ISAC-1-4 Patient–derived Tumor Xenograft Model for Gynecologic Cancer

Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea 1, Department of Pathology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea 2
Jeong-Won Lee 1, Young Jae Cho 1, Sang-Yong Song 1, Yoo-Young Lee 1, Tae-Joong Kim 1, Byoung-Gie Kim 1, Duk-Soo Bae 1

[Objectives] Patient–derived tumor xenograft model (PDTX) may provide more accurate and reliable information about individual patients' tumor biology when compared with established cell line model. This study was designed to study the development of PDTX mice and their genetic and phenotypic stability for gynecologic cancer including ovarian, endometrial and cervical cancer. [Methods] Small pieces (3 × 3 × 3 mm) of human gynecologic cancer tissue (n = 94) were meticulously grafted under renal capsules of female BALB/C-nude mice within 2 h of surgical removal. Grossly visible tumor tissues were serially transplanted for 2–5 generations. After the development of tumors in mice, phenotypic and genetic comparisons were performed between primary tumor and corresponding transplantable xenografts using H&E, IHC, Flow cytometry, and array–comparative genomic hybridization (aCGH) analysis. [Results] Total tumor tissue engraftment rate was 37.6% (35/94) including ovarian cancer 32.8% (21/64), cervical cancer 47.6% (10/21) and endometrial cancer 44.4% (4/9). The mean time to the development of first generation in mice was 66 month in ovarian, 55 month in cervical and 4 month in endometrial cancer. Comparison of primary and PDTX tumor tissues showed highly similar histopathological features. Moreover, analysis of IHC and aCGH indicated that all examined mutation and genomic alterations found in primary cancer tissues were precisely replicated in the corresponding PDTX tumors. [Conclusions] PDTX mice for human gynecologic cancer can be developed as a method of subrenal capsule implantation and have very similar phenotypic and genetic alteration of the original tissues. This has the potential to provide a very effective tool for future personalized therapy and for conducting translational gynecologic cancer research.

ISAC-1-5 Clinical significance of regulatory T cells and NK cells in patients with human cervical carcinoma

National Taiwan University Hospital, Taipei, Taiwan 1, Buddhist Tzu Chi general, Taipei Branch, Taipei, Taiwan 2, Cathay General Hospital, Taipei, Taiwan 1, Taiwan Adventist Hospital, Taipei, Taiwan 3
Wen-Chun Chang 1, Bor-Ching Sheu 1, Suzu-Yu Chen 1, Li-Yun Chou 1, Pei-Shen Huang 2, Su-Cheng Huang 3

[Objective] To determine the functional attributes of CD4+ CD25+ regulatory T cells (Tregs) in cancer progression by suppressing antitumor immunity. [Methods] Triple-color flow cytometry was utilized to study the phenotype expression of CD4+ CD25+ Tregs and natural killer (NK) cells in the peripheral blood lymphocytes (PBLs) and tumor infiltrating lymphocytes (TILs) of cervical carcinoma. [Results] We found that the CD152 + CD105 + and Foxp3 + CD103 + Treg cell population of TILs were apparently more than the cells population of PBLs. The GITR expression of Treg cells was also higher in TILs than in PBLs. It was found that the NK cells of TILs are triple less than the NK cells of PBLs. The inhibiting CD158a, CD158b, and NKG2A expressions of NK cells were lower in PBLs than in TILs. On the other hand, the activating NKG2D, NKp46 and NKp30 expressions of NK cells were higher in PBLs than in TILs. In our data, we found that the perforin expression of NK cells in TILs was less than in PBLs. The granzyme B expression of NK cells was no difference between PBLs and TILs. The percentages of Treg cells expressing LAP (TGF–β1) and TGF–β RII were higher in TILs than in PBLs. It is showed that TGFβ1 inhibited the IFNγ expression of NK cells. We found that the IFNγ expression of NK cells was inhibited by incubated with TGF–β, but activated by cocultured with IL–2. The decreasing IFNγ expression of NK cells of the group incubated with TGF–β, was also repressed further by cocultured with IL–12 or IL–15. The decline trend of the IFNγ expression of NK cells cocultured with Treg cells was presented. Alternatively, after cocultured with Tconv cells, the IFNγ expression of NK cells was apparently increased by cultured with IL–2 and IL–12. [Conclusion] We determine that the Treg cells from cervical cancer microenvironment are functional Tregs. The functional Tregs secret TGF–β to inhibit secretion of IFNγ from NK cells, thus might inhibit cytolytic activity and proliferation of NK cells.

ISAC-1-6 Copy number variations of the antimicrobial–gene, defensin beta 4, is associated with the susceptibility to cervical cancer

Nagasaki University
Shuhei Abe, Kiyonori Miura, Kentaro Yamashiki, Shoko Miura, Daisuke Nakayama, Kouhei Kotera, Akira Fujishita, Tetsuro Samejima, Masaki Fuse, Makoto Murakami, Koh-Ichiyo Yoshiura, Hideaki Masuzaki

[Objective] Cervical cancer (CC) has the two critical transition steps: persistent oncogenic human papillomavirus (HPV) infection and progression to CC. Oncogenic HPV infection alone is insufficient to cause CC. Host genetic factors may also contribute to CCPathogenesis, but their roles remain to be determined. The defensin beta4 gene, DEFAB, which has antimicrobial properties, is a candidate host genetic factor for susceptibility to CC. [Methods] The study subjects comprised 204 women with CC, a population having a high-risk of persistent HPV infection (CC group), and 200 healthy uncomplicated women from the general population (control group) after obtaining their informed consent. Copy number (CN) variations of DEFAB4 in each test sample was determined by relative quantitation using the comparative Ct method. Differences between the two groups were evaluated. [Results] The median of DEFAB4 CN in CC group and in control group was 44.67 (p = 2.77e-4, t-test). The odds ratio (OR) of CN individuals with 4 DEFAB4 copies or less was higher (OR of 4:02; 95% Confidence Interval (CI) 1.36–3.02), compared with that in individuals with 5 or more copies was relatively lower (OR of 0.49; 95% CI: 0.33–0.74). Therefore, both groups indicated a two-tailed significant difference from an OR of 1.00 at the 5% level. [Conclusion] We found CN variation of DEFAB4 was a host genetic factor conferring susceptibility to CC. A lower DEFAB4 CN was associated with susceptibility to CC.