

## G2A AND RELATED G PROTEIN-COUPLED RECEPTORS IN IMMUNITY AND INFLAMMATION

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G protein-coupled receptors (GPCRs) represent the single largest family of cell-surface molecules involved in signal transduction. With the exception of the chemokine receptor subfamily, immune functions of other GPCRs are still poorly characterized. G2A, TDAG8, OGR1 and GPR4 represent a novel group of GPCRs defined by sequence homology, overlapping expression in hematopoietic cells and ligand specificity towards pro-inflammatory lysophospholipids and glycosphingolipids. Ligand recognition by ectopically overexpressed receptors mediates intracellular calcium flux and ERK MAP kinase activation. G2A, the first analyzed member of this GPCR subfamily, couples to the G $\beta$ 13 heterotrimeric G protein to activate RhoA leading to the assembly of actin stress fibers and transcriptional activation of Serum Response Factor. Additional experiments are in progress to address in greater details which of these biological effects are cell context dependent. In mice, genetic ablation of G2A function results in dysregulated lymphocyte homeostasis and loss of immunological tolerance with systemic autoimmunity. The late onset (> 12 months) of this pathology and co-expression of the G2A related receptors in lymphocytes and antigen presenting cells, indicate the possibility of functional redundancy within this GPCR subfamily. We are directly addressing this hypothesis by generating mouse strains genetically deficient for TDAG8, OGR1 and GPR4 that will be intercrossed with G2A deficient animals. Significantly, a preliminary analysis of TDAG8 null mice suggests that at least in young and adult animals (< 6 months) the phenotype is similar to that previously described for G2A deletion with no detectable pathology. We are currently aging these mice to determine if they will develop autoimmunity. Double knockouts for these GPCRs are also being generated to analyze if TDAG8 inactivation will modify the G2A phenotype. Collectively, these studies should shed light on the complex regulation of immunological tolerance by the G2A subfamily of GPCRs.