Established LMP2-Biomarker for Development of Diagnosis and Anti-tumor Drug against Uterine Leiomyosarcoma

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Objectives: Patients with uterine leiomyosarcoma (LMS) typically present with vaginal bleeding, pain, and a pelvic mass, with atypical presentations of hypercalcemia and eosinophilia also being reported. Radiographic evaluation with combined positron emission tomography/computed tomography may assist in diagnosis and surveillance in women with uterine LMS, which is commonly used with stage and tumour grade as prognostic indicators and a recently developed risk-assessment index to predict disease-specific survival. Recent studies have shown that the addition of adjuvant therapy after surgical management does not seem to improve survival, and ovarian preservation does not appear to negatively impact outcome. Importantly, diagnostic biomarker, which distinguishes malignant tumour leiomyosarcoma and benign tumour leiomyoma, is not established yet. Experimentally, it is noteworthy that LMP2 deficient mice exhibit spontaneous development of uterine LMS, with a disease prevalence of ~37% by 12 months of age. It must therefore be demonstrated whether human uterine leiomyosarcomas show the weak expression of LMP2.

Methods: Immunohistochemistry (IHC) was performed using the avidin-biotin complex method previously described. Briefly, one representative 5-micro m tissue section was cut from a paraffin-embedded sample of the radical hysterectomy specimen from 29 patients with uterine leiomyosarcoma, 24 patients with leiomyoma. Sections were deparaffinized and rehydrated in graded alcohols and then incubated with normal mouse serum for 20 min. Sections were incubated at room temperature for 1 h with anti-LMP2 antibody (Affinity Res, Products Ltd., Exeter; dilution 1/100). Afterwards, sections were incubated with a biotinylated secondary antibody (Dako, Carpinteria, CA) and then exposed to a streptavidin complex (Dako). Complete reaction was revealed by 3,3'-diaminobenzidine, and the slide was counterstained with hematoxylin. Twenty one normal uterine smooth muscle sections from specimens were used as positive controls. Negative controls consisted of tissue sections also incubated with normal rabbit IgG instead of the primary antibody.

Results: The IHC experiments demonstrated that although normal uterine smooth muscle tissues (44 cases) and uterine leiomyoma tissues (43 cases) markedly expressed LMP2, uterine leiomyosarcoma tissues (41 cases) did not.

Conclusions: Defective LMP2 expression is likely to be one of the risk factors for the development of human uterine neoplasm, as it is in the LMP2 deficient mouse. Thus, LMP2 is useful for a novel diagnostic maker for human uterine leiomyosarcoma. Additionally, gene therapy with LMP2 expression vectors may be a new treatment for uterine leiomysarcomas that exhibit a defect in LMP2 expression. Because there is no effective therapy for unresectable uterine leiomyosarcoma, our results may bring us to specific molecular therapies to treat this disease.