CD6-ALCAM Signaling Regulates Multiple Effector/Memory T Cell Functions

Jeanette Ampudia[1], William W. Young-Greenwald[2], Jana Badrani[3], Sole Gatto[2], Adam Pavlicek[2], Taylor Doherty[3], Stephen Connelly[1], Cherie Ng[1]

[1] Equillium, Inc, La Jolla, CA 92037, [2] Monoceros Biosystems LLC, San Diego, CA 92130, [3] Division of Rheumatology, Allergy & Immunology, UC San Diego School of Medicine, La Jolla, CA 92037

AAI 2020 Abstract

CD6 is a T-cell costimulatory receptor that has been implicated in the pathogenesis of multiple autoimmune and inflammatory diseases. Primarily expressed on CD4 T cells, CD6 promotes immune synapse formation, T-cell activation and T-cell migration *via* interaction with its ligand activated leukocyte cell adhesion molecule (ALCAM). While the contribution of CD6 to T cell activation has been well described, less is known regarding the role of CD6 on effector and memory T cells (T_{eff}). Thus, to better characterize this, we examined phosphorylation signaling patterns during CD6 co-stimulation together with the impact of CD6 on differentiated T_{eff} functions. Profiling of ~100 phosphorylation targets associated with T-cell receptor signaling revealed that CD6 co-stimulation on T cells activates factors in pathways involved in actin polymerization, motility, integrin activation and T-cell activation. Comparison of T_{naive} cells vs. T_{eff} demonstrated differing levels of phosphorylation in response to CD6 stimulation. Furthermore, CD6 signaling on T_{eff} sustained phosphorylation of these pathways at later timepoints compared to CD28 stimulation. Blockade of the CD6 pathway, using the clinically tested anti-CD6 mAb itolizumab during re-stimulation of CD4 T_{eff} cells in the presence of ALCAM, inhibited multiple effector functions including proliferation and changes in blast size. This effect was observed exclusively in the presence of ALCAM, indicating that the effect was specific to blockade of the CD6-ALCAM pathway. These findings demonstrate that the CD6-ALCAM pathway is a key regulator of effector T-cell functions and further support targeting this pathway to directly inhibit both naïve and effector T cell populations.

