PAG Facilitates Immune Synapse Organization and PD-1 Function

Cancer remains the second leading cause of death in the US. Immunotherapy seeks to bolster immune cells’ ability to target malignant cells and has brought immense improvements in the field. One important inhibitory protein in T cells, Programmed Cell Death Protein 1 (PD-1), has become an invaluable target for cancer immunotherapy. While anti-PD-1 antibody therapy is extremely successful in some patients, in many others, it fails to help or causes complications, including cancer hyper-progression and immune-related adverse events. Study of the inhibitory transmembrane protein Phosphoprotein Associated with Glycosphingolipid Rich Microdomains 1 (PAG), a downstream target of PD-1 signaling, will help us better understand the PD-1 pathway, and offer another, perhaps more nuanced, target to potentially improve response rates and/or avoid immune-related adverse events. As a link between lipid-rich/signaling-protein-rich membrane regions and the actin cytoskeleton, PAG is an exciting and novel target for manipulating immune function. Prior therapeutic methods of immune manipulation all disrupt ligand binding or enzyme function. In contrast, innovative use of an anti-PAG antibody to simply disrupt appropriate PAG localization within the synapse could disturb immune synapse architecture. Synapse organization is tightly regulated to prevent inappropriate immune responses, but the precise interaction between cytoskeletal dynamics and synaptic organization is not fully understood. Investigating the role of PAG in this process provides added clarity. PAG mutated to prevent its link to actin results in disorganized actin architecture and PAG localization within the synapse. It also disrupts Ras signaling, an early signaling mediator downstream of TCR ligation. Determining which PD-1 downstream targets are dependent on the PAG-actin link will provide evidence for whether PAG and PD-1 could serve as good co-targets in cancer therapy regimens. Ultimately, this ongoing study hopes to illuminate crucial control mechanisms associated with T cell synapse organization, opening more avenues of targeting the immune synapse.