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Review

Proton-sensing and lysolipid-sensitive G-protein-coupled receptors: A novel type of multi-functional receptors

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Abstract

OGR1, GPR4, G2A, and TDAG8 share 40% to 50% homology with each other and seem to form a family of GPCRs. They have been described as receptors for lipid molecules such as sphingosylphosphorylcholine, lysophosphatidylcholine, and psychosine. Recent studies, however, have revealed that these receptors also sense extracellular protons or pH through histidine residues of receptors and stimulate a variety of intracellular signaling pathways through several species of hetero-trimeric G-proteins, including G_s, G_i, G_q, and $G_{12/13}$. Thus, this family of GPCR seems to recognize both lipid molecules and protons as ligands. Although our knowledge of proton-sensing and lysolipid-sensitive GPCRs is preliminary, the receptor levels and ligand levels especially protons are both sensitively modulated in response to a variety of microenvironmental changes. These results suggest a multiple role of proton-sensing GPCRs in a variety of physiological and pathophysiological states.

Keywords: Proton-sensing GPCR; Acidosis; OGR1; GPR4; G2A; TDAG8; Psychosine; Lysolipid

Contents

Abbreviations: OGR1, ovarian cancer G-protein-coupled receptor 1; TDAG8, T-cell death-associated gene 8; GPCR, G-protein-coupled receptor; SPC, sphingosylphosphorylcholine; LPC, lysophosphatidylcholine; PTX, pertussis toxin; $[Ca^{2+}]_i$, intracellular calcium concentration; ERK, extracellular signal-regulated kinase; TNF-α, tumor necrosis factor-α; CaR, calcium-sensing receptor.

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1. Introduction

OGR1 (ovarian cancer G-protein-coupled receptor 1) and GPR4 were previously described as G-protein-coupled receptors (GPCRs) for sphingosylphosphorylcholine (SPC) and lysophosphatidylcholine (LPC) [1,2]. Ludwig et al. [3], however, discovered that these receptors sense extracellular protons through histidine residues of receptors and are

Table 1
Expression, ligand, signaling mechanism, and function of proton-sensing and lysolipid-sensitive G-protein-coupled receptors

		OGR1	GPR4	G2A	TDAG8
	Expression	Spleen, testis, heart, brain, placenta, lung, bone tissue	Ovary, liver, lung, kidney, lymph node, subthalamic nucleus	Lymphoid tissues (spleen and thymus), T- and B-lymphocytes, monocyte, macrophage	Lymphoid tissues (leukocytes, spleen, lymphonodes, thymus)
Ligand	Induction	Not known	TNF-α (endothelial cell)	DNA-damaging agents, BCR-Abl tyrosine kinase	Activation of T-cells (anti-T-cell receptor-antibodies), glucocorticoids, PMA plus ionomycin
	Refs.	[1,8]	[13,14]	[17,18]	[25–27]
Lipid	Agonist	SPC	SPC, LPC	LPC, (SPC)	Psychosine
	G-protein	G_i, G_q	G_i,	$Gq_{/11}$, $G_{12/13}$	G_i, G_q
	Signal	Ca^{2+} mobilization, ERK activation	Ca^{2+} mobilization, ERK activation, Rho activation	Rho activation	cAMP inhibition, Ca^{2+} mobilization
	Function	Inhibition of proliferation	Migration, proliferation	Migration of T-cell and macrophage	Multi-nuclea formation, apoptosis
	Binding affinity (K_d)	SPC; 33.3 nM	SPC; 36 nM: LPC; 159 nM		Not examined
	Ref.	[9]	[13]	[19–22]	[7,28]
Proton	Agonist	Proton			
	Antagonist	Psychosine, SPC	Psychosine	LPC	Psychosine, SPC
	G-protein	G_q	G_s	G_q, $G_{12/13}$	G_s, $G_{12/13}$(?)
	Signal	Phospholipase C/Ca^{2+}	cAMP accumulation	Phospholipase C/Ca^{2+}, Rho activation, cAMP accumulation	cAMP accumulation
	Function	Bone resorption (?)	?	Actin rearrangement	Apoptosis of thymus (?), actin rearrangement
	Threshold pH	7.6–7.4	7.6–7.4	<8.0	7.6–7.4
	Ref.	[3,5,12,29]	[3,5,29]	[4,29]	[5,6,29]
Ligand not identified	Agonist	Not identified			
	G-protein		Multiple G-proteins	$Gq_{/11}$, G_{13}, G_s	Multiple G-proteins
	Signal		Stimulation of SRE-, NFAT- and CRE-driven transcription, ERK inhibition	Phospholipase C/Ca^{2+}, Rho activation, cAMP accumulation	Stimulation of SRE- and CRE-driven transcription
	Function		Transformation	Cell cycle arrest, actin rearrangement, apotheosis of lymphocytes, transformation	Transformation
	Phenotype of KO mouse	?	?	Late-onset autoimmune syndrome	Not reported
	Ref.		[15,16]	[18,23,24,64]	[16,29]

G2A was previously reported to be a receptor for LPC and SPC [19], in which LPC and SPC bound to G2A with a binding affinity of 65 nM for LPC and 230 nM for SPC, and stimulated phospholipase C and ERK in G2A-expressing cells. However, the paper was later retracted [20]. SRE, serum response element; NFAT, Nuclear Factor of Activated T-cell; and CRE, cAMP response element.