



A large-scale single-cell transcriptomic atlas indicates the immune panorama of influenza A infection

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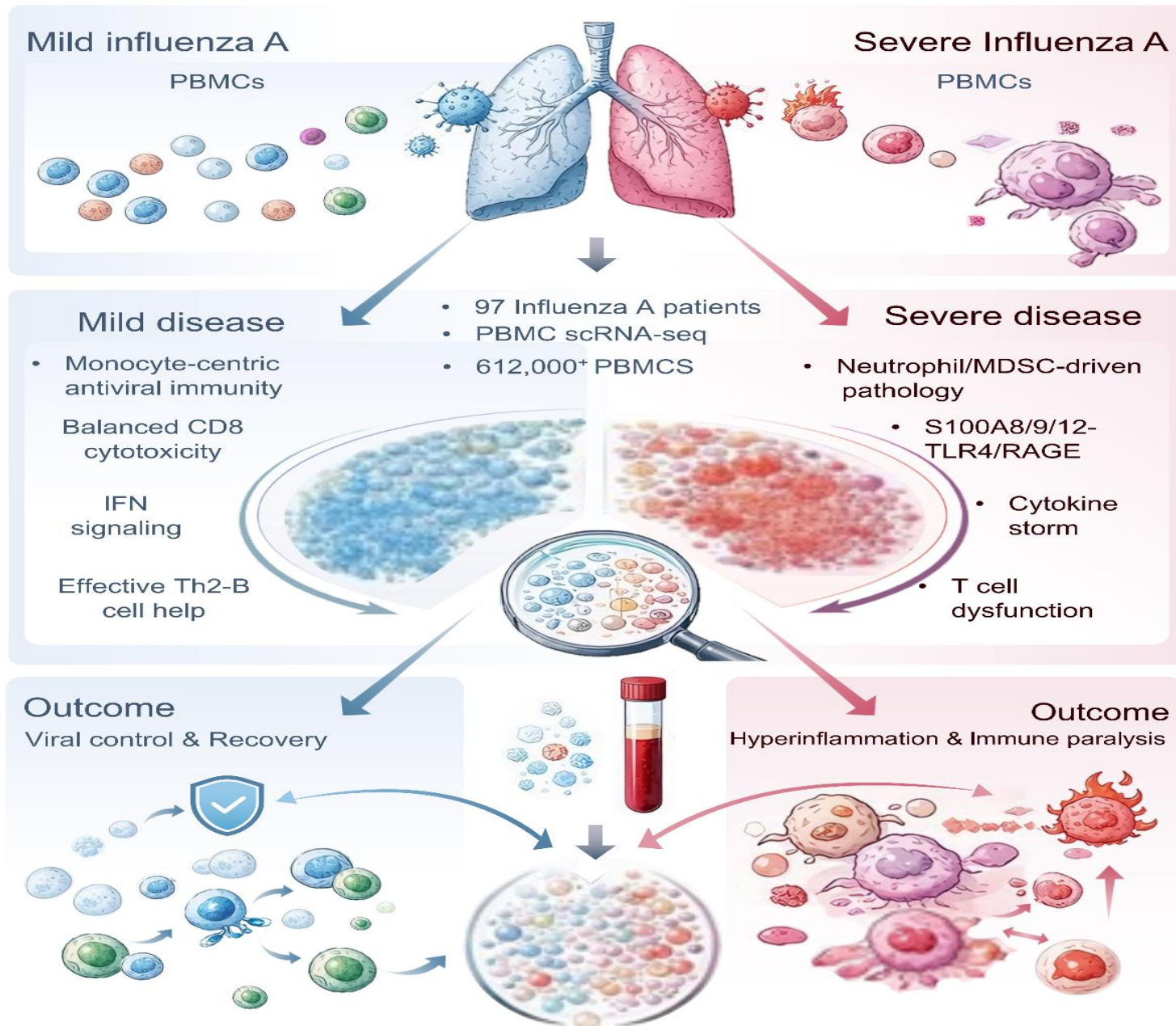


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Introduction





Highlights

- ❑ scRNA-seq analysis indicates a core immune dichotomy in influenza infection, distinguishing a protective monocyte-centric trajectory in mild disease from a pathological granulocyte-driven state in severe cases.
- ❑ Severe infection is characterized by a hyperinflammatory storm mediated by the S100A8/9/12–TLR4/RAGE signaling axis, coupled with immune paralysis driven by the expansion of MDSCs.
- ❑ Severe disease is marked by profound T cell dysfunction linked to metabolic collapse and mitochondrial failure, alongside the emergence of pathogenic, pro-inflammatory regulatory T cells.



Single-cell transcriptomics defines the immune panorama during IAV infection

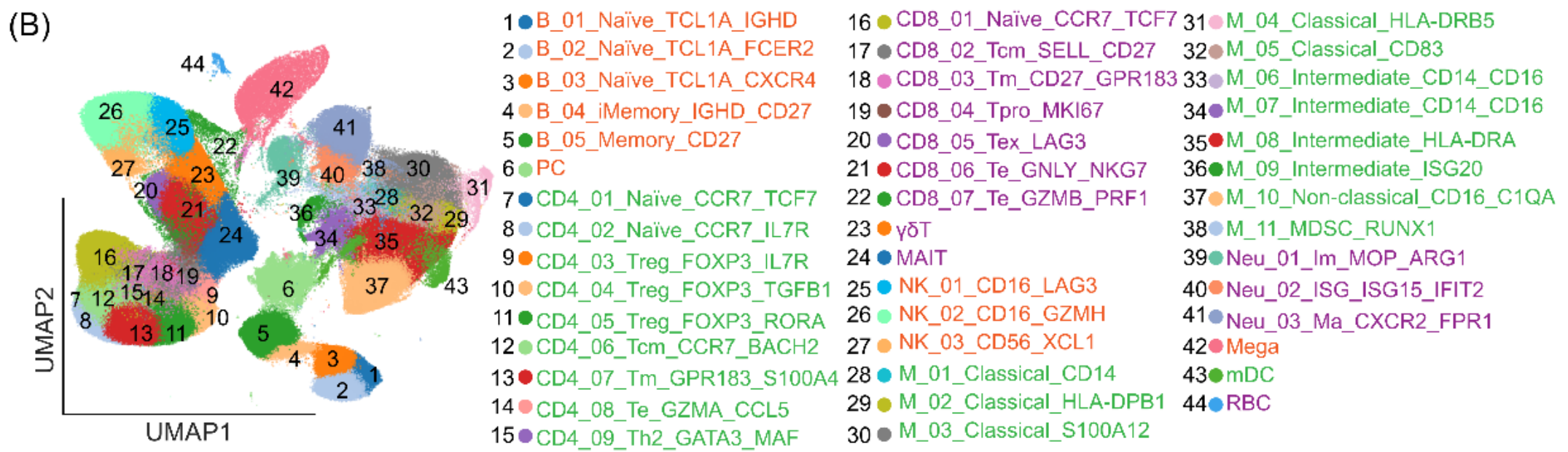
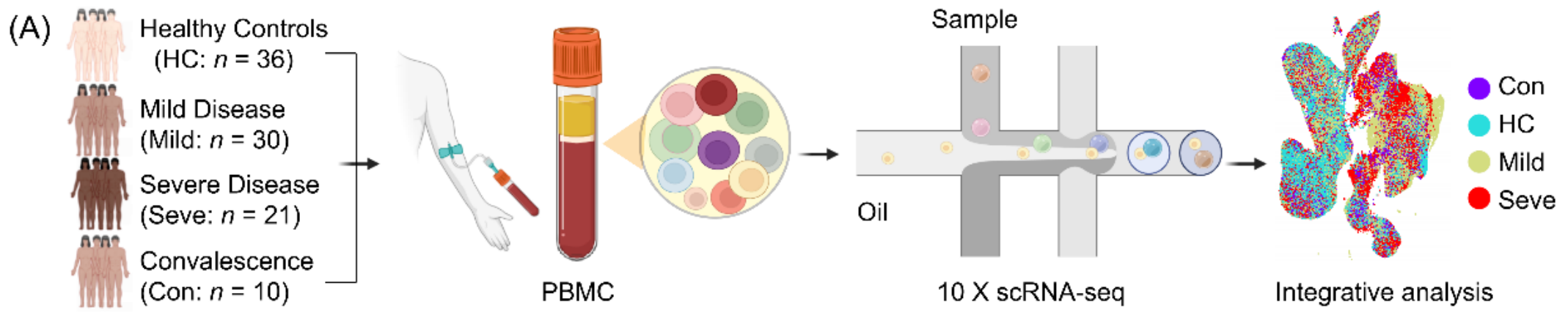


Figure 1. A single-cell atlas of the peripheral immune response to influenza A virus infection.

Single-cell transcriptomics defines the immune panorama during IAV infection

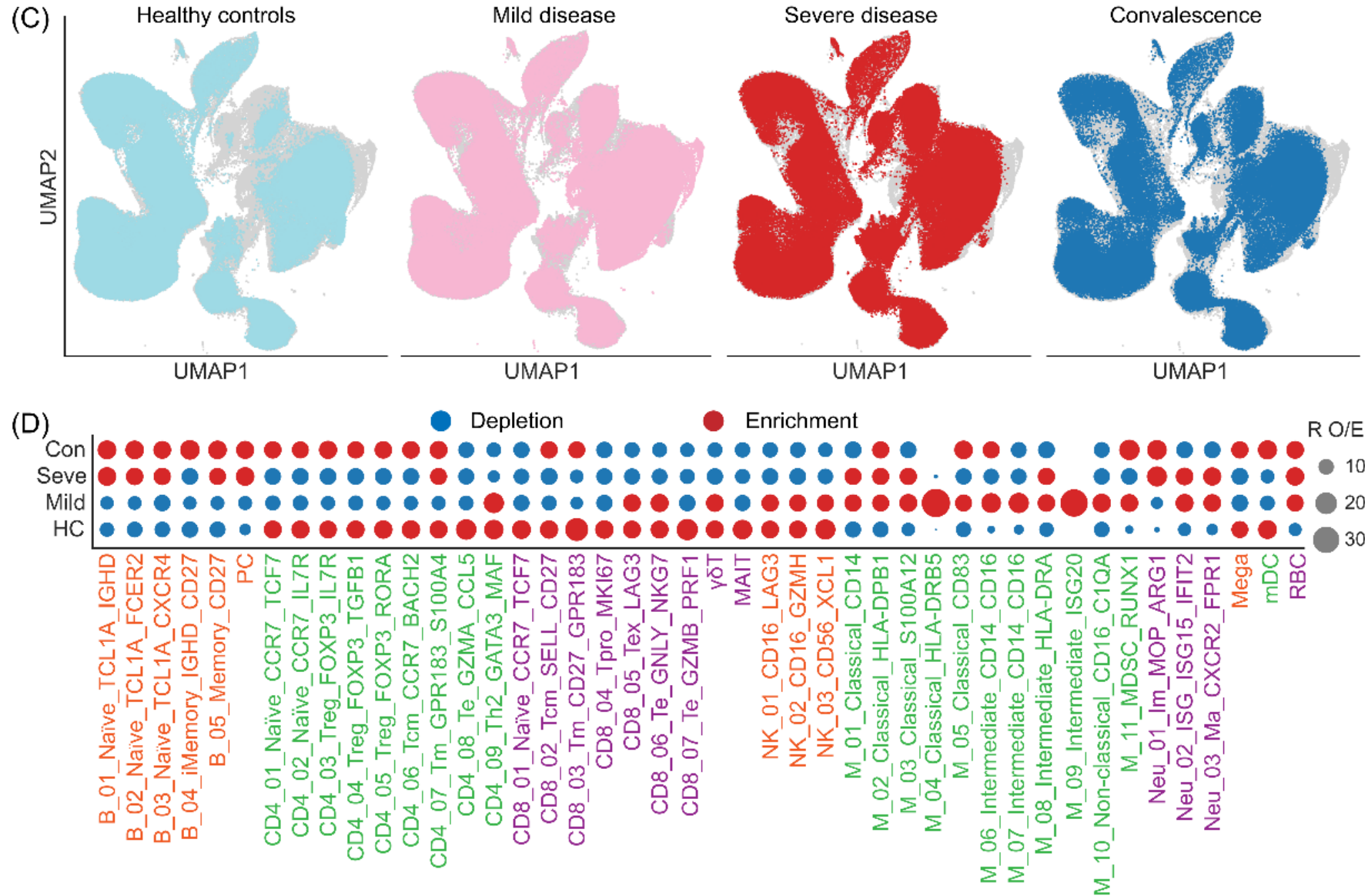


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Monocytes and neutrophils orchestrate the peripheral inflammatory storm in severe patients

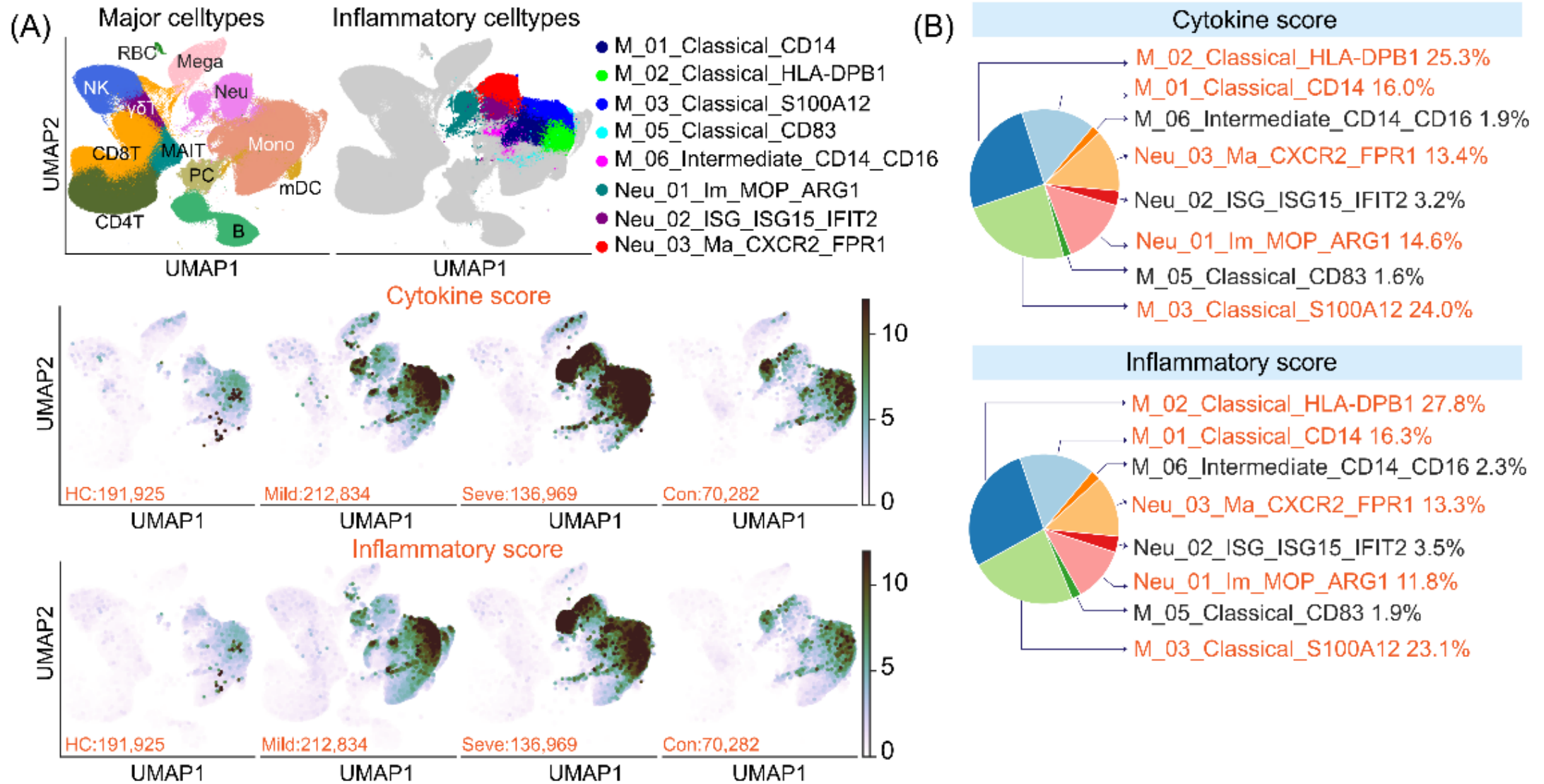


Figure 2. Hyperinflammatory monocytes and neutrophils drive the cytokine storm in severe IAV infection.



Monocytes and neutrophils orchestrate the peripheral inflammatory storm in severe patients

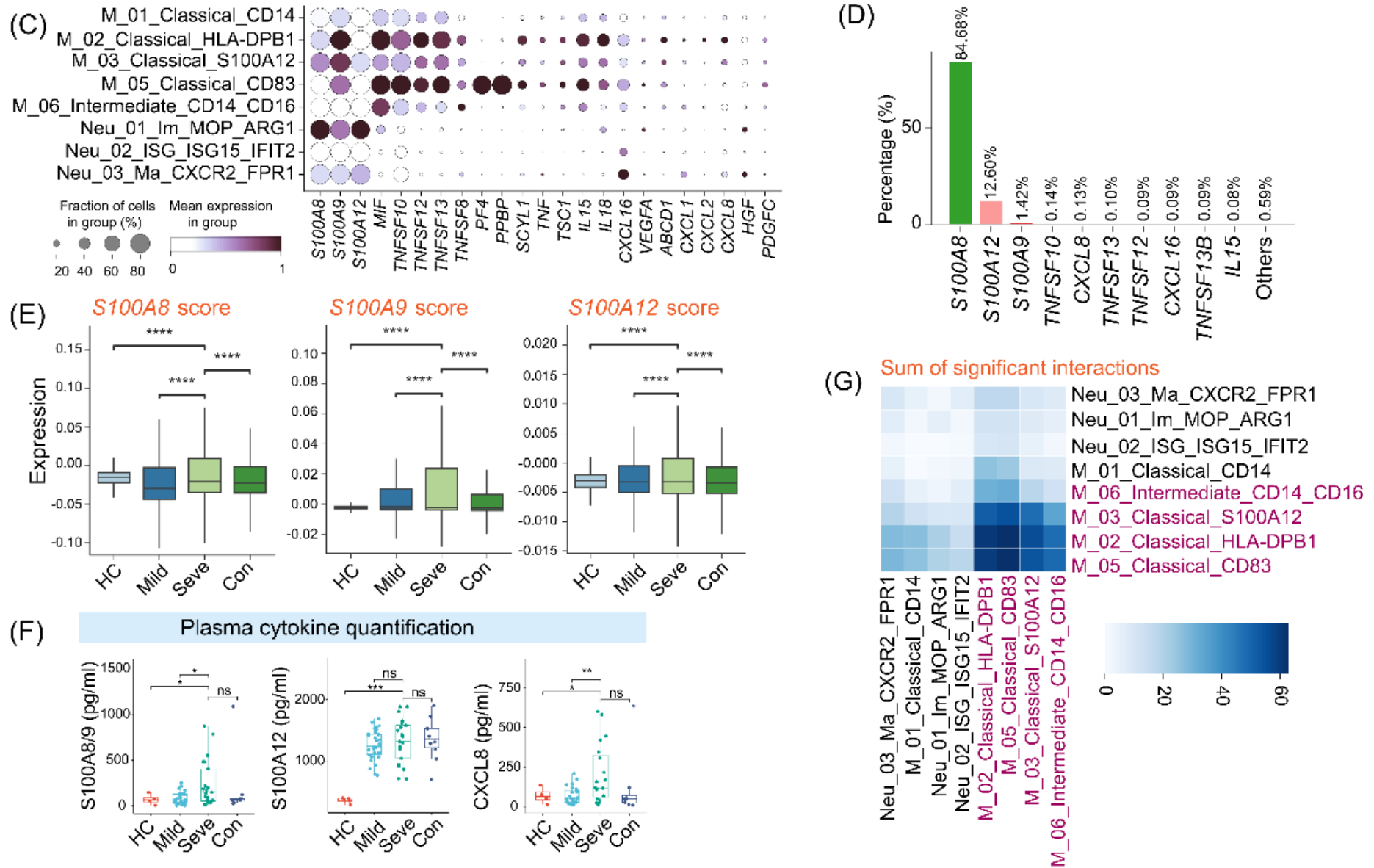


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Distinct CD8⁺ T lymphocyte trajectories distinguish disease severity

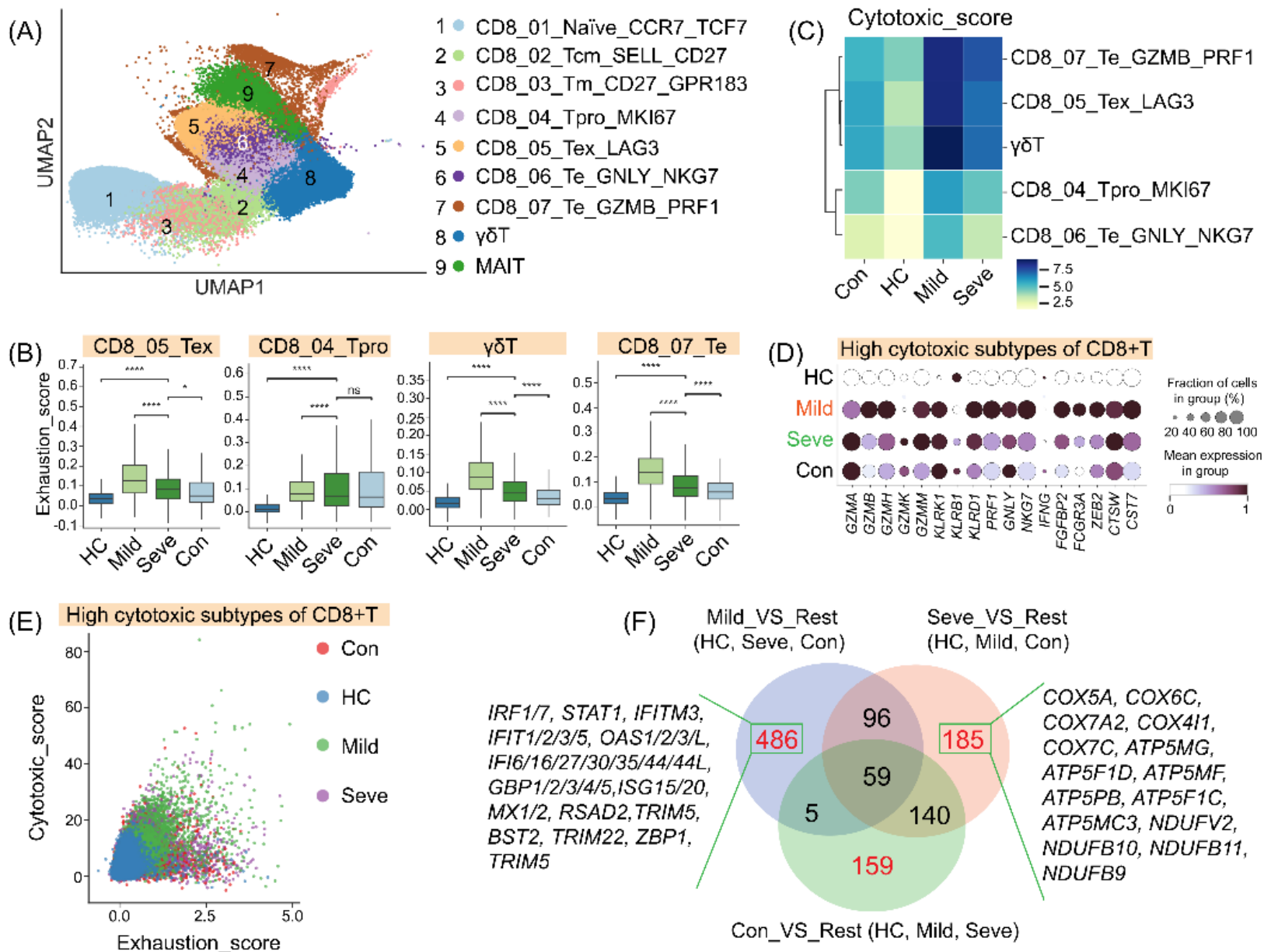


Figure 3. Dysfunctional CD8⁺ T cell states are associated with severe IAV infection.



Distinct CD8⁺ T lymphocyte trajectories distinguish disease severity

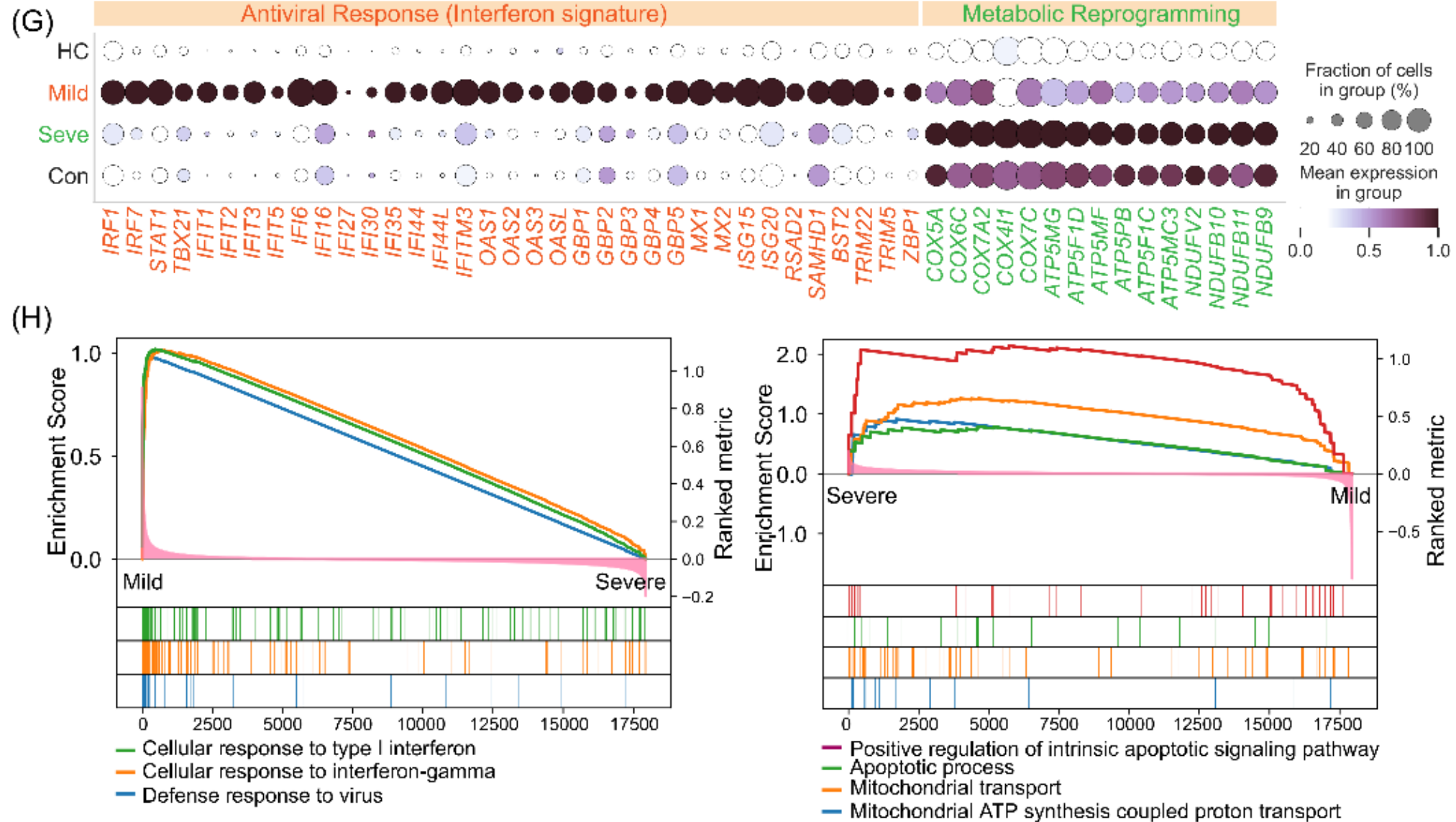


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CD4⁺ T cell heterogeneity defines disease severity

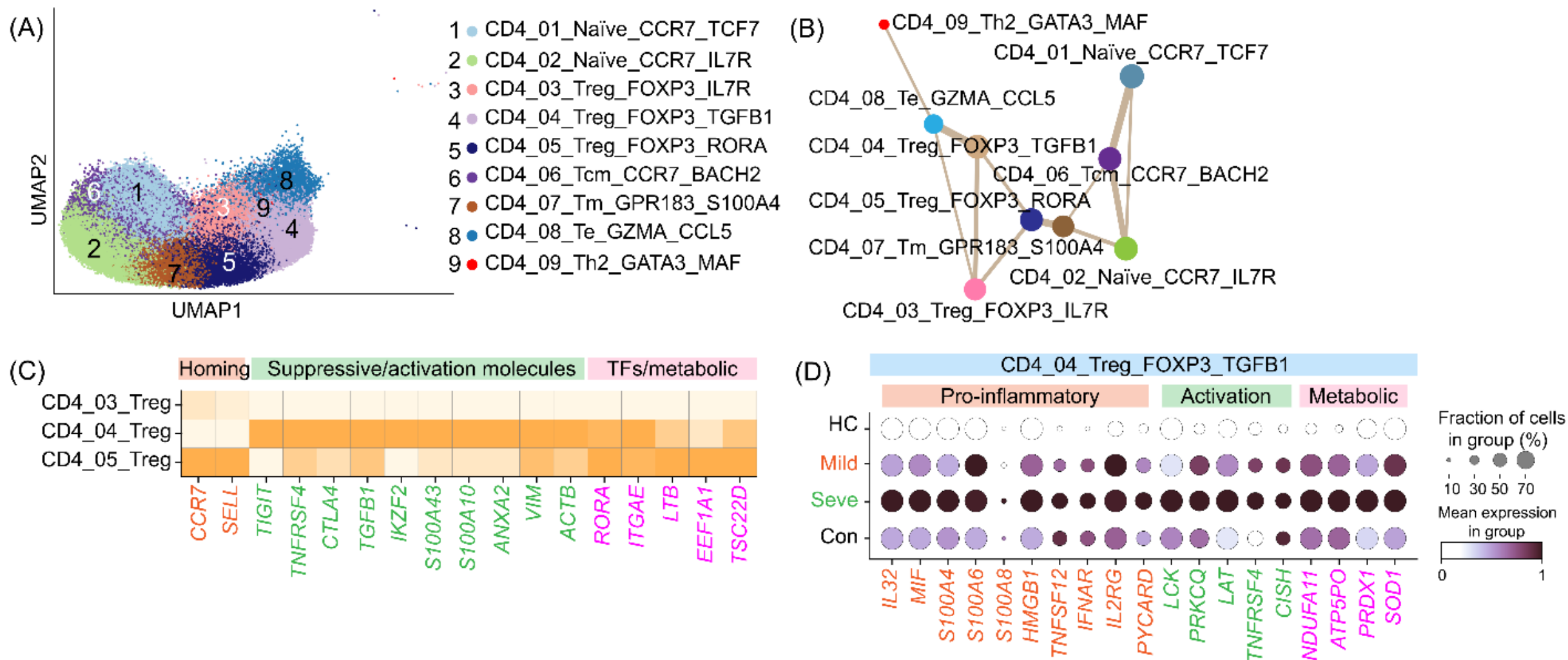


Figure 4. Pathogenic Tregs and dysfunctional effector CD4⁺ T cells characterize severe IAV infection.



CD4⁺ T cell heterogeneity defines disease severity

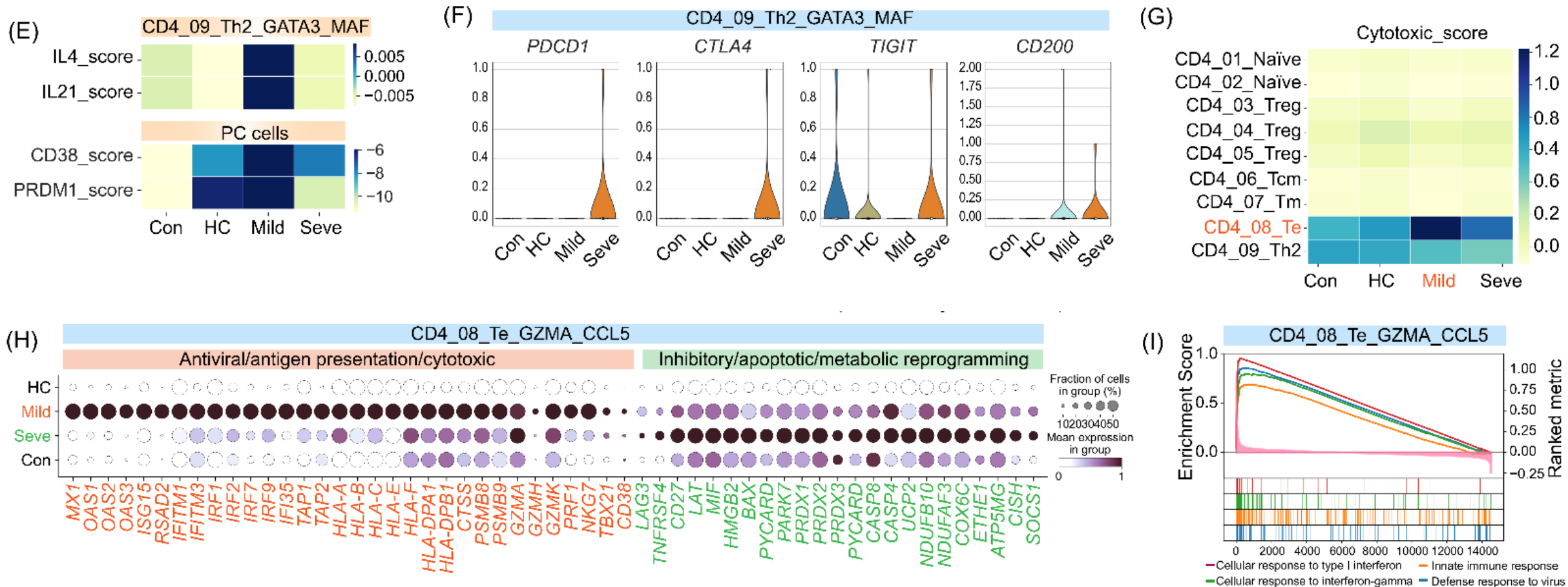


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Distinct B cell profiles are associated with disease severity

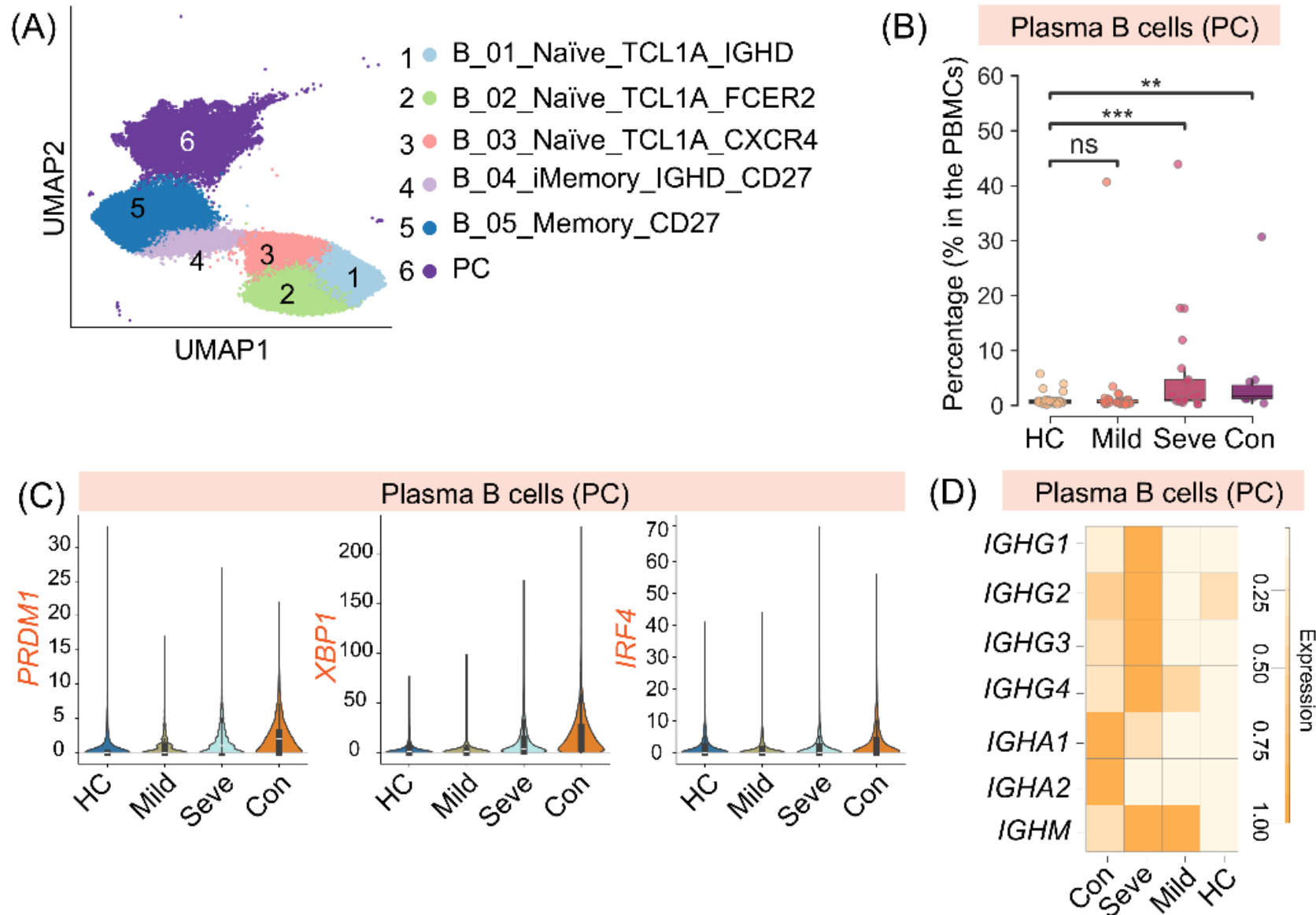


Figure 5. Dysregulated B cell activation and differentiation characterize severe IAV infection.



Distinct B cell profiles are associated with disease severity

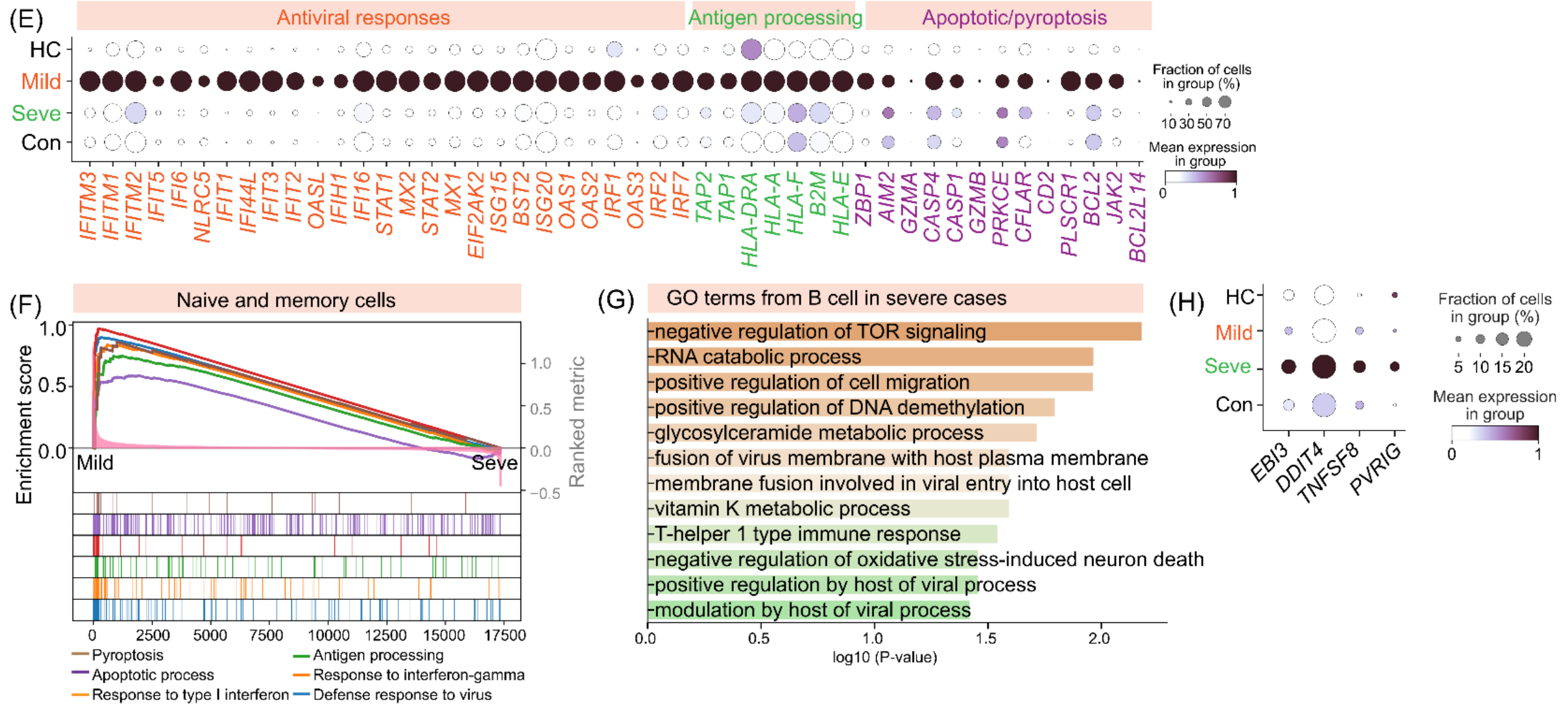


Figure 5. Dysregulated B cell activation and differentiation characterize severe IAV infection.



Dichotomous myeloid responses define disease severity and outcome

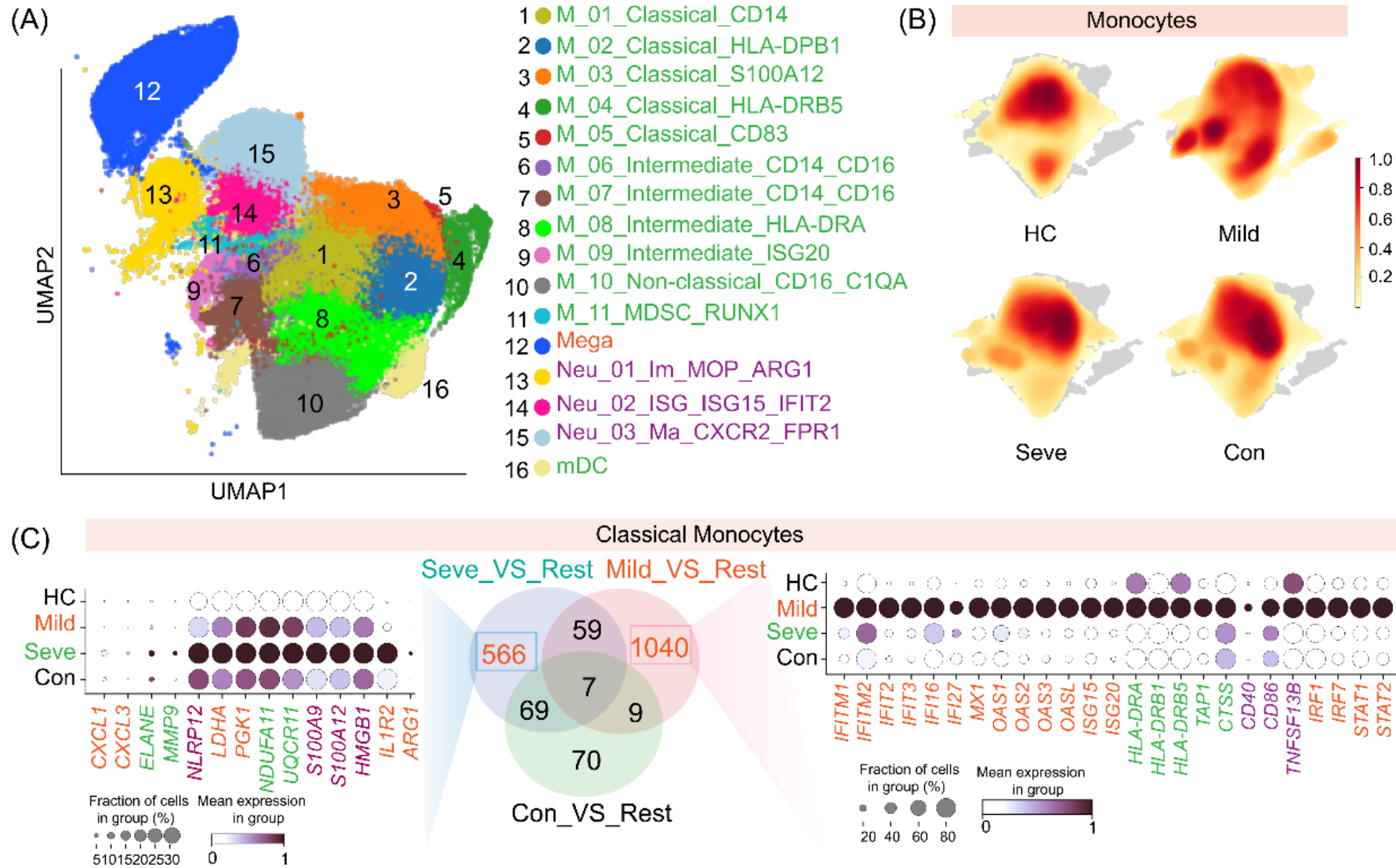


Figure 6. A monocyte-to-neutrophil shift and myeloid dysfunction define severe IAV infection.



Dichotomous myeloid responses define disease severity and outcome

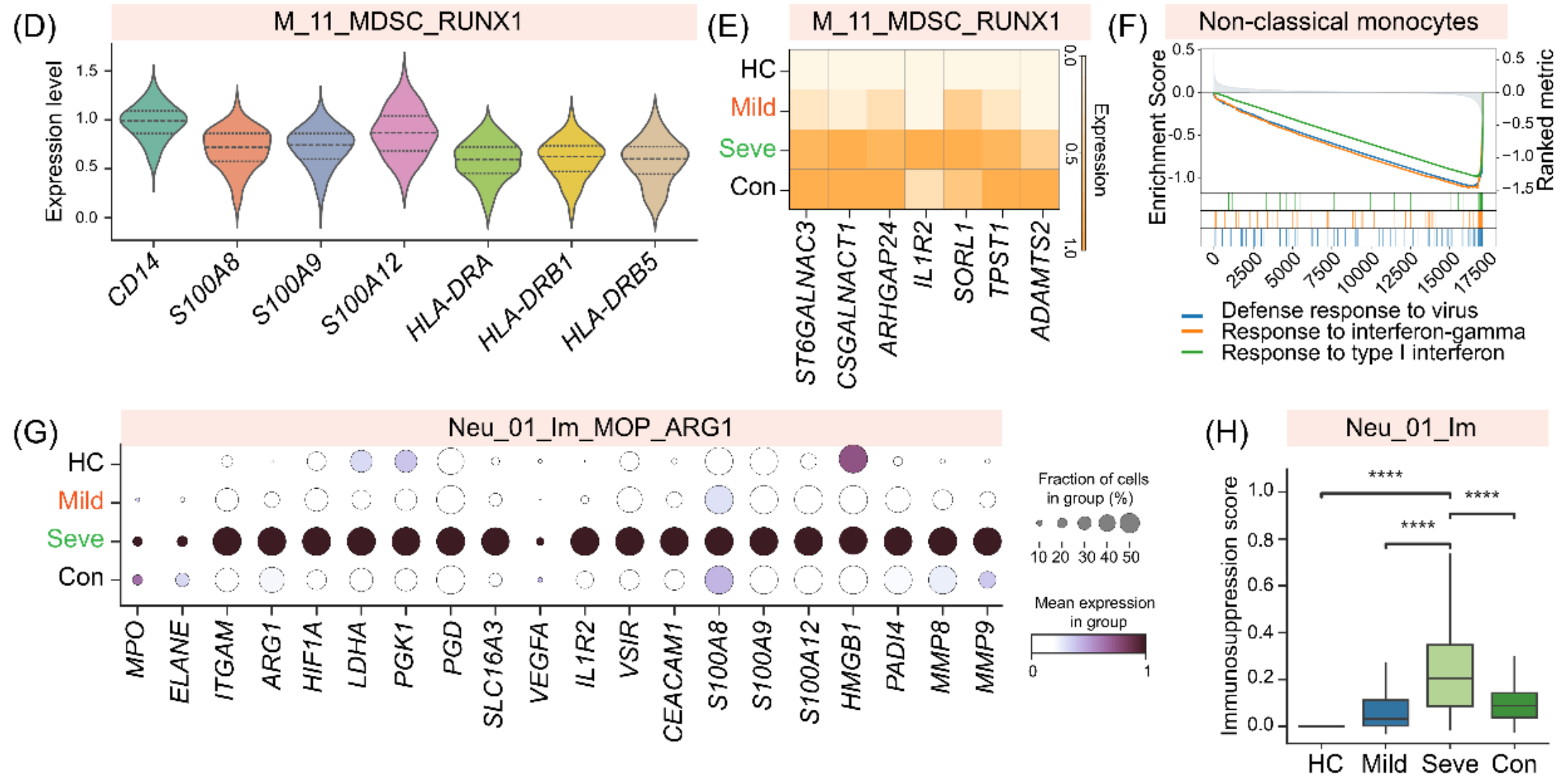


Figure 6. A monocyte-to-neutrophil shift and myeloid dysfunction define severe IAV infection.



Summary

- ❑ Our large-scale single-cell atlas provides a high-resolution immunological map of human IAV infection, indicating the dichotomy of peripheral immune responses associated with clinical severity.
- ❑ Protective immunity in mild illness relies on a coordinated myeloid, T and B cell response, characterized by robust antiviral signaling and balanced effector functions. Severe disease is driven by a dysregulated myeloid circuit generating hyperinflammation and immunosuppression, with concomitant systemic T and B cell dysfunction exacerbating pathology.
- ❑ Specifically, we conclude that this immune dichotomy is driven by the functional differentiation of monocytes and neutrophils, where the *S100A8/9/12–TLR4/RAGE* axis and MDSCs represent the key pathogenic targets.
- ❑ Collectively, our atlas elucidated key mechanisms of IAV host-immune pathogenesis and provides a foundational resource for designing targeted immunotherapies to ameliorate severe IAV infection.

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