様式 6-C）(Form6-C) C. 学位論文（Thesis）で発表論文のない場合

LIYANAGE MANOSIKA BUDDHINI PERERA 氏から学位申請のため提出された論文の審査要旨

題目 The regulation of skin fibrosis in systemic sclerosis by extracellular ATP via P2Y2 purinergic receptor
(細胞外ATPによるP2Y2受容体を介した全身性強皮症における皮膚線維化の制御)

学位論文（Thesis）

発表予定論文

タイトル The regulation of skin fibrosis in systemic sclerosis by extracellular ATP via P2Y2 purinergic receptor
Annals of Rheumatic diseases.（投稿中）

Liyanage Manosika Buddhini Perera, Akiko Sekiguchi, Akihiko Uchiyama, Akihito Uehara, Chisako Fujiwara, Sahori Yamazaki, Yoko Yokoyama, Sachiko Ogino, Ryoko Torii, Mari Hosoi, Osamu Ishikawa, Sei-ichiro Motegi

論文の要旨及び判定理由

Tissue injury/hypoxia and oxidative stress induced-extracellular ATP can act as a damage-associated molecular pattern molecules (DAMPs), which initiates inflammatory response. Objective was to elucidate the role of extracellular ATP in skin fibrosis in systemic sclerosis (SSc). Dr.Buddhini identified that hypoxia enhanced ATP release, and extracellular ATP enhanced IL-6 production more significantly in SSc fibroblasts than in normal fibroblasts. There were no significant differences in the expression of P2X and P2Y receptors between normal and SSc fibroblasts. Non-selective P2 receptor antagonist and selective-P2Y2 receptor antagonists, kaempferol and AR-C118925XX, significantly inhibited ATP-induced IL-6 production and phosphorylation of p38 in SSc fibroblasts. ATP-induced IL-6 production was significantly inhibited by p38 inhibitors, SB203580 and doramapimod. Collagen type I
production in SSc fibroblasts by ATP-induced IL-6/IL-6 receptor trans-signaling was inhibited by kaempferol and SB203580. Amount of ATP in bleomycin-treated skin was increased, and administration of kaempferol significantly inhibited bleomycin-induced dermal fibrosis in mice. These results suggest that vasculopathy-induced hypoxia and oxidative stress might enhance ATP release in the dermis in SSc, and extracellular ATP-induced phosphorylation of p38 via P2Y₂ receptor might enhance IL-6 and collagen type I production in SSc fibroblasts. P2Y₂ receptor antagonists therapy could be an alternative treatment for skin sclerosis in patients with SSc. This study elucidates the mechanism of fibrosis and vascular disorder of systemic sclerosis and is judged to be worthy of a Ph.D. degree.

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参考論文

Mechanistic insight into the norepinephrine-induced fibrosis in Systemic sclerosis.