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Peer Review

Review of: "γδ T Cells and the Extracellular Matrix: An Unmapped Sensing Axis in Barrier Immunity, Neuroinflammation and Cancer"

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The manuscript is well organized and presents an interesting and potentially important conceptual framework. However, the central claim that ECM sensing by γδ T cells is largely "unmapped" should be moderated, as previous studies have already demonstrated γδ T-cell interactions with ECM components and integrin-dependent adhesion. The authors should also incorporate recent literature showing direct effects of matrix mechanical properties on γδ T-cell migration and effector function. Importantly, the proposed integrin–actin–YAP pathway should be clearly distinguished from experimentally established mechanisms in conventional αβ T cells, as its operation in γδ T cells remains to be demonstrated. Overall, the review would be strengthened by a more comprehensive and balanced discussion of existing evidence, clearer separation of established findings from hypotheses, and a more precise definition of the unresolved molecular mechanisms of γδ T-cell mechanosensing.

The authors should incorporate recent evidence demonstrating that matrix mechanical properties can directly regulate γδ T-cell biology. In particular, recent work using tunable collagen-based matrices shows that matrix viscoelasticity influences γδ T-cell migration, differentiation state, phenotype, and effector function, with proteomic evidence implicating actin remodeling and metabolic pathways. In parallel, studies in conventional T cells demonstrate that matrix stiffness can regulate integrin-dependent actin remodeling, nuclear deformation, and YAP signaling. These findings provide an important framework for the manuscript, but they also highlight several unresolved questions: whether γδ T-cell responses to matrix mechanics are integrin-dependent, whether they involve the actin–nuclear deformation–YAP axis

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described in αβ T cells, whether different γδ subsets use distinct mechanisms, and whether stiffness, viscoelasticity, matrix architecture, or ligand density represents the dominant mechanical cue. The authors should also clearly distinguish ECM mechanosensing from TCR mechanosensing, as these may involve fundamentally different molecular mechanisms. Finally, recent evidence that γδ T cells themselves regulate stromal cells and ECM composition suggests a potentially important bidirectional γδ T-cell–ECM feedback loop that should be discussed.

Declarations

Potential competing interests: No potential competing interests to declare.