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Author(s)	Hsieh, Han-Yun
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論 文 内 容 の 要 旨
Synopsis of Thesis

氏 名 Name	HSIEH Han-Yun
論文題名 Title	High expression of PSF1 promotes drug resistance and cell cycle transit in leukemia cells (白血病細胞において、PSF1高発現が薬剤抵抗性と細胞周期移行を促進する)

論文内容の要旨

〔目 的(Purpose)〕

Escape of cancer cells from chemotherapy is a problem in the management of cancer patients. Chemotherapy resistance research has mainly been focused on the heterogeneity of cancer cells, multiple gene mutations, and quiescence of malignant cancer cells. However, some studies have indicated that interactions between cancer cells and vascular cells promote resistance to chemotherapy. Previous study shown that PSF1$^{+/-}$ mice exhibit reduced HSC proliferation after bone marrow (BM) ablation with anti-cancer drugs. These data indicate that PSF1 is essential for acute cell proliferation, especially of undifferentiated/progenitor cells. Moreover, PSF1 not only plays a crucial role under physiological conditions, but is also highly expressed in cancer cell proliferation. Therefore, PSF1 may represent a prognostic marker in several types of cancers. However, it remains unknown whether PSF1 levels are associated with chemo-resistance.

〔方法ならびに成績(Methods/Results)〕

We established mouse leukemia models using the cell lines THP-1 or MEG-1, these are derived from acute and chronic myeloid leukemias, respectively, and highly express DNA replication factor PSF1, a member of GINS complex. Intravenous injection of these leukemia cells results in their occupation of the mouse BM and constitutes an animal model of human leukemia. Using this mouse model, we investigated whether PSF1^{high} cells localize near blood vessels in BM and manifest chemo-resistance. For subsequent in vitro analysis of chemo-resistance in these leukemia cells, we conducted experiments to knock-down PSF1 to determine whether it is involved in cell cycle progression and apoptosis.

We found that after anti-cancer drug administration, surviving GFP-positive leukemia cells in the BM were located adjacent to blood vessels, as previously reported in a subcutaneous solid tumor transplantation model. Treating THP-1 and MEG-1 cells with anti-cancer drugs in vitro revealed that those most strongly expressing PSF1 were most chemo-resistant, suggesting that PSF1 induces not only cell cycle progression but also facilitates cell survival. Indeed, when PSF1 expression was suppressed by shRNA, the growth rate was reduced and apoptosis enhanced in both cell lines.

〔総 括(Conclusion)〕

In the present study, we treated mice with an anti-cancer drug in a leukemia transplantation model, and found that cancer cells strongly expressing PSF1, a DNA initiation regulating factor, localized to vascular areas and were drug-resistant. These findings suggest that the vascular niche might play a critical role in chemotherapy resistance. Moreover, PSF1 might act as a potential therapeutic target to enhance the effect of chemotherapy and prognosis.

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論文審査の結果の要旨及び担当者

（申請者氏名）　HSIEH Han-Yun （謝 函芸）

		（職）	氏　名
論文審査担当者	主　査	大阪大学教授	島倉 伸幸
	副　査	大阪大学教授	原 英二
	副　査	大阪大学教授	三木 裕明

論文審査の結果の要旨

本論文は、ヒト白血病細胞に発現するPSF1について、遺伝子ノックダウンの手法と、免疫不全マウスへの移植モデルを駆使し、その機能を解析したものである。PSF1はPSF1, 2, 3とSLD5でGINS複合体を形成し、DNA複製の開始（複製フォークの形成）に重要な役割を持つことが示されてきている分子である。本研究では、PSF1をノックダウンした際に、ヒト白血病細胞の細胞周期が抑制され、また細胞死が誘導されることを明らかにした。また、マウスへの移植モデルにおいては、抗がん剤（この際Ara-C）を投与した後の骨髄におけるPSF1陽性細胞を解析し、PSF1をこう発現する白血病細胞は、抗がん剤に抵抗性を示し、骨髄の血管領域に局在していることを解明した。これは従来から、がん細胞の血管ニッチの概念とも類似しており、固形がんに限らず、白血病においても悪性度の高いがん細胞（白血病幹細胞）の血管領域における薬剤抵抗性を示唆した。この研究は、今後の白血病の治療において、新たな分子ターゲットを示すとともに、白血病の悪性化の現象を解明する手がかりを与えたとして、学位の授与に値すると考えられた。