PROJECT SUMMARY/ABSTRACT

Down syndrome cell adhesion molecule (DSCAM) is a member of the Ig superfamily of adhesion molecules associated with Down syndrome and autism spectrum disorder (ASD). In the mouse retina, DSCAM is responsible for neuronal self-avoidance at the cell type level; in *Dscam*-null retinas neurons lose their normal spacing as they form clusters with other cells of the same subtype (homotypic) and their dendrites fasciculate with each other. This is unusual, as DSCAM (like most homophilic adhesion molecules) drives adhesion and cell clustering when expressed in heterologous cell lines. Previous work from the PI found that DSCAM "masked" adhesion mediated by members of the cadherin superfamily and that masking in different cell subtypes had a differential dependence on DSCAM's PDZ-interacting C-terminus. The molecular mechanisms of this masking remain unknown. Here we propose experiments to define these molecular mechanisms. We hypothesize that DSCAM masks diverse cell adhesion molecules (CAMs), not only cadherin adhesion, and that the differential dependence on C-terminal interactions reflect different cell type specific adhesion systems. In Specific Aim 1 we will use an *in vitro* assay of adhesive masking to test candidate signaling pathways and cellular processes. This assay takes advantage of homophilic interactions between CAMs in a neuron and on a bead, which results in clustering of the neuronal CAM around the bead. Homophilic DSCAM interactions prevent the clustering of other CAMs (e.g., cadherins). We will use a variety of pharmacological and genetic manipulations to test candidate mechanisms in this assay, and we will verify findings with *in vivo* electroporation. In Specific Aim 2, we will test our hypothesis that differential clustering and fasciculation in C-terminal mutants reflects different sets of cell-type-specific CAMs, and DSCAM's PDZ-interacting motif is only required to mask a subset of CAMs. To do this, we will leverage new datasets describing cell type specific gene expression to identify candidate CAMs expressed in cell types that either require DSCAMs C-terminal PDZ interactions for normal spacing or do not require DSCAM's C-terminus. Using *in vivo* electroporation into retina-specific conditional loss of function mutants and into C-terminal truncation mutants, we will test if these CAMs require DSCAM's C-terminus for masking. In Specific Aim 3, we will test ASD-associated DSCAM mutations in the neuron/bead assay by rescuing masking in *Dscam*-deficient neurons. Cell adhesion has emerged as a major theme in ASD pathology and DSCAM is positioned as a key regulator of this process. The completion of these studies will provide crucial first steps towards understanding how DSCAM dynamically regulates adhesive systems during development to prevent excessive adhesion while allowing appropriate CAM interactions, addressing fundamental questions in retinal neural development with implications in neurodevelopmental disorders like ASD.