

# Organogenesis depends on adhesion G-protein-coupled receptors (aGPCRs)

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## ABSTRACT

Adhesion Organogenesis, neurodevelopment, reproduction, and other functions rely on G-protein-coupled receptors (aGPCRs) The Stachel sequence is a conserved internal (tethered) agonist sequence that activates several aGPCRs. GPR133 and GPR114, two aGPCRs in complex with Gs, were studied using cryogenic electron microscopy (cryo-EM).

Both receptors' Stachel sequences adopt a helical-bulge sheet structure and insert into a binding site generated by the transmembrane domain, according to the structures (TMD). The majority of intramolecular interactions with the TMD are mediated by a hydrophobic interaction motif (HIM) within the Stachel sequence. Biochemical study of the HIM motif, when combined with cryo-EM structures, gives insight into the cross-reactivity and selectivity of the Stachel sequences.

## INTRODUCTION

The mutation in the TFAZZIN gene, which codes for the Cardiolipin (CL) transacylase protein tafazzin, causes Barth syndrome (BTHS), a rare X-linked genetic disorder. Tafazzin transforms nascent de novo generated CL into a kind of CL present in the mitochondrial membrane of particular tissues<sup>4</sup>. CL, as the mitochondria's characteristic lipid, is necessary for several mitochondrial processes, including energy generation, which is required for B lymphocyte adaptive immunity. Despite the fact that cardiomyopathy is the leading cause of death in BTHS, many patients have serious infections as a result of their neutropenia. Several laboratories, including ours, have studied BTHS pathology using Epstein-Barr virus converted B lymphoblasts from patients. The argument for using these cells is that they are simple to maintain in culture and that their altered nature allows for straightforward experimental manipulation. Furthermore, they are reflective of a patient's unique mutation. Epstein-Barr virus transformation of human B cells, on the other hand, has been shown to impair host immune function in investigations. Toll-Like Receptors (TLRs), such as TLR4, are expressed in B lymphoblasts and can be activated by Lipopolysaccharide (LPS). Furthermore, cytosine connected to guanine by a phosphate bond deoxyribonucleic acid (CpG DNA) activates human B cells through TLR9 regardless of whether the DNA is in the form of a phosphate bond. We wanted to see if Epstein-Barr virus-transformed control and BTHS B lymphoblasts exhibit surface markers that indicate LPS and CpG

DNA activation. In Epstein-Barr virus transformed human B lymphoblasts from control and BTHS patients, we show that chosen surface marker expression is resistive to stimulation with LPS and variable to stimulation with CpG DNA. Because B lymphocyte surface marker expression is required for B cell development, cell-cell interaction with other immune cells, and the adaptive immune response, our findings suggest that immunological data obtained from Epstein-Barr virus transformed B lymphoblasts from BTHS patients should be Bassil M. interpreted with caution. The lymphoblasts were centrifuged at 1400 rpm for 10 minutes after being stimulated with LPS or CpG DNA for 24 hours. PBS was used to wash the pellets, which were then suspended in 100 l of PBS. Lymphoblasts were stained for 5 minutes in the dark at 4°C with propidium iodide (5 g/ml). Flow cytometry analysis was then performed. Surface marker expression was evaluated in untreated and stimulated lymphoblasts using anti-CD19-APC, anti-CD24-BV421, anti-CD27-perCP-CY5.5, anti-CD38-APC-H7, anti-CD138-PE, anti-CD80 PE-A, and anti-PD1-APC, as directed by the manufacturer. The cells were subsequently examined using a BD FACS Canto II equipment at the Flow Cytometry Core Facility at the Rady Faculty of Health Sciences, University of Manitoba. The data was analysed using the FlowJo programme. The survivability of control and BTHS B lymphoblasts treated with LPS and CpG DNA was first investigated. B lymphoblasts from three control patients and three BTHS patients with various mutations were treated for 24 hours with 10 g/ml LPS or 5 mM CpG DNA, then stained with propidium iodide and flow cytometry was used to measure cell survival. Incubation of normal and BTHS lymphoblasts with 10 g/ml LPS M CpG DNA for 24

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hours resulted in cell viability being preserved. After stimulation with LPS or CpG DNA, cell viability is preserved in Epstein-Barr virus-infected human control and BTHS B lymphoblasts. We investigated whether Epstein-Barr virus-transformed control and BTHS B lymphoblasts exhibited surface markers associated with classical B lymphocyte activation in response to LPS or CpG DNA stimulation in this work. Surprisingly, our findings show that Epstein-Barr virus-transformed human control and BTHS B lymphoblasts are resistant to chosen surface marker expression when stimulated with LPS, yet show varied selected surface marker expression when stimulated with CpG DNA. CD24 is a protein that is expressed on the surface of activated B lymphocytes and is necessary for B cell growth as well as cell-cell adhesion. In CD4 T-cell driven clonal expansion, CD24 expression on B cells is also essential for T cell co-stimulation. CD38 is a crucial surface marker for B cell activation and proliferation, as well as a regulator of B cells. Previous research has shown that a lack of CD38 expression inhibits the immune response and increases infection susceptibility.

CD138 is a plasma cell surface marker that is necessary for long-term humoral immunity. B cells mature into antibody secreting cells and upregulate CD138 on their surface in response to stimulation, which promotes antibody secreting cell maturation and accumulation. A recent examination of global gene expression profiles revealed substantial changes in gene expression patterns between Epstein-Barr virus-infected and normal host cells, suggesting that transformation may impair normal immune function. We previously showed that LPS treatment of isolated naive primary murine B lymphocytes boosted surface marker expression quickly, and that tafazzin deficiency in these cells significantly reduced surface marker expression when stimulated with LPS<sup>22</sup>. The absence of increased surface marker expression in human control and BTHS lymphoblasts in response to LPS, along with the fact that same surface markers were clearly visible in unstimulated cells, suggests that these cells have reduced LPS-mediated activation responsiveness.