Insights into granuloma resolution upon mTOR inhibition in sarcoidosis patients

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Introduction

In a recent clinical trial, systemic inhibition of mTORC1 (mechanistic target of rapamycin complex 1) resulted in a long-lasting remission in a subset of patients with cutaneous sarcoidosis, a granulomatous disease. To unravel the molecular mechanisms behind the response, we leveraged single-cell RNA sequencing and spatial transcriptomics to analyze skin biopsies from different trial timepoints. Our objective is to decode the transcriptional landscape of granuloma resolution and explore key cellular and molecular interactions driving disease persistence.

Results

We recovered all expected cell subsets, alongside distinct granuloma-specific cell populations. Significant transcriptional changes were observed in macrophages, helper T cells and fibroblasts after systemic mTOR inhibition, predominantly in genes linked to granulomatous inflammation. These changes result in a transcriptional profile mirroring that of healthy skin and correlate with clinical response. We have identified the cell sub-populations most affected by the treatment, along with their functions and spatial location in the tissue. The elimination of these granuloma-associated cell subsets from the tissue is a key factor in the observed transcriptional changes. Importantly, T cell-derived cytokine signalling emerged as driver of fibroblast reprogramming within granulomas, a process we successfully recapitulated in vitro.

Conclusions

mTOR inhibition reshapes the granulomatous microenvironment, driving a return toward homeostatic gene expression by the elimination of granuloma-associated macrophages, T cells and fibroblasts. Overall, our findings not only provide insight into the cellular mechanisms underlying granuloma resolution, but also establish an in vitro model for further exploration of pathomechanisms of persistent granulomas.