学位論文審査結果の要旨

所　属	三重大学大学院医学系研究科 甲　生命医科学専攻　臨床医学系講座 血液・腫瘍内科学分野	氏　名	南　博仁
審　査　委　員	主　査　平山　雅浩 副　査　山崎　英俊 副　査　野阪　哲哉		

（学位論文審査結果の要旨）

CXCL12-CXCR4 Axis Is Required for Contact-Mediated Human Lymphoid and Plasmacytoid Dendritic Cell Differentiation but Not T Lymphoid Generation

【主論文審査結果の要旨】

著者らは論文において下記の内容を述べている。

We investigated the involvement of CXCL12-CXCR4 interactions in human lymphohematopoiesis by coculture with telomerized human stromal cells. CXCR4 expression was low in $CD34^+CD38^-CD45RA^-CD10^-CD7^-CD19^-$ immature hematopoietic stem/precursor cells (HSPCs) but higher in $CD34^+CD38^-CD45RA^+CD10^+CD7^{+/-}CD19^-$ early lymphoid precursors and even higher in $CD34^+CD38^+CD45RA^+CD10^+CD7^-CD19^+$ pro-B cells. Inhibition of the effect of stromal cell-produced CXCL12 by an anti-CXCR4-blocking Ab suppressed the generation of $CD45RA^+CD10^-CD7^+CD19^-$ early T lymphoid precursors (ETPs) and $CD45RA^+CD10^+CD7^-CD19^{+/-}$ B lymphoid precursors on stromal cells, but it did not affect the generation of ETPs in conditioned medium of stromal cell cultures. Replating assays showed that contact with stromal cells was critical for HSPC-derived $CD45RA^+CD10^+CD7^-CD19^-$ B lineage-biased precursors to differentiate into $CD19^+$ pro-B cells, which was suppressed by the anti-CXCR4 Ab. Conversely, HSPC-derived ETPs possessed T and B lymphoid and monocytic differentiation potential; stromal cell contact was not required for their growth but rather promoted B lymphoid differentiation. The anti-CXCR4 Ab did not affect the growth of ETPs in

conditioned medium, but it suppressed their B lymphoid differentiation on stromal cells. $CD14^{-}CD11c^{-}HLA\text{-}DR^{+}CD123^{high}CD303^{+}$ plasmacytoid dendritic cells developed from HSPCs and ETPs exclusively in contact with stromal cells, which was suppressed by the anti-CXCR4 Ab. These data indicate that CXCL12 plays an essential role in stromal cell contact-mediated B lymphoid and plasmacytoid dendritic cell differentiation from immature hematopoietic and early T lymphoid precursors with a multilineage differentiation potential, but it does not participate in contact-independent generation of early T lymphoid precursors.

CXCL12/CXCR4軸は造血幹・前駆細胞あるいはT前駆細胞のストローマ細胞との接着を介したBリンパ球系およびpDC分化に必須であるが、ストローマ細胞非接着下でのT前駆細胞の生成には必要でないことを明らかとした論文であり、学術上極めて有益であり、学位論文として価値あるものと認めた。

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著者名

Hirohito Minami, Keiki Nagaharu, Yoshiki Nakamori, Kohshi Ohishi, Naoshi Shimojo, Yuki Kageyama, Takeshi Matsumoto, Yuka Sugimoto, Isao Tawara, Masahiro Masuya, Hiroshi Miwa, Naoyuki Katayama