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Effect of inflammatory cytokines and high fat diet on inositol-1,4,5-trisphosphate (IP3) receptors binding protein released with IP3 (IRBIT) expression in intestinal cells

Kelli Cook
Valparaiso University, kelli.cook@valpo.edu

Natasha Petreska
Valparaiso University

Jesse Smallwood
Valparaiso University

Kenneth Bridgmon
Valparaiso University

Chase Jones
Valparaiso University

Effect of inflammatory cytokines and high fat diet on inositol-1,4,5-trisphosphate (IP_3) receptors binding protein released with IP_3 (IRBIT) expression in intestinal cells

Natasa Petreska*, Kelli Cook*, Kenneth Bridgmon, Chase Jones, Jesse Smallwood and Patrice G Bouyer. * equally contributed author**.** Valparaiso University.

IP_3 upon binding to the IP_3 receptor (IP_3R) causes the release of intracellular calcium from the endoplasmic reticulum, which drives many cellular responses (*e.g.,* cell spreading, exocytosis). In addition to releasing calcium, IP_3 also causes the release of IRBIT from the IP_3R. Over the past decade IRBIT has been described as a protein that regulates calcium release due to interaction with the IP_3R, the activity of the Na-HCO_3 cotransporter, the cystic fibrosis transmembrane regulator and the Na/H exchanger (NHE3). Lack of reabsorption of Na^+ by NHE3 in the intestine is responsible for diarrhea. Recently it was shown that IRBIT and NHE3 expression was decreased in a mouse model of diabetes and the loss of NHE3 expression induced diarrhea in this model. Insulin treatment restored IRBIT and NHE3 expression, resulting in a decrease of diarrhea. Besides insulin, very little is known about factors regulating IRBIT expression in intestinal epithelial cells. In this work, we set to study the effect of inflammatory cytokines and high calorie diet on IRBIT expression due to the fact that diabetes is associated with chronic inflammation and high caloric intake. To test the effect of inflammatory cytokines we used the human colonic crypt cells T84. Exposing T84 cells to interleukin 13 or tumor necrosis factor alpha for 72 hours decreased IRBIT expression by 36% ($P < 0.001$, $n = 5$), 44% ($P < 0.001$, $n = 3$) respectively. Finally, we compared the expression of IRBIT in mice fed with low fat milk (control) versus high milk fat (37%). We found that in the duodenum of 3 mice with a high fat diet a substantial increase of IRBIT expression compared to the control. Our work is the first to demonstrate that inflammatory cytokines and dietary fat can alter IRBIT expression.