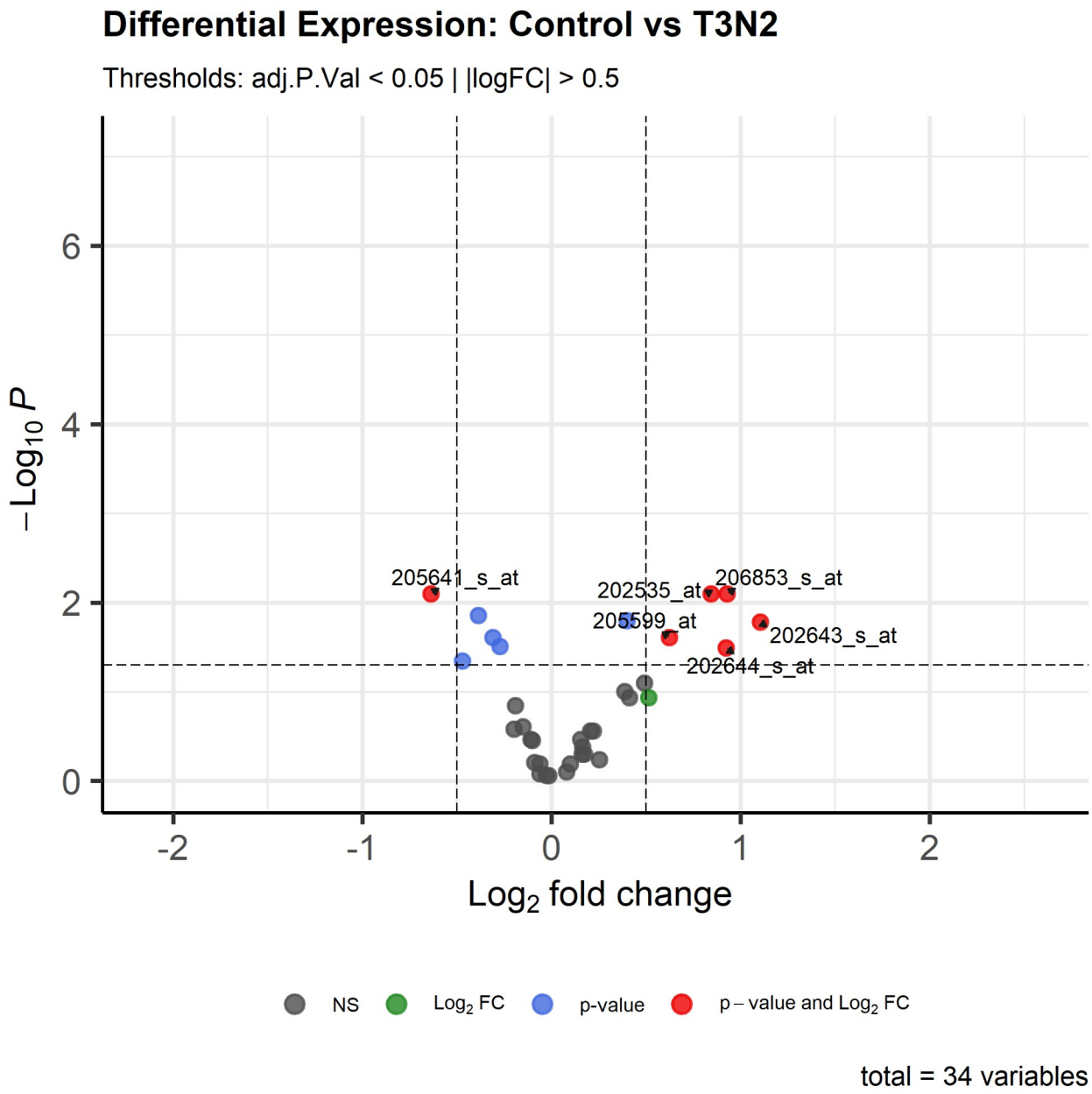
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D



(Figure 1 continued)

E



Sequential volcano plots displaying the differential expression of 34 primary human genes from the TNF pathway (Table 1S) comparing distinct pathological stages against healthy epithelial controls. The vertical dashed lines indicate the absolute log2-Fold Change threshold (|logFC| >= 0.5). The horizontal dashed line marks the statistical significance threshold (-log10 P-value corresponding to an adjusted P-value < 0.05). Dots are color-coded based on thresholds: grey indicates statistically non-significant (NS) transcripts; green represents transcripts passing only the |logFC| >= 0.5 threshold; blue indicates transcripts passing only the adjusted P-value < 0.05 threshold; and red represents highly significant differentially expressed genes passing both criteria.

- **Panel A: Control vs T1N0 Cohort.** The transcriptomic profile of early, localized lesions demonstrates complete pathway quiescence, with zero variables shifting into significant quadrants under the established screening cuts.
- **Panel B: Control vs T1N1 Cohort.** Tracking the transition into early nodal involvement reveals sustained pathway stability, showing no distinct transcriptional acceleration or gene mobilization.

- **Panel C: Control vs T2N1 Cohort.** Intermediate-stage specimens maintain a conserved and inactive baseline profile, validating the absence of typical host microenvironmental inflammatory alterations during early tumor expansion.
- **Panel D: Control vs T2N2 Cohort.** The intermediate advanced-nodal interface remains quiet, further supporting the model that classical extracellular host cytokine drives are not active.
- **Panel E: Control vs T3N2 Cohort.** The advanced-stage phenotype unmasks an explosive, highly localized intracellular activation loop. While the main exocrine cytokine TNF remains completely invariant and basal in the center of the plot, a targeted cluster of downstream intracellular transducers emerges in the high-significance quadrants. This critical boundary is led by the intense up-regulation of TRAF1 and MAP3K7/TAK1, accompanied by the selective structural repression of the pro-apoptotic adapter TRADD, serving as the host cell's integrated surrogate signature of latent, episomal viral LMP1 oncoprotein activity.

Supplementary Files

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- ManucriptRomeuCetalSupplementaryMaterial.pdf