Contribution ID : **130** Type : **Oral**

Disulfide bond formation between T-cell receptor and peptide antigen lowers the threshold of T cell activation

Thursday, 25 November 2021 11:00 (15)

The immune system is vigilant in detecting foreign pathogens. Our cells present peptides (p), small fragments of proteins, atop Major Histocompatibility Complex (MHC) glycoproteins. These pMHC molecules are displayed on the cell's surface and monitored by T cells of the immune system that patrol the body. T cells use their specialized T cell receptors (TCRs) to recognize and bind to pMHCs, where the quality of binding influences T cell activation. Activated T cells are responsible for killing off infected cells and clearing infection. The contribution of individual parameters that dictate activation for this cell-to-cell TCR-pMHC interaction are unclear. However, a long reigning hypothesis is that the threshold of T cell activation can be determined by the dissociation constant or binding affinity. We have engineered a disulfide bond (DSB) between two cysteine residues introduced into a TCR and peptide that are known to form a TCR-pMHC complex. The formation of the DSB was validated using biophysical assays and X-ray crystallography. This approach represents a model in which the covalently bonded TCR-pMHC do not dissociate, prolonging the confinement time of the interaction almost indefinitely. When this TCR and pMHC model were reproduced in T cells, we discovered that the DSB interaction was 10,000-fold more sensitive in activating T cells than the wild-type counterpart without altering binding affinity. Thus, we show that confinement time plays an important role in the activation of T cells, which could be useful in designing T cell therapies or peptide vaccines.

Level of Expertise

Early Career <5 Years

Presenter Gender

Man

Pronouns

Which facility did you use for your research

Australian Synchrotron

Students Only - Are you interested in AINSE student funding

Do you wish to take part in the Student Poster Slam

Condition of submission

Yes

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Session Classification : Biomedicine, Life science & Food Science

Track Classification : Biomedicine, Life science & Food Science