

# 学位論文審査結果の要旨

所 属	甲 三重大学大学院医学系研究科 生命医科学専攻病態解明医学講座 小児科学	氏 名	Vipin Shankar
審 査 委 員	主 査 野阪 哲哉 副 査 島岡 要 副 査 片山 直之		

(学位論文審査結果の要旨)

Mesenchymal Stromal Cell Secretome Up-Regulates 47 kDa CXCR4 Expression, and Induce Invasiveness in Neuroblastoma Cell Lines

著者らは論文において下記の内容を述べている。

Neuroblastoma accounts for 15% of childhood cancer deaths and presents with metastatic disease of the bone and the bone marrow at diagnosis in 70% of the cases. Previous studies have shown that the Mesenchymal Stromal Cell (MSC) secretome, triggers metastases in several cancer types such as breast and prostate cancer, but the specific role of the MSC factors in neuroblastoma metastasis is unclear. To better understand the effect of MSC secretome on chemokine receptors in neuroblastoma, and its role in metastasis, we studied a panel of 20 neuroblastoma cell lines, and compared their invasive potential towards MSC-conditioned-RPMI (mRPMI) and their cytokine receptor expression profiles. Western blot analysis revealed the expression of multiple CXCR4 isoforms in neuroblastoma cells. Among the five major isoforms, the expression of the 47 kDa isoform showed significant correlation with high invasiveness. Pretreatment with mRPMI up-regulated the expression of the 47 kDa CXCR4 isoform and also increased MMP-9 secretion, expression of integrin α3 and integrin β1, and the invasive potential of the cell; while blocking CXCR4 either with AMD 3100, a CXCR4 antagonist, or with an anti-47 kDa CXCR4 neutralizing antibody decreased the secretion of MMP-9, the expression of integrin α3 and integrin β1, and the invasive potential of the cell. Pretreatment with mRPMI also protected the 47 kDa CXCR4 isoform from ubiquitination and subsequent degradation. Our data suggest a

modulatory role of the MSC secretome on the expression of the 47 kDa CXCR4 isoform and invasion potential of the neuroblastoma cells to the bone marrow.

本論文は、神経芽腫細胞における 47kDa の CXCR4 の発現を評価することで、その腫瘍細胞の骨髄浸潤能・悪性度診断が行える可能性を示すとともに、CXCR4 シグナル経路を標的とした新しい神経芽腫治療の開発への科学的根拠を示すものであり、学位論文として価値あるものと認めた。

PLoS One

第 10 巻 第 3 号 e0120069

2015 年 3 月掲載

Vipin Shankar, Hiroki Hori, Kentaro Kihira, Qi Lei, Hidemi Toyoda,

Shotaro Iwamoto, Yoshihiro Komada