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Mechanoregulation of T-cell Function through Yap

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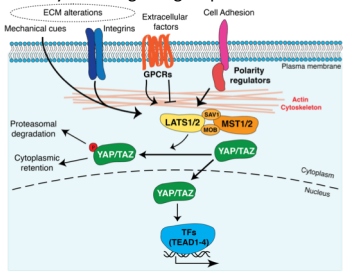
Objectives

Although tumor immunotherapy has been developed for various cancers, sustaining T-cell activation and recruitment in immunosuppressive solid tumors remains a major hurdle. T-cell function is modulated by mechanical cues, such as extracellular matrix (ECM) stiffness, but the molecular details by which such signals direct T-cell function are poorly understood. In this study, we investigate the role of Yap, a key mechanotransduction effector, in T-cell function in response to matrix stiffness. We aim to gain a better understanding of mechanoregulation on T-cell function through Yap, which will offer insights for the development of immunotherapies with improved T-cell response.

Background

- The Hippo signaling pathway transduces both internal and external signals to regulate cell proliferation, survival and fate.[1] Yes-associated protein (Yap) and transcriptional coactivator with PDZ-binding motif (Taz) are the major effector in the Hippo pathway which sense mechanic forces to transduce signals that impact gene expression and cytokine signaling responses.[2]



- In T cells, receptor interactions and soluble factors lead to T cell activation, clonal expansion and differentiation to perform a variety of functions central for adaptive immunity.
- T cells receive physical cues in the form of stiffness, shear stress, and tension from surface receptors, which can be transduced into biochemical signals that regulate T-cell responses through activation of ion channels, metabolism, chromatin reprogramming, and gene expression [3].
- **In this study, we investigated the role of Yap in T-cell activity and examine how these signals are regulated by matrix stiffness.**

Results

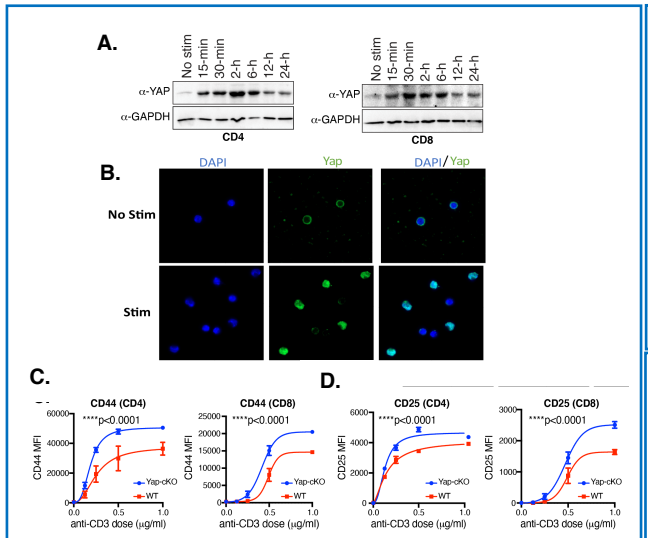


Figure 1. Yap expression is induced upon TCR activation and results in suppression of T-cell activation.
A. Yap expression in both CD4⁺ and CD8⁺ T cells after TCR activation.
B. Immunofluorescent of Yap in non-stimulated and stimulated CD4⁺ T cells.
C. CD25 and CD44 levels in Yap-cKO CD4+ and CD8+ T cells by flow cytometry.

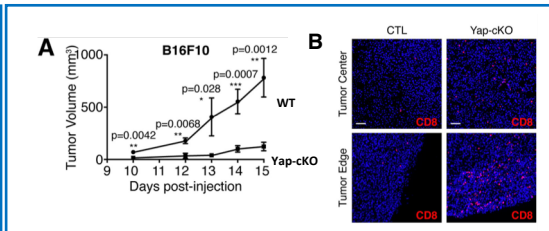


Figure 2. Yap depletion in T cells results in decreased tumor growth and increased tumor infiltration.
A. B16 tumor growth curve in WT and Yap-cKO mice.
B. CD8⁺ T cell infiltration by immunofluorescent staining on B16 tumors.

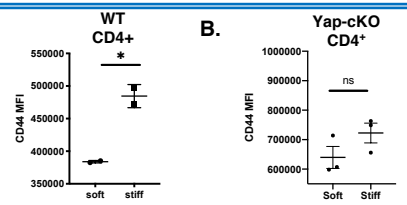


Figure 3. Effects of Matrix stiffness on T-cell response using PDMS culture surface.
A. CD44 expression of WT CD4⁺ T cells cultured on soft and stiff PDMS surfaces after 96hr of activation.
B. CD44 expression of Yap-cKO CD4⁺ T cells cultured on soft and stiff PDMS surfaces after 96hr of activation.

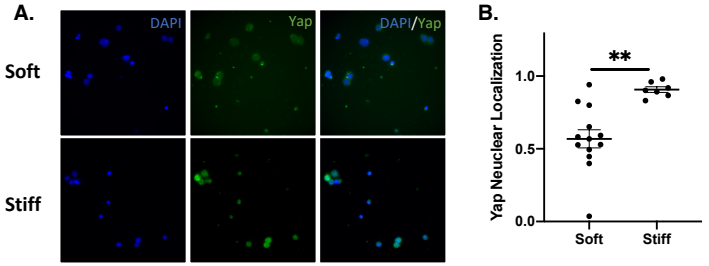


Figure 4. Nuclear localization of Yap in T cells under stiff environment.
A. Representative immunofluorescence images show YAP localization in WT CD4⁺ T cells on soft or stiff PDMS scaffolds.
B. Yap nuclear localization analyzed by colocalization analysis.

Conclusions/Future Direction

- Yap is upregulated in both CD4⁺ and CD8⁺ T cells after TCR activation and exhibits higher nuclear localization.
- Using a T-cell specific Yap conditional knock out mouse model and B16 melanoma tumor model, we observed an inhibitory role of Yap in T-cell activation and anti-tumor immunity, in which Yap-cKO T cells exhibit better activation and increased tumor infiltration[4].
- A Polydimethylsiloxane (PDMS) culture surface was used to construct culturing conditions for T cells with various rigidity. We observed increased T-cell activation in WT cells under stiff environment, whereas Yap-cKO T cells do not show similar responses to stiffness changes.
- Yap shows a higher nuclear localization under stiff microenvironment.
- Overall, our data suggests Yap is playing a key role in modulating T-cell function, and that Yap activity is regulated by matrix stiffness.
- We plan to further investigate the cytoplasmic and transcriptional roles of Yap in T-cell function and how Yap is regulated under different stiffness environments.

References

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