IS-MW-3-1 Nuclear receptor coactivator-6 (Ncoa6) plays as a potent tumor suppressor of endometrial cancer

Yamagata University[1], Baylor College of Medicine, Department of Molecular and Cellular Biology, USA[2]
Jun Kawagoe[1], Jianming Xu[2], Kazuhiro Takahashi[1], Satoru Nagase[1]

[Objective] Nuclear receptor coactivator-6 (Ncoa6) plays an interesting role in regulating estrogen sensitivity in uterus by both up-regulating transcription of estrogen receptor alpha (ERα) and down-regulating ERα expression via ubiquitin-proteasome pathway. In this study, we pursed the role of Ncoa6 in the development of endometrial cancer (EMC). [Methods] We used 1) uterine specific Ncoa6 knock-out (KO) mice (PRcre/+ ; Ncoa6f/f), 2) uterine specific Ncoa6 and Pten KO mice (PRcre/+ ; Ncoa6f/f ; Ptenf/f), and 3) transplant model of uterine epithelial cells from PRcre/+ ; Ncoa6f/f ; Ptenf/f to SCID mice, to demonstrate if the loss-of-Ncoa6 promotes EMC development. Then, we performed mRNAseq to detect responsible gene targets of Ncoa6. Moreover, Ncoa6 expression in normal human endometrium and human EMC were compared in the database. [Results] We found that loss-of-Ncoa6 promoted 1) onset of EMC in aged PRcre/+ ; Ncoa 6f/f) mice, and 2) massive growth of EMC in PRcre/+ ; Ncoa6f/f ; Ptenf/f mice. Importantly, the strong promotion of EMC was observed in ovariectomized mice. Epithelial loss-of-Ncoa6 was sufficient for EMC promotion. The mRNAseq showed that Ncoa6 regulated several carcinogenic pathways. Down-regulation of Ncoa6 in human EMC was frequently observed in the database. [Conclusion] Our data strongly indicated that Ncoa6 could be a potent tumor suppressor of EMCs.

IS-MW-3-2 Retinoic acid receptor β : a potential therapeutic target in retinoic acid treatment of endometrial cancer

Tohoku University[1], Department of Disaster Obstetrics and Gynecology, International Research Institute of Disaster Science (IRIDeS), Tohoku University[2]
Keita Tsuji[1], Hiroki Utsunomiya[1], Chiaki Hashimoto[1], Kiyoshi Ito[2], Nobuo Yaegashi[1]

[Objective] The effects of retinoic acid are mediated by the retinoic acid receptor (RAR), and RARα/RARβ especially acts as a tumor suppressor. However, little is known about its role in human endometrial cancer. [Methods] The effects of all-trans retinoic acid (ATRA) on cell proliferation, apoptosis and migration were analyzed in RL95-2 and Hec1A. We also carried out these assays with knockdown of RARα and RARβ. Furthermore we performed analyzed correlation between immunoreactivity of RARα/RARβ and clinicopathological factors endometrial cancer tissue. This study was approved by the Ethics Committee. [Results] We found inhibitory effects of ATRA on cell proliferation, apoptosis, and migration in RL95-2 cells, but not in Hec1A cells. RARα or RARβ knockdown individually could not cancel out the inhibition of cell proliferation by ATRA in RL95-2 cells, but simultaneous knockdown of RARα and RARβ could block its effect on proliferation. RARα and RARβ knockdown dose-dependently reduced the inhibition of migration by ATRA, but the effect was more pronounced with RARβ knockdown than with RARα knockdown. In immunohistochemistry, RARα expression was positively correlated with tumor grade, and RARβ showed the opposite tendency. [Conclusion]RA might have multiple anti-tumor effects and RARβ may be a potential therapeutic target in RA treatment for endometrial cancers.

IS-MW-3-3 17β-estradiol promotes cervical cancer progression by stimulating the production of myeloid derived suppressor cells from hematopoietic stem cells

Osaka University
Katsumi Kozasa, Seiji Mabuchi, Hiromasa Kuroda, Tomoyuki Sasano, Ryoko Takahashi, Yuri Matsumoto, Kae Hashimoto, Kenjiro Sawada, Tadashi Kimura

[Objective] We previously reported that cervical cancer (CC) patients displaying tumor related leukocytosis (TRL) have poor prognosis and that myeloid derived suppressor cells (MDSC) induced by tumor-derived G-CSF are involved in the mechanism. As younger age is known to be associated with poorer prognosis in CC patients, we speculated estrogen may play roles in the development of TRL, induction of MDSC from hematopoietic stem cells (HSC), and the progression of CC. [Methods] 1. Using HSCs isolated from the bone marrow of ICR mice, the in vitro effect of 17β-Estradiol (E2), ICI 182780 (ICI), or both on the proliferation of HSC were examined by BrdU Assay. 2. Using ovariectomized ICR mice, the effect of E2 on the number of HSC, MDSC and WBC in bone marrow, spleens, and peripheral blood was examined using flow cytometry. 3. Ovariectomized BALB/c nude mice were subcutaneously inoculated with estrogen receptor negative CC cells : HeLa. Then we treated the mice with E2 and examined the tumor growth and the mice survival. [Results] 1. Treatment HSC with E2 increased the number of HSC in vitro. ICI abolished the effect of E2. 2. Treatment mice with E2 increased the number of HSC, MDSC, and WBC. 3. Treatment mice with E2 promoted the growth of CC, leading to the decreased survival in mice. [Conclusion] E2 promotes CC progression by stimulating the induction of MDSCs from HSCs.