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Potential role of LMP2/b1i as negative regulator defines new targets for uterine leiomyosarcoma therapy

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Background: Although the majorities of smooth muscle neoplasm found in the uterus are benign, uterine leiomyosarcoma (LMS) is extremely malignant, with high rates of recurrence and metastasis. We earlier reported that mice with a homozygous deficiency for Lmp2/b1i, an interferon (IFN)-γ-inducible factor, spontaneously develop uterine LMS. The IFN-γ signaling pathway is important for control of tumor growth and invasion and has been implicated in several malignant tumors.

Aim: It is necessary to analyze risk factors associated with human uterine LMS, in order to establish a diagnostic biomarker and a clinical treatment method.

Methods and Results: In this study, experiments with mouse uterine tissues and human clinical materials revealed a defective LMP2/b1i expression in human uterine LMS that was traced to the IFN-γ signaling pathway and the specific effect of JAK-1 somatic mutations on the transcriptional activation of Lmp2/b1i gene. Furthermore, analysis of a human uterine LMS cell line and human clinical materials clarified the biological significance of LMP2/b1i in malignant myometrium transformation and tumor senescence, thus implicating LMP2/b1i as an anti-sarcomagenic candidate.

Conclusion: LMP2/b1i differential expression may be potential diagnostic biomarker for human uterine mesenchymal tumours, especially human uterine LMS. This role of LMP2/b1i as a tumour suppressor may lead to new diagnostic biomarker and therapeutic target molecule in human uterine LMS.

Biography:

Dr. Takuma Hayashi is Professor at Dept. of Medical Technology, International University of Health and Welfare since 2016. He received his Doctorate from Inst. for Medical Science, University of Tokyo in 1994. He was clinical research training as a resident staff in National Cancer Center, Tokyo Japan for 3 years until 1994 and joined Whitehead Institute (WI)/Mass.Inst. of Tech.(M.I.T.) that year. He did postdoctoral training in the laboratory of Dr. Rick A. Young (Membership in the National Academy of Sciences, WI/M.I.T.), and also was a research member of USA Project of AIDS vaccine development (Project Leader: Dr. David Baltimore, Nobel Laureate, Cal.Tech.). After postdoctoral training, he got faculty position Lecture, Mass. General Hospital (MGH)/Harvard Medical School (HMS) in 1997. He has been studying the antigen presentation system by MHC class I with LMP2/b1i-deficient mice, under the cooperation of Dr. Susumu Tonegawa (Nobel Laureate, M.I.T.). He identifies diagnostic biomarkers, LMP2, Cyclin B1 and Cyclin E, for malignant tumour uterine leiomyosarcoma. Current research focus: molecular approach of tumorigenesis of uterine leiomyosarcoma.