Abstract

Celiac disease is an autoimmune disease which occurs in susceptible individuals after ingestion of food containing gluten. Gluten and its monomeric fraction gliadin induce inflammatory damage of the small intestine by activating the immune cells that react strongly to gluten peptides. Gluten peptides have the ability to activate cells of adaptive as well as innate immune system. This work is focused on the production of interleukin (IL)-1 in antigen presenting cells stimulated with peptic gliadin digest. We found that monocytes and peripheral blood mononuclear cells (PBMC) isolated from blood of celiac patients secrete significantly more IL-1α and IL-1β than cells of healthy donors after stimulation with gliadin digest. The gliadin-induced IL-1β expression is controlled by a signaling cascade that includes MAPK kinase family molecules and transcription factor NF-κB. Moreover, we found that the adaptor proteins MyD88 and TRIF as well as Toll-like receptor (TLR) 2 and 4 play a role in the signaling cascade underlying gliadin-induced IL-1β expression by using murine bone marrow derived dendritic cells (BMDC). The precursor form of IL-1β in gliadin-stimulated PBMC and murine BMDC is maturated by caspase-1. In celiac PBMC the gliadin-induced maturation and secretion of IL-1β depends on the potassium ions release from the cells and the production of reactive oxygen species in the cell cytosol. Finally, in addition to caspase-1, the NLRP3 protein (nucleotide-binding oligomerization domain, leucine rich repeat and pyrin domain-containing protein 3) and ASC protein (the apoptosis-associated speck-like protein containing a caspase recruitment domain – CARD), two members of NLRP3 inflammasome complex, are required for gliadin-induced IL-1β production in BMDC. Overall, this work presents the molecules and mechanisms that enable the production of IL-1β in cells stimulated with gliadin digest.