Session A6: Cancer Genetics and Tumor Biology

Monday, September 3

A6-01 Cancer Genetics and Tumor Biology, Mon, 13:45 - 15:30

Immune tolerance of cancer is mediated by IDO which is inhibited by COX-2 inhibitor through Treg cells

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Background: PGE2, synthesized by cyclooxygenase-2 (COX-2), is related with cellular immune tolerance in cancer development. Although the potential of immune tolerance associated with tumor-produced COX-2 has been suggested, the mechanism of immune tolerance is not yet well defined. Induction of tolerance required a specific environment in which plasmacytoid dendritic cells (pDCs) and regulatory T cells (Treg) play an essential role. It was recently shown that maturation of DCs in the presence of indoleamine 2,3-dioxygenase (IDO) results in activation of Treg, and inhibition of COX-2 activity regulates IDO expression within the tumor microenvironment. IDO is an emerging immuno-regulatory enzyme that can block T lymphocyte activation and induce Treg. Thus, we hypothesized that the anti-tumor immunity of COX-2 inhibitor could be partly due to IDO-dependent Treg activation. To test this hypothesis, we evaluated Treg and IDO expression in mouse tumor model treated with COX-2 inhibitor.

Methods: The Lewis lung cancer cells (3LL) originated from C57Bl/6 mouse were inoculated in each mouse. Total 20 mice were randomized into normal control, 3LL inoculated control, and low and high dose COX-2 inhibitor (celecoxib was given once a day for 3 weeks by oral gavage, 10 or 100mg/kg/day) treated groups (N=5 per group). Mice were sacrificed on day 28. The tumor mass and spleen were removed for immunoblotting and flow cytometry analysis. The pDCs were isolated from splenocytes by magnetic cell sorting. The number of surface lung tumor and tumor mass size were compared between groups.

Results: The pDCs cultured in COX-2 inhibitor supernatants showed a significant decrement in IL-10 production ($p<0.05$). The COX-2, IDO and Foxp3 expression were decreased in the tumor mass of COX-2 inhibitor treated mice, and this was found to correlate with reduced tumor mass and metastasis. Treg cells were decreased in COX-2 inhibitor treated groups ($p<0.05$) and positive correlation exists between Treg cell and tumor volume.

Conclusion: The COX-2 inhibition decrease immune tolerogenic IL-10 production in pDCs. The expression of IDO and Treg cells are decreased in COX-2 inhibited 3LL tumor bearing mice groups. The present study shows that COX-2 inhibitors promote antitumor reactivity by inhibiting IDO and Treg activity.

A6-02 Cancer Genetics and Tumor Biology, Mon, 13:45 - 15:30

A novel heterozygous germline mutation of NBS1 leading to loss of the MRE11-binding domain predisposes to common types of cancers

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Background: DNA damage response (DDR) pathways play important roles in the maintenance of genomic stability, and their inactivation is critically involved in multi-step carcinogenesis. We have shown the presence of frequent impairment of DNA damage checkpoints as well as of mitotic checkpoints in lung cancer, suggesting their involvement in lung carcinogenesis. A hypomorphic 657del5 mutation of NBS1, a key DDR component, is responsible for the rare cancer-predisposing, Nijmegen breakage syndrome (NBS), which has been reported almost exclusively in the Slavic population thus far.

Methods: We evaluated the S phase checkpoint status by examining radioresistant DNA synthesis (RDS) in 14 lung cancer cell lines and normal human fibroblasts. NBS1 alteration was sought for in a small cell lung cancer (SCLC) cell line with impaired S-phase checkpoint in RDS assay, and was characterized by sequencing and biochemical analyses. The identified NBS1 mutation was screened for in the germline of 1,743 patients with various types of cancers as well as of 2,348 control subjects. Association between NBS1 mutation and cancer incidence was examined using two-sided Fisher's exact test.

Results: We identified for the first time in the Japanese population an unprecedented type of heterozygous NBS1 mutant, termed IVS11+2insT, lacking the MRE11- and ATM-binding sites at the C terminus. It was found to be profoundly defective in terms of the crucial binding to MRE11, ATM, wt-NBS1, BRCA1, and unexpectedly also to MDC1, while the mutant also demonstrated impaired ATM phosphorylation in response to low dose irradiation (IR) in the heterozygous state. In our initial screening, the IVS11+2insT mutation was in fact identified in 1 tumor among 200 primary lung cancer cases. Importantly, while IVS11+2insT was found in only 2 (0.09%) of 2,348 control subjects, it was identified in 2% (2 of 96) of heterozygotes with gastric cancer, 0.8% (3 of 376) of those with colorectal cancer, and 0.4% (2 of 532) of those with lung cancer, which were comparable to frequencies reported for other DDR-related genes conferring cancer susceptibility, with odds ratios of 25.0 (95% confidence interval (CI) [1.78-346.0]) for gastric and 9.43 (95%CI [1.08-113.3]) for colorectal cancer.

Conclusion: This novel NBS1 mutation, IVS11+2insT, may be crucially involved in the predisposition to common types of cancers in the Japanese patients. Thus, additional investigation is warranted, including more detailed phenotypic characterization, such as frequency and penetrance in cases with familial aggregation as well as screening in other ethnic groups.