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Dual dysregulation of TNF/IFN signaling and classical monocytes are implicated in reactive infectious mucocutaneous eruptions

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To the Editor: Reactive infectious mucocutaneous eruption (RIME) is a severe mucocutaneous adverse reaction characterized by mucocutaneous blisters that occur days to weeks after an infection. RIME exists morphologically on a spectrum with Stevens-Johnson syndrome (SJS) but is clinically distinguished because it principally affects mucous membranes and is not triggered by medication. Various pathogens, especially Mycoplasma pneumoniae, trigger RIME, although some cases have no identifiable pathogen. RIME often requires hospitalization due to compromised oral intake and may cause permanent mucosal scarring (1). Treatment involves identification and treatment of the pathogen trigger, wound care, topical therapy, pain management, nutritional support, and expedient immunomodulatory therapy. Systemic immunomodulatory treatment for RIME includes corticosteroids, TNF inhibitors, cyclosporine, and intravenous immunoglobulin (IVIg). Recent studies on SJS–toxic epidermal necrolysis (SJS-TEN) validate TNF-targeted therapy based on multiomic single-cell analysis, confirming TNF upregulation in T cells, NK cells, and macrophages. JAK/STAT signaling was upregulated, supporting treatment using JAK inhibitors (2). Here, single-cell RNA sequencing (scRNA-Seq) and multiplex serum profiling were performed on samples from patients with RIME to characterize pathophysiologic mechanisms and identify biomarkers. This study obtained samples from a 10-year-old female patient who was hospitalized for 19 days with severe adenovirus-triggered RIME. The patient had fever and eye, mouth, and vaginal blistering. Treatment included 3-day methylprednisolone (1-gram pulse per day) with a 7-day taper, 2 IVIg infusions […]

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Systemic immunomodulatory treatment for RIME includes corticosteroids, TNF inhibitors, cyclosporine, and intravenous immunoglobulin (IVIg). Recent studies on SJS–toxic epidermal necrolysis (SJS-TEN) validate TNF-targeted therapy based on multiomic single-cell analysis, confirming TNF upregulation in T cells, NK cells, and macrophages. JAK/STAT signaling was upregulated, supporting treatment using JAK inhibitors (2). Here, single-cell RNA sequencing (scRNA-Seq) and multiplex serum profiling were performed on samples from patients with RIME to characterize pathophysiologic mechanisms and identify biomarkers. This study obtained samples from a 10-year-old female patient who was hospitalized for 19 days with severe adenovirus-triggered RIME. The patient had fever and eye, mouth, and vaginal blistering. Treatment included 3-day methylprednisolone (1-gram pulse per day) with a 7-day taper, 2 IVIg infusions of 2 g/kg on days 5 and 7 of hospitalization, and 2 doses of 0.8 mg/kg of etanercept on days 7 and 9 of hospitalization. Mucosal and skin biopsies demonstrated neutrophilic infiltrate accompanied by mononuclear perivascular infiltrate (Supplemental Figure 1; supplemental material available online with this article; https://doi.org/10.1172/jci.insight.194642DS1). Transcriptomics were performed on PBMCs during active disease (before immunomodulation) and 6 months after hospitalization. Single-cell clusters and subclusters were annotated using canonical gene markers (Figure 1A and Supplemental Figure 2A). In active RIME, nonclassical monocytes and myeloid dendritic cells were absent (Figure 1B and Supplemental Figure 2B). Other myeloid subsets or T cell subclusters showed no striking changes in their proportions (Supplemental Figure 3A). Differential expression analysis of classical monocytes revealed *IL1R2*, *TNFAIP6*, *S100A8/9/12*, *FKBP5*, *CXCL1/2/3/8*, *RNASE2*, and *IFI27* upregulation in active disease, which suggests stimulation from TNF, type I and II IFNs, IL-6, and IL-2 (Figure 1C).

Differential expression analysis was performed on regulatory T cells, NK T cells, $CD8^+$ T cells, and $CD4^+$ T cells (Supplemental Figure 3, B–F). During active RIME, regulatory T cells differentially expressed elevated levels of *PIM1*, a negative regulator of FOXP3. $CD8^+$ T cells highly expressed *CD69*, indicating tissue-resident memory cytolytic T cells. $CD8^+$ T cells had elevated *TNFSF8*, which encodes CD30L, a regulator of $CD4^+$ effector and memory T cell accumulation in tissues, similar to OX40/OX40L. Both $CD8^+$ and $CD4^+$ T cells demonstrated decreased levels of *OAS3* and *STAT1* after patient recovery, suggesting reduced IFN signaling. Of note, $CD8^+$ T cells, NK T cells, and classical monocytes had increased levels of *FKBP5* during active RIME, which promotes NF-κB activity and is associated with limited corticosteroid response (3). Monocyte cell-cell communication analysis comparing active to recovered samples supports heightened ligand-receptor interactions involving monocyte-produced CXCL1/2/8 with CXCR2 expression on NK cells, suggesting augmented NK cell recruitment. Furthermore, elevated CCL3-CCR1 and CCL5-CCR3 interactions between NK cells and monocytes and CCR3-CCL3 interactions between monocytes suggests a feedback loop promoting monocyte and NK cell recruitment (Figure 1D).

Multiplex analysis of 261 proteins was performed on serum from the patient with adenovirus-triggered RIME and 4 patients with active RIME (Figure 1E). Disease severity varied between patients. Three patients required hospitalization, 3 had multiple mucosal sites affected, and 3 had fevers. Pathogen triggers included *Mycoplasma pneumoniae*, adenovirus, SARS-CoV-2, and unknown triggers (Supplemental Table 1). Protein profiling identified significantly upregulated CXCL9, CXCL10, IL-6,

Authorship note: ZT, GW, and DSF contributed equally to this work. BC, FA, and RO contributed equally to this work.

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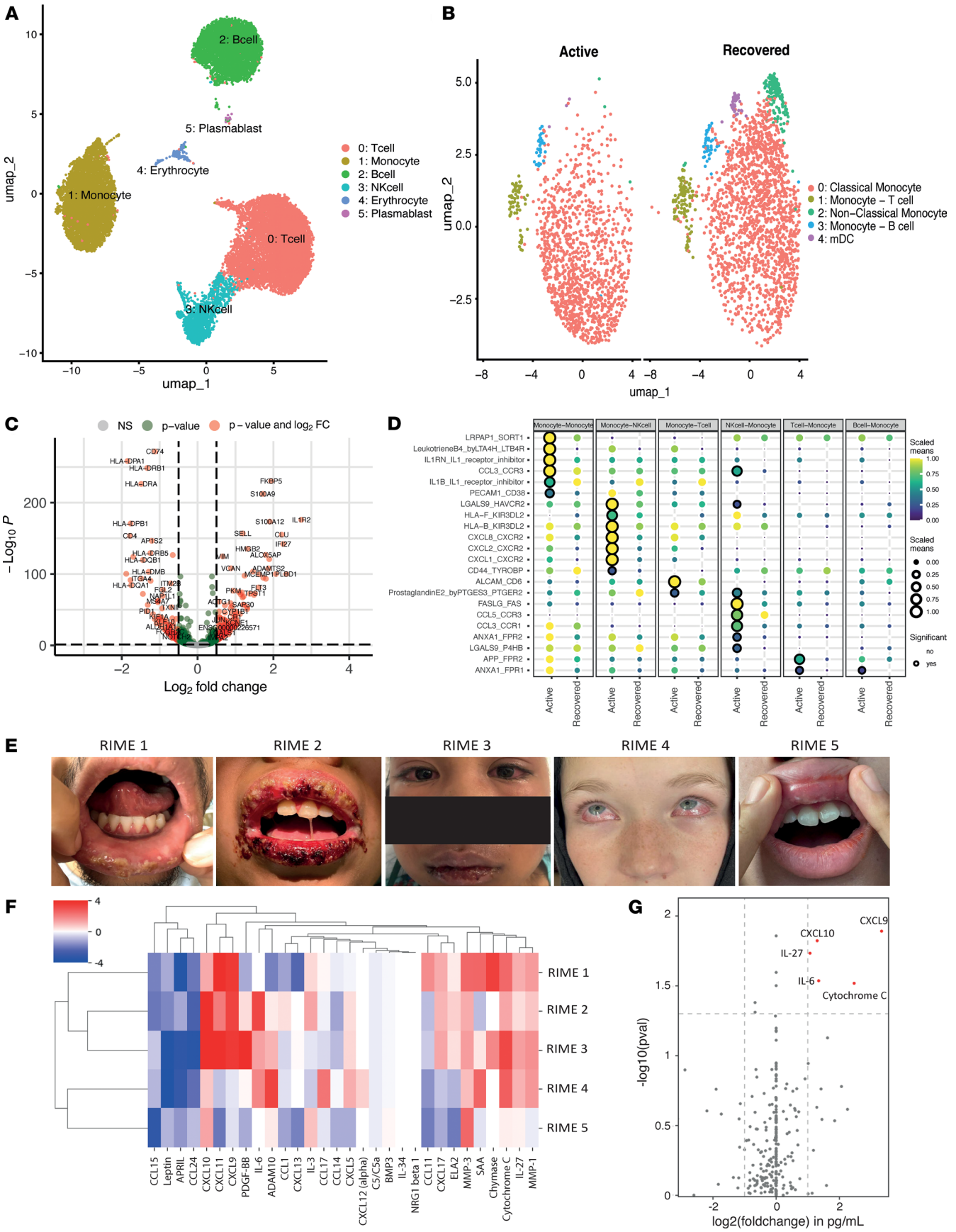

Figure 1. Clinical and inflammatory profiling of 5 patients with RIME. (**A**) UMAP visualization of PBMCs from adenovirus-triggered RIME using single-cell multiomics. (**B**) UMAP visualization of monocyte subclusters in active disease versus recovered samples. (**C**) Volcano plot of differentially

expressed genes in classical monocytes comparing active disease to recovered. Genes with a $-\log_{10}$-adjusted *P* value of greater than 1.3 (adjusted $P < 0.05$) and an absolute $\log_2$(fold change) of greater than 0.5 are highlighted in red. Statistical significance was determined using the quasi-likelihood *F* test. (**D**) Dot plot of ligand-receptor interactions involving classical monocytes in active disease. Color and dot size represent the mean of expression levels of interacting molecules. Significant interactions ($P < 0.05$) are highlighted with a black dot border. (**E**) Clinical photographs of patients with active RIME. (**F**) Multiplex protein analysis clustergram of 30 proteins with highest variability compared with healthy controls. Variance depicted with +4 maximum (red) and –4 minimum (blue). Hierarchical clustering using dendrograms clustered similar patient samples and analytes. (**G**) Volcano plot depicts statistically significant analytes when comparing patients to healthy controls. Dashed vertical lines: 2-fold change; dashed horizontal line: $P < 0.05$, (2-sided unpaired *t* test, false discovery rate adjusted).

IL-27, and cytochrome *c* when comparing patients with RIME with 8 healthy controls (Figure 1, F and G). Corresponding changes in cytokine and chemokine mRNA was not detectable in scRNA-Seq data, suggesting noncirculating cells contribute to elevated levels in the serum (Supplemental Figure 3G). Hierarchical clustering using dendrograms identified similarities between RIME patients 1–3, correlating with mucositis severity.

This study provides insight into the inflammatory profile of RIME. scRNA-Seq from a patient with adenovirus-triggered RIME implicates multiple inflammatory signals, including TNF and type I and II IFNs. Monocytes emerged as key drivers of RIME based on transcriptional and histopathologic analyses. Infiltrating MPO^+CD68^+ myeloid cells were identified in the skin of patients with SARS-CoV-2–triggered RIME (4). Serum profiling of 5 patients identified elevated CXCL9, CXCL10, IL-27, and IL-6, implicating dysregulation of TNF and IFN signaling. Inflammatory cytokine and chemokine production in RIME likely arises from affected skin, consistent with other inflammatory dermatologic diseases, such as lichen planus (5). Further evaluation of blood, blister fluid, immune cell infiltration using techniques such as flow cytometry, and spatial tissue transcriptional profiling will help to clarify inflammatory signaling in RIME.

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