Abstract of the 2011th Maruyama Memorial Lectures of the 80th Annual Meeting of the Medical Association of Nippon Medical School

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The Abstract of the 2011th Maruyama Memorial Research Fund Prize Memorial Lecture

In situ Search for Breast Cancer Stem Cells and Their Niche: The Film Sheet Epoxy Resin Embedding Method and Breast Cancer Stem Cells

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Because of the significant increase in the number of cases, breast cancer has attracted much attention in Japan. Breast cancer now kills more than 10,000 Japanese women each year. Recent reports of small subgroup of cells called “cancer stem cells” that have self-renewal and differentiating abilities and are capable of forming tumors have caused a paradigm shift in our understanding of cancer¹. For example, because cancer stem cells contain a type of ATP-binding cassette transporter, they are highly resistant to anticancer agents². Furthermore, cancer stem cells are greatly affected by their “niche”, and/or microenvironment³. We believe that by focusing on cancer stem cells and their niches, new treatments to suppress the recurrence and metastasis of tumor cells can be developed.

Both CD44+/CD24−/low and aldehyde dehydrogenase 1 are candidate markers for identifying cancer stem cells in breast cancer⁴. However, the location of breast cancer stem cells has not been identified. Therefore, we are using a new technology for in situ identification of breast cancer stem cells, the film sheet epoxy resin embedding method (FSEM)⁵. The FSEM is a new technology that allows nanoscale in situ observation with electron microscopy of target cells and the neighboring microstructure through comparison with hematoxylin and eosin (HE)-stained and immunohistochemical specimens or in situ hybridization specimens (Fig. 1). Basal clear cells identified with electron microscopy in the normal milk duct are candidate stem cells⁶. They lie at the base of the normal milk duct, contacting the basement membrane, and have a clear cytoplasm, a circular nucleus, and few cytoplasmic organelles. Because identification with standard light microscopy is difficult, we search cancer cells with the feature of basal clear cells extensively with the FSEM (Fig. 2). Breast cancer cells appear relatively uniform on light microscopy. However, differences in cell size are clearly visible on electron microscopy. Furthermore, occasional cells have few cytoplasmic organelles.

A major advantage of the FSEM is that an electron micrograph can be acquired with positional information corresponding to an HE-stained specimen. Therefore, the FSEM has an affinity with digital pathology. We are

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pursuing this technology with the integration of virtual slides. In addition, we are also pursuing the development of an indicator—a stable marker for breast cancer stem cells—that can be used instead of CD44+/CD24−/low, whose staining ability is variable.

Today, molecular biological approaches, including genetic analysis, have become mainstream, and morphologic analysis is sometimes considered a relic of the past. However, morphologic analysis remains superior for searching for the structures of cancer stem cell niches and/or microenvironment. We believe that morphologic analysis can develop new approaches for cancer research.

References