学 位 論 文 の 要 旨

所　属	三重大学大学院医学系研究科 甲　生命医科学専攻　病態解明医学講座 皮膚科学分野	氏　名	明　田　智　子

主論文の題名

CD8+T cell granzyme B activates keratinocyte endogenous IL-18

主論文の要旨

IL-18 is a pro-inflammatory cytokine of the IL-1 family involved in Th1/Th2 polarization. IL-18 is produced and stored as an inactive precursor (proIL-18) in several cells including keratinocytes, and appropriate processing is required to release its active form. Previously we demonstrated that granzyme B (GrB) cleaves proIL-18 into its active forms. GrB released from cytotoxic T lymphocyte (CTL) and NK cells has roles in apoptosis and cytotoxic activity. In certain inflammatory skin diseases, the epidermal keratinocytes are targets of CTL/NK cells. However, IL-18 activation during the direct interaction of CTL/NK with keratinocytes has not been described. We here investigated the interaction between CTL and keratinocytes, and IL-18 processing by CTL derived GrB using cultured CD8+T cells and keratinocyte cell line HaCaT. GrB(+)/caspase-1(-)CD8+T cells cultivated from healthy human PBMC were co-cultured with interferon(IFN)-γ-treated HaCaT cells. The expression of GrB and the IL-18 concentration in the culture supernatant were measured. The interaction between HaCaT cells and CTL increased the number of cytoplasmic GrB-positive HaCaT cells with limited endogenous GrB mRNA expression. The concentration of mature IL-18 levels increased in the co-culture supernatant. GrB from CTLs acts double roles to keratinocytes: an IL-18 converting enzyme and pro-apoptotic factor in the skin inflammatory diseases.