Form 3

Report for Joint/usage program for Endocrine/Metabolism

Date: 2016/04/1

To: Director of Institute for Molecular and Cellular Regulation

1. Program No. 13010
2. Research title:

   Role of OGR1 family GPCRs in inflammation

3. Objective of the research:

Clarification of inflammatory regulation mechanism of protons and lipid signaling molecules by using knockout mice of OGR1 family GPCRs. We will characterize immune regulatory responses and signal transduction mechanisms of protons through TDAG8 and OGR1 in microglia and airway by using TDAG8 and OGR1 knockout mice. We also try to clarify effects of extracellular proton and lipid molecules in the cells involved in airway inflammation.

4. Period

   From 2015/04/01 to 2016-03-31

5. Project organization

Name of Applicant: Dong-Soon Im
Position/Affilation: Professor/department: College of Pharmacy, Pusan National University

Name of Co-applicant: Jung-Min Lee
Position/Affiliation: Graduate student/College of Pharmacy, Pusan National University

Name of Co-applicant: Ae-Yeon Lee
Position/Affiliation: Graduate student/College of Pharmacy, Pusan National University

Name of Researcher in IMCR: Fumikazu Okajima

Position: Professor

6. Research plans:

In our previous study on this project, we found that extracellular proton inhibited lipopolysaccharide (LPS)-induced inflammatory cytokine release in macrophages in TDAG8-dependent manner. Here, we will examine the role of TDAG8-mediated regulation of cytokine production in vivo. To this end, we will analyze LPS-induced acute lung injury model in TDAG8 knockout mice. We also characterize proton-sensing GPCR antagonists and also some lipid molecules.

7. Research results:

We explored the role of TDAG8 in lung injury induced by lipopolysaccharide (LPS) administrated intratracheally. We found that LPS treatment increased TDAG8 expression in the lungs and confirmed its expression in resident macrophages in bronchoalveolar lavage (BAL) fluids. LPS administration remarkably increased neutrophil accumulation without appreciable change in the resident macrophages, which was associated with increased penetration of blood proteins into BAL fluids, interstitial accumulation of inflammatory cells, and damage of the alveolar architecture. The LPS-induced neutrophil accumulation and the associated lung damage were enhanced in TDAG8-deficient mice as compared with that in wild-type mice. We are now examining expressions of inflammatory cytokines and chemokines in lungs and BAL fluids. We also characterized GPR4 antagonists and lipid molecules for future analysis of lysolipid-sensitive proton-sensing receptors.

8. Publications and/or Presentations made through this collaboration

Kim JM, Lee KP, Park SJ, Kang S, Huang J, Lee JM, Sato K, Chung HY, Okajima F, and Im DS: Omega-3 fatty acids induce Ca2+ mobilization responses in human colon epithelial cell lines endogenously expressing FFA4. ***Acta Pharmacol. Sin.*** 36:813-820 (2015)

Tobo A, Tobo M, Nakakura T, Ebara M, Tomura H, Mogi C, Im DS, Murata N, Kuwabara A, Ito S, Fukuda H, Arisawa M, Shuto S, Nakaya M, Kurose H, Sato K, and Okajima F: Characterization of imidazopyridine compounds as negative allosteric modulators of proton-sensing GPR4 in extracellular acidification-induced responses. ***PLoS One.*** 10:e0129334 (2015)

(Please summarize the report in 2 pages)