THE ORIGIN OF HISTIOCYTE-LIKE CELLS AND MULTINUCLEATED GIANT CELLS IN MALIGNANT FIBROUS HISTIOCYTOMA: NEOPLASTIC OR REACTIVE?

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INTRODUCTION
The origin of histiocyte-like cells and multinucleated giant cells in malignant fibrous histiocytoma (MFH) is controversial. We previously demonstrated that histiocyte-like cells were reactive macrophages in heterotransplantation of human MFH, using a DNA in situ hybridization (ISH) system (1). However, the origin of multinucleated giant cells has not been elucidated. Therefore, we examined here, cases of MFH to reveal the origin of multinucleated giant cells in MFH to confirm the reactive nature of histiocyte-like cells. In addition, we analyzed the mRNA expression of mouse c-fms to confirm the origin of multinucleated giant cells in MFH.

MATERIALS & METHODS
Three human MFH specimens were obtained after surgical resection at the Department of Orthopaedic Surgery, Niigata University School of Medicine. Histological examination of resected tumors confirmed the diagnosis of storiform-pleomorphic MFH. The tumors were transplanted into nude mice and harvested when they were over 2 cm in diameter. We compared the morphological appearance of the parental tumors and transplanted tumors with hematoxylin eosin staining. DNA ISH was performed with DIG-11-dUTP-labeled probes for human specific "Alu" and mouse specific "m-L1" probes. Mouse specific c-fms probes were used for mRNA ISH. Immunohistochemical examination was performed with polyclonal antibodies against human HLA-DR. Both of these antibodies recognized human histiocytes. In the transplanted tumor, histiocyte-like cells reacted with mouse c-fms and human colony stimulating factor-1 (c-fms); the immunohistochemical expression of markers detected in cells of the monocyte/macrophage lineage. The fibroblast-like cells showed positive signals for the mouse-specific L1 probe and RNA ISH with Mouse mouse c-fms in the Transplanted Tumors. The fibroblast-like cells in the tumor showed positive signals for the human specific Alu DNA probe. In this study, the origin of multinucleated giant cells was of human origin, whereas the histiocyte-like cells showed intense positive signals for the mouse specific gene. RT-PCR and mRNA ISH showed that these histiocyte-like cells also expressed mRNA for mouse c-fms, which codes for the CSF-1 receptor. The histiocyte-like cells expressing c-fms were considered to be infiltrated monocyt/macrophages of mouse origin. Immunohistochemically, there were no positive cells bearing anti-human macrophage antigens that were identified in their parental tumors. This heterotransplantation experiment demonstrated that monocyt/macrophage lineage cells in human MFH did not proliferate in mouse tissue and MFH cells did not differentiate toward monocytes/macrophages. Histiocyte-like cells in MFH should be considered a reactive monocyt/macrophage lineage rather than an element of neoplasm.

DISCUSSION
In this study, the origin of fibroblast-like cells, histiocyte-like cells and multinucleated giant cells in the MFH were clearly distinguished at the single cell level with this system. Consistent with our previous study, the fibroblast-like cells were of human origin, whereas the histiocyte-like cells showed intense positive signals for the mouse specific gene. RT-PCR and mRNA ISH showed that these histiocyte-like cells also expressed mRNA for mouse c-fms, which codes for the CSF-1 receptor. The histiocyte-like cells expressing c-fms were considered to be infiltrated monocyt/macrophages of mouse origin. Immunohistochemically, there were no positive cells bearing anti-human macrophage antigens that were identified in their parental tumors. This heterotransplantation experiment demonstrated that monocyt/macrophage lineage cells in human MFH did not proliferate in mouse tissue and MFH cells did not differentiate toward monocytes/macrophages. Histiocyte-like cells in MFH should be considered a reactive monocyt/macrophage lineage rather than an element of neoplasm.

In this study, we also revealed the origin of multinucleated giant cells. The transplanted tumors contained abundant bizarre giant cells of human origin. It was suggested that some multinucleated giant cells in MFH are neoplastic whereas the others belong to a macrophage subpopulation (4). At least 3 types of giant cells exist in MFH: bizarre giant cells, osteoclast-like giant cells, and Touton giant cells. Based on the morphological characteristics, only bizarre giant cells were considered neoplastic cells. The other 2 types of giant cells may represent reactive cells derived from the normal histiocytic lineage. In the presented study, these 2 cell types were not present in the transplanted tumors. We did not determine the histogenesis of osteoclast-like giant cells or Touton giant cells, however, our results support the theory that bizarre giant cells in MFH are neoplastic.

In conclusion, MFH produces chemotaxins and/or differentiation factors, such as CSF-1, to stimulate proliferation and infiltration of the host (non-tumor) monocytes/macrophage lineage. The non neoplastic nature of histiocyte-like cells supports the concept that "MFH" is a phenotypic description and not a distinct entity.

REFERENCES

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Fig. 1a  DNA ISH of the transplanted tumors. (serial sections)
a: Positive signals for the human specific Alu probe in fibroblast-like cells. Note that the positive signal in multinucleated giant cell (arrow) c, Negative signals for mouse specific L1 probe in the small round cells (arrows).

Fig. 1b  Positive signals for mouse specific L1 probe in the multinucleated giant cell (asterisk).