Investigation of novel mechanisms in the sarcomagenesis and hematogenous metastasis of uterine leiomyosarcoma

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Abstract

Uterine leiomyosarcoma (ULMS) is a highly aggressive malignant tumor with rapid growth and hematogenous metastasis, and the prognosis is extremely poor. There is no standard treatment other than surgery.

In this study, we performed sleeping beauty (SB) transposon screening, a comprehensive cancer gene identification method using immunocompetent mice, and identified several candidate driver genes (CGCs) for ULMS development and hematogenous metastasis from ULMS. Zfp217, a zinc finger protein with the highest frequency of transposon insertions among 19 genes considered to be involved in sarcomagenesis of ULMS, and Nrd1, encoding nardilysin, considered to be involved in metastatic lung tumors, were validated as oncogenes in human ULMS. The CGCs catalog including these genes can be therapeutic targets in human ULMS.

Background & Results

ULMS is an extremely aggressive malignant tumor with rapid growth and high metastatic potential and has a very poor prognosis because of its resistance to chemotherapy and radiation therapy. Due to its rarity, drug discovery for ULMS is challenging from the problems of validation and funding. In this study, we performed a forward genetic screening, which is a powerful tool for discovering novel therapeutic targets for various cancers, using the SB transposon, in which random insertional mutagenesis of transposons is repeated genome-wide in target organs in mice.

Mice with uterine myometrial-specific Pten deletion and Kras activation did not develop uterine tumors, however when further SB transposon insertions occurred, most developed ULMS between 2-3 months of age (Fig.1, 2). Tumor DNA was analyzed by next-generation sequencing to identify transposon insertion sites, and a list of 19 CGCs associated with sarcomagenesis was compiled. Among them, Zfp217, one of zinc finger proteins, showed highest frequency of transposon insertions. ZNF217, human homolog of Zfp217, was found to be expressed at the protein level in human ULMS, and ZNF217 suppression inhibited cell proliferation and migration in human ULMS cell lines, and its overexpression promoted these capacities. Because of the rapid growth of the uterine tumors, it was impossible to observe hematogenous metastasis until it occurred. Hence, lung metastasis model was created by establishing cell lines from mouse tumors and injecting them through the tail vein of immunocompetent mice. One of the CGCs, Nrd1, encoding nardilysin, was identified in the lung metastatic lesions. NRDC, human homolog of Nrd1, was expressed in human ULMS metastatic tissue at the protein level, indicating that it functioned as an oncogene. These results indicate that the CGCs catalog identified by SB transposon screening is useful for elucidating the pathogenesis and metastasis mechanisms of human ULMS.

Significance of the research and Future perspective

There are no large-scale gene profile data sets for ULMS due to its rarity, thereby hampering the development of new therapeutics based on its pathogenesis. Our findings of CGCs involved in the pathogenesis and progression of ULMS may lead to the development of novel therapeutic strategies.

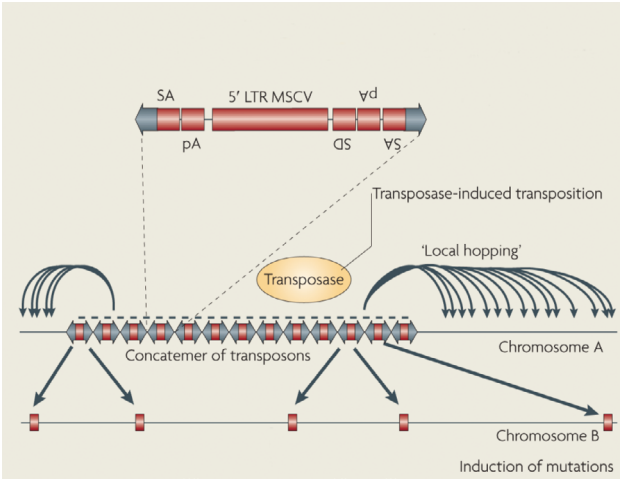

Fig.1

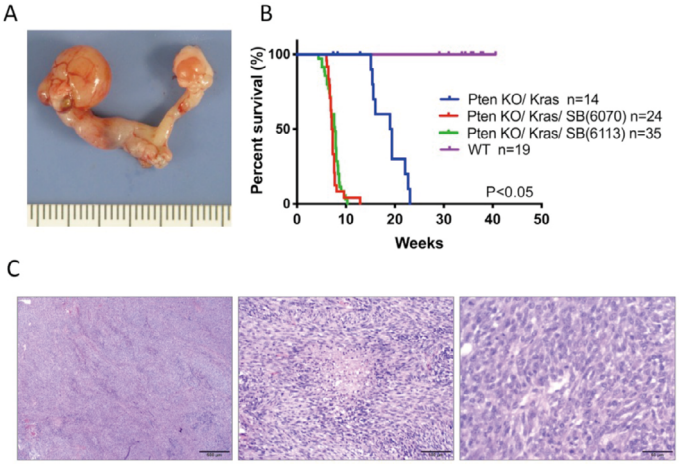

Fig.2

Patent

Treatise Kodama, Michiko; Shimura, Hiroko; Kimura, Tadashi et al. Sleeping Beauty Transposon Mutagenesis Identifies Genes Driving the Initiation and Metastasis of Uterine Leiomyosarcoma. Cancer Res. 2021, 81, p. 5413-5424, doi: 10.1158/0008-5472.CAN-21-0356

URL

Keyword uterine leiomyosarcoma, forward genetic screening, sleeping beauty transposon