ISP-2-5  Efficacy of PET/CT for the differentiation of uterine sarcomas from leiomyoma

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[Objective] We respectively analyzed the efficacy of the PET/CT for the diagnosis of uterine sarcomas. [Methods] The patients were divided into sarcoma group (n=21) and leiomyoma group (n=20) retrospectively, which were suspected malignancy by MRI with high intensity area on T1-weighted images, heterogeneous high-signal intensity on T2-weighted images and/or the enhancement on contrast-enhanced MRI. All patients were measured the maximum standardized uptake values (SUVmax) of all lesions by PET/CT. We calculated the optimal cutoff value. Informed consent was obtained from all of the patients. [Results] The median SUVmax of uterine sarcomas and leiomyoma were 12 and 4.1, which were significantly different. The cutoff of SUVmax greater than 7.1 was able to exclude leiomyoma, with 85% sensitivity and 84.2% specificity (area under the curve 95%). [Conclusion] PET-CT is a good diagnostic tool for uterine sarcomas with an optimal cutoff value of SUVmax 7.1.

ISP-2-6  Uterine Leiomyosarcoma Tumorigenesis in Lmp2-deficient Mice : Involvement of Impaired Anti-oncogenic Factor IRFI

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[Objective] Uterine leiomyosarcoma (Ut-LMS) is a highly metastatic smooth muscle neoplasm. We previously reported that Lmp2-deficient mice spontaneously developed Ut-LMS, which implicated this protein as an anti-oncogenic candidate. IRFI has been shown to play roles in the immune response, and tumor suppression. The aim of this study was to elucidate the molecular mechanism of sarcomagenesis of Ut-LMS using human and mouse uterine tissues. [Methods] The expressions of the IFN-g signal molecules, IRF1 and IRF2, STAT1, and LMP2, -3, -7 and -10 were examined by western blot analysis, electrophoretic mobility shift assay and immunohistochemistry with human and mouse uterine tissues. Physiological significance of IRF1 in sarcomagenesis of Ut-LMS was demonstrated by xenograft studies. [Results] In the present study, several lines of evidence indicated that although treatments with IFN-g strongly induced the activation of STAT1 as a transcriptional activator, its target molecule, IRF1, was not clearly produced in Lmp2-deficient uterine smooth muscle cells (Ut-SCMs). [Conclusion] Defective expression of IRFI in the IFN-g-induced signaling molecules may result in the malignant transformation of Ut-SCMs. The modulation of LMP2 may lead to new therapeutic approaches in human Ut-LMS. These experiments were conducted in accordance with institutional ethical guidelines.

ISP-2-7  ATP7A is a promising therapeutic target for uterine leiomyosarcoma

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[Objective] Resistance to platinum drugs remains a significant problem in uterine leiomyosarcoma (LMS). We investigated the role of ATP7A in the resistance to platinum drugs in LMS using both in vitro and in vivo models. [Methods] The expression of the typical platinum transporters (MDR1, MRP2, ATP7A, and ATP7B) was examined in LMS cell lines using Western blotting analysis. ATP7A expression was investigated by immunohistochemistry (IHC) using clinical samples of LMS. IC50 values to cisplatin were measured in SK-LMS cells, SK-LMS-AP7A-suppressed cell line (SK-LMS-7A cells), which permanently transfected PRS ATP7A shRNA vector. We established xenografted mice by inoculating SK-LMS cells and SK-LMS-7A cells, and examined in vivo platinum sensitivity with cisplatin for both tumors. (approved by IRB) [Results] The expression of ATP7A was identified in the SK-LMS cells. ATP7A expression was identified in 70% (14/20) of the LMS clinical samples using IHC. The IC50 values to cisplatin improved from 17 nM to 4.3 nM after the suppression of ATP7A in SK-LMS-7A cells. A significant anti-tumor effect of cisplatin was observed in SK-LMS-7A xenografted mice than in SK-LMS xenografted mice. We also identified omeprazole as an inhibitor of ATP7A in vitro. [Conclusion] ATP7A is associated with platinum resistance. Omeprazole acting as an inhibitor of ATP7A can be a therapeutic agent for LMS.