学 位 論 文 内 容 の 要 旨

博士の専攻分野の名称　博士（ソフトマター科学）　氏 名 熊 谷 祐 二

学 位 論 文 題 名

Study on molecular mechanisms and morphological characteristics of collective cancer cell invasion
（がん細胞の集団浸潤における分子機構と形態学的特徴に関する研究）

Metastasis is the translocation of cancers to distant organs from the primary tumor, and metastasis is a major cause of cancer-related deaths. During metastasis, cancer cells undergo invasion, in which cancer cells disseminate into the normal surrounding tissues. Here, we got to the bottom of collective invasion, one of the modes of cancer invasion. Collective invasion, in which cancer cells invade as a cell cluster, is considered a critical mode of cancer invasion for determining the prognosis of patients. However, the cellular characteristics responsible for collective invasion remain largely unknown. In the present study, molecular mechanisms and morphological characteristics were investigated to better understand collective invasion.

Contact following, the phenomenon which is mediated by intercellular adhesion for the movement of neighboring cells in the same direction, is required for collective behavior of cancer cells; however, the molecular mechanism in collective invasion is poorly understood. Here, we established a unique experimental system with a collagen gel overlay condition to assess contact following and found that integrin-β1, an extracellular matrix (ECM) receptor, and its ligand ECM proteins are expressed in the intercellular site of A431 human skin squamous carcinoma cells. Furthermore, inhibitors and siRNAs targeting integrin-β1 and ECM proteins suppressed collective invasion via collapse of contact following, indicating the interaction between integrin–β1 and ECM proteins in the intercellular site contributes to collective invasion via regulation of contact following.

Collective invasion occurs in a cell cluster consisting of polyclonal cancer cells; however, the cell types that trigger collective invasion among polyclonal cells are unknown. Here, we successfully established subclones with various invasive potentials derived from A431 cells. Analysis on gene expression and morphological characteristics of A431 subclones demonstrated that interferon-β is present in the sealed intercellular spaces of the highly invasive subclone and promotes collective invasion through STAT1 activation. Furthermore, co-culture system of subclones revealed that highly invasive sub-clonal cells with activated STAT1 were located at the invasive fronts and lead the low invasive sub-clonal cells to the collective invasion. Histological analysis on skin squamous cell carcinoma (SCC) specimens also showed that enrichment of activated STAT1 at the invasive fronts of SCC cell groups during collective invasion. These findings indicate that the IFNB/STAT1 axis promotes the collective invasion of cancer cells with sealed intercellular spaces and that cancer cells with elevated STAT1 signaling drive the collective invasion of SCC.

In conclusion, we propose the interaction between integrin-β1 and ECM proteins and the interferon-β/STAT1 axis as therapeutic targets to inhibit collective cancer cell invasion through this study.