［課程－２］

審査の結果の要旨

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PTEN (phosphatase and tensin homologue) acts through a lipid phosphatase activity and is a phosphatidylinositol 3-kinase (PI3K) antagonist. PTEN dephosphorylates phosphatidylinositol (3,4,5)-trisphosphate (PtdIns(3,4,5)P_3) to phosphatidylinositol (4,5)-bisphosphate (PtdIns(4,5)P_2) and is frequently mutated in most human cancers which lead to increased growth and motility of cancer cells. It has been known for quite some time that different phosphatidylinositol phosphates (PtdInsPs) play important role in amoebic physiology, particularly during different endocytic mechanisms including phagocytosis and trogocytosis. In this research, a PTEN homolog (EhPTEN1, EHI_197010) which is highly expressed in the trophozoite stage in *E. histolytica* was identified and characterized by cell biology and biochemical approaches. Localization was assessed using a GFP-tagged protein in migrating trophozoites, and in trophozoites undergoing trogocytosis or phagocytosis. Live imaging of GFP-EhPTEN1 expressing amebic trophozoites showed localization mainly in the cytosol with higher concentration to pseudopods and to the leading edge of the trogo-phagocytic cup. Effects of augmentation of EhPTEN1 function by overexpression of wild type or inhibition of EhPTEN1 by gene silencing were investigated on trogo-/phagocytosis, endocytosis, and motility using a confocal quantitative image cytometer. Expression of the GFP-EhPTEN1 led to increased cell motility, decreased trogo-/phago-cytosis, and increased pinocytosis. Conversely, *EhPTEN1* gene silencing led to decreased cell motility, increased trogo-/phago-cytosis,

and decreased pinocytosis. EhPTEN1 is enzymatically highly active against PtdIns(3,4,5)P_3 and is required for optimal growth of the parasite.

This research shows the involvement of EhPTEN1 in the regulation of different modes of endocytosis, namely fluid-phase endocytosis, receptor-mediated endocytosis, trogo-/phago-cytosis, and cell migration. Delineation of these processes is highly desirable as this may help to find new drug targets as well as help us understand the biology of *E. histolytica*.

よって本論文は博士（保健学 ）の学位請求論文として合格と認められる。