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Single-Cell Transcriptomics Reveals Divergent Interferon Programs in Anti-TNFα Responders and Non-Responders

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Tumor necrosis factor-α (TNF-α) inhibitors are widely used in the treatment of rheumatoid arthritis (RA), yet therapeutic responses remain highly heterogeneous, with a substantial proportion of patients failing to achieve clinical benefit. To elucidate the cellular and molecular determinants underlying differential responses, we performed single-cell RNA sequencing of peripheral blood mononuclear cells (PBMCs) obtained from RA patients before anti-TNF-α therapy. Systematic analyses across immune subsets revealed distinct transcriptional programs associated with treatment outcome. Notably, interferon-α–related gene signatures and signaling pathways were significantly enriched in responders, whereas interferon-γ–driven programs predominated in non-responders. Cell–type–specific analyses highlighted responder-enriched activation of interferon-stimulated genes within interferon classical monocytes, alongside perturbation-based modeling that confirmed their strong association with favorable clinical trajectories. In contrast, non-responders exhibited heightened interferon-γ–linked activation in NK and T cell subsets, consistent with pro-inflammatory circuitries previously implicated in autoimmune pathogenesis. Collectively, our findings suggest that divergent interferon axis utilization, that type I interferon in responders versus type II interferon in non-responders, represents a critical immunological determinant of anti-TNF-α efficacy in RA. These insights may inform predictive biomarker development and guide rational therapeutic stratification.