Editorial

Interface of cancer stem cells and cancer immunity

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Immune checkpoint inhibitors have established their clinical position as the fourth primary treatment of non-small cell lung cancer (NSCLC) in addition to surgery, chemotherapy, and radiotherapy (1-3). However, not all patients received a survival benefit from the immunotherapies. Many researchers are attempting to reveal the underlying mechanisms, which may lead to development of novel biomarkers to predict the clinical outcome of the immunotherapy as well as novel therapeutic targets for immunotherapy (4). Infiltration of tumor reactive $CD8^+$ T cells such as neo-antigen specific $CD8^+$ T cells in tumor tissues, and subsequent expression of programmed cell death ligand 1 (PD-L1) in tumor cells and other stromal cells induced by IFN-γ from T cells, which indicates high immunogenicity of cancer cells, appear to be essential for PD-1/PD-L1 antibody monotherapy to work out. Therefore, the understanding of the factors influencing $CD8^+$ tumor-infiltrating lymphocytes (TILs) is important.

Masciale *et al.* demonstrated the possible positive relationship between high aldehyde dehydrogenase (ALDH), lung cancer cells which may contain lung cancer stem cells (LCSCs) and TILs, particularly $CD8^+$ T cells (5). The relationship between TILs and LCSCs has not been investigated well in lung cancer. In spite of its small numbers of the analyzed patients, this study would bring new insights into tumor immunology in lung cancer. However, this result seems to be contradictory to the previous reports. High concentration of TILs was reported to correlate with improved disease free survival and decreased risk of recurrence in lung cancer (6-9), whereas cancer stem cell (CSC) is generally linked to tumor recurrence and metastasis (10,11). CD133 has been widely used as a CSC marker in NSCLC (12). A meta-analysis of 11 studies with total 1,004 NSCLC patients confirmed that high CD133 expression was correlated with significantly worse 5-year overall survival than those with low CD133 expression. CD133 expression was also associated with various clinical parameters such as tumor stage, grade, differentiation status and lymph node metastasis (13,14). Regarding its relationship with immune responses, Huang *et al.* reported that CD133 expression on lung cancer cells was negatively correlated with infiltration of $CD56^+$ cells, but not of $CD8^+$ T cells (15). They speculated that CSC may not be able to initiate immune responses without help of other immune cells and cytokines, and that the immunosuppressive ability of CSCs may be dominant over the induction of anti-tumor immune responses. Indeed, several reports suggested that CSCs evolve strategies to evade from T-cell attacks (16,17).

ALDH1 discussed in Masciale's study has emerged as one of the prominent markers for CSCs in various solid cancers including lung cancer (18). ALDH1 overexpression was associated with poor prognosis in NSCLC patients, where high ALDH1 expression was significantly associated with a more aggressive and advanced pathological grade and stage (19). Furthermore, increased ALDH1 expression has been associated with increased metastasis in multiple cancers (20). These results of CD133- or ALDH-related CSCs study may be contradictory to the Masciale's study.

Although ALDH1-positive cells are highly resistant to chemotherapeutic agents commonly used as first-line therapy in the clinical setting, such as cisplatin, gemcitabine, doxorubicin, vinorelbine and docetaxel (18), the relationship between ALDH1 positive cells and immune responses/immunotherapies have not been elucidated.

Li *et al.* reported that positive ALDH1A1 (isoform of ALDH1) expression was correlated with patients' smoking status and advanced stage (21). Patel and colleagues revealed that ALDH1A1 and ALDH3A1 were upregulated in lung tissues as a result of exposure to carcinogenic aldehydes in cigarette smokers. Atypical pneumocytes expressed ALDH1A1 and ALDH3A1 significantly higher than normal pneumocytes, suggesting upregulation during malignant transformation to lung cancer (22). On the other hand, we have previously reported that NSCLC developed in smokers have higher numbers of $CD8^+$ TILs than those in nonsmokers, and was correlated with better post-surgery prognosis (6). Although Masciale *et al.* enrolled only smokers with NSCLC, either adenocarcinoma or squamous carcinoma, environmental factors such smoking habit could have some influence on the relationship between CSCs and TILs.

Masciale *et al.* discussed one possibility that CSCs could stimulate $CD8^+$ T cells specific for CSCs. Morita and their colleagues reported that $CD8^+$ T cells specific tumor antigens such as cancer germ line antigens could be induced in multiple types of cancers such as colon cancers, and those CSC expressing such tumor antigens could be important therapeutic targets (23). However, CSCs may also express various immune-inhibitory molecules including PD-L1, and may evade from T cell attack (15).

Another important point to be discussed is characteristics of $CD8^+$ TILs. $CD8^+$ T cells are important cytotoxic effector cells for tumor eradication in various types of cancers including NSCLCs. However, exhaustion of $CD8^+$ T cells that lost anti-tumor activity, or immunosuppressive $CD8^+$ regulatory T cells (Tregs), might be induced possibly by ALDH positive CSCs. Actual function of $CD8^+$ TILs and their correlation with prognosis have not been evaluated in Masciale's study. Kiniwa *et al.* reported that $CD8^+$ $Foxp3^+$ T-cells had immunosuppressive activity similar to $CD4^+$ $Foxp3^+$ Tregs in prostate tumors (24). We also reported immunosuppressive $CD8^+$ TILs including immunodysfunctional $CD8^+$ $GATA3^+$ or immunoregulatory $CD8^+$ $FOXP3^+$ T cells in lung adenocarcinoma (7). More detailed characterization of $CD8^+$ TILs may provide new insights on this controversial issue. Additionally, Masciale *et al.* evaluated only 12 NSCLCs including 9 adenocarcinomas and 3 squamous cell carcinomas. More detailed studies on both histological types is required, because we reported that histological type would have a great influence on the subset status of TILs (6).

Nevertheless, the intriguing study by Masciale *et al.* may stimulate the field of the interfaces of cancer immunology and CSC biology, and we believe that further studies will reveal detailed interactions between CSCs and immune system and will lead to the development of new diagnostic and therapeutic strategies for patients with NSCLCs.

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Footnote

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