Mechanobiological control of T-cell activation

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New perspective of mechanobiology is currently emerging across multiple disciplines in the biomedical sciences. In contrast to conventional believes, recent evidence indicates that cells regulate their cell mechanics not downstream of signalling events triggered by ligand–receptor binding, but that cells employ a diversity of feedback mechanisms to dynamically adjust their mechanics in response to external stimuli. Quantifying cellular forces has therefore become an contentious challenge across multiple disciplines at the interface of biophysics, cell-biology, and immunology. Mechanical forces are especially important for the activation of immune T cells. Using a suite of advanced quantitative super-resolution imaging and force probing methodologies to analyse resting and activated T cells, we demonstrate activating T cells sequentially rearrange their nanoscale mechanobiology, creating a previously unreported ramifying actin network above the immunological synapse (IS). We show evidence that the kinetics of the antigen engaging the T-cell receptor controls the nanoscale actin organisation and mechanics of the IS. Using an engineered T-cell system expressing a specific T-cell receptor and stimulated by a range of antigens, force measurements revealed that the peak force experienced by the T- cell receptor during activation was independent of the kinetics of the stimulating antigen. Conversely, quantification of the actin retrograde flow velocity at the IS revealed a striking dependence on the antigen kinetics. Taken together, these findings suggest that the dynamics of the actin cytoskeleton actively adjusted to normalise the force experienced by the T-cell receptor in an antigen specific manner. Consequently, tuning actin dynamics in response to antigen kinetics may thus be a mechanism that allows T cells to adjust the length- and time- scale of T-cell receptor signalling.