**Surface expression of G2A is regulated by its ligand LPC**

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Abstract:

Cell surface expression of many G-protein-coupled-receptors (GPCR) is down-regulated by ligand activation through endocytic pathway. In this study, we are trying to determine how the surface expression of G2A is regulated by its ligand Lysophosphatidycholine LPC. In contrast to other well studied GPCRs such as LPA and S1P receptor, as well as other G2A family members including TDAG8 and OGR1, we found that G2A is normally sequestered on intracellular vesicles with relatively low surface expression level. Upon LPC addition, majority of G2A is relocated to cell surface. This process does not require protein synthesis (insensitive to cyclohexamide inhibition), and is specific only for LPC but not other structurally related lipids (i.e LPA and S1P). Several chemical inhibitors were tested and found to block this process within their normal dosage range. These include: azide (abolish ATP), latrunculin B (affect actin cytoskeleton), and BAPTA-AM (chelate intracellular calcium). Thus G2A surface translocation in response to LPC is an active biological process, arguing against the possible detergent effects of LPC. Mutation in the DRY motif, a well conserved domain critical for coupling of many GPCRs to trimeric G proteins, abolished the response of G2A towards LPC. This data suggests that this redistribution process requires G protein signaling. In conclusion, we propose that a ligand-binding induced G protein signaling pathway regulates the surface expression of G2A, which might amplify and maximize its functional output. Such regulation might be critical for the function of G2A in autoimmunity control.