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Commentary Open Access

Dynamic Immune Activation: Upregulation of Immune Inhibitory Pathways in Gastric Cancer

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Commentary

In the tumor microenvironment (TME), aberrant inducement of co-inhibitory molecules (including programmed cell death 1(PD-1), cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), lymphocyte-activation gene 3 (LAG-3), etc.) is a critical factor contributing to immune escape by the tumor. Effector immune cells with phenotype that upregulates these markers are associated with functional exhaustion, conferring upon tumor the potential to avoid immune control. However, these key molecules have been exploited as advantageous weapon in tumor immunotherapy, gradually reshaping recent cancer therapy mode. Until recently, the total remission rate of PD-1/programmed cell death 1 ligand 1 (PD-L1) blockade therapy in most tumors has been reported from about 20 to 30 percent [1,2]. For those patients who do not respond, the priority is to maximize the treatment effect through combinatorial therapy. As such, understanding of biological function of multiple immune checkpoints and their underlying molecular mechanism is of great value for exploring novel immune targets and combinatorial therapy mode.

However, the data on patient prognosis and disease progression relevant to immune checkpoints in gastric cancer is unsubstantial, although there are few reports presenting some conflicting results [3-5].

Recently, PD-L1 expression as well as multiple additional immune checkpoints within the same gastric cancer cohort was detected to ascertain their survival correlation. The study revealed that higher tumor-infiltrating lymphocytes (TIL) density correlated with less risk of disease progression, exhibiting survival benefit in gastric cancer patients, and PD-L1 positivity showed a significant association with the presence of high TIL infiltration [6], and this part of observation was consistent with the similar results in another study discussing the positive association of PD-L1 expression with longer survival and higher TIL infiltration within gastric cancer tissue [7]. Additionally, to broaden the investigation for immune status of the same examined cohorts, it further revealed that patients with higher levels of other immune checkpoints, such as CTLA-4 and LAG-3, were significantly correlated with longer survival. However, the result seems paradoxical when compared to the previous studies with the opposite finding that higher levels of these immune inhibitory molecules are associated with worse outcomes [8-11]. One hypothesis was that up-regulation of these immunomodulatory molecules might reflect an immune activation status driven by effector immune cells as a feedback mechanism for the prevention of immune-associated adverse damage. In spite of their up-regulation that might weaken anti-tumor reaction, activated immune cells would still attack the tumor and exhibit a survival advantage over those with unactivated immunity. Recently, It has been discovered in mice model that high expression of immunosuppressive factors: indoleamine 2,3-dioxygenase 1 (IDO1)PD-L1 and forkhead box P3+ regulatory T (Foxp3+Treg) cells were shown in the subset of T cell-inflamed tumors, rather than T cell-cold tumors, indicating that these inhibitory pathways might serve as a negative feedback mechanism that followed, rather than preceded, immune infiltration. This mechanistic study demonstrated that up-regulation of these three inhibitory elements in the tumor microenvironment depended just on the presence of effector T cell infiltration [12]. Previous experiment also showed an immediate increase in PD-L1 expression on the gastric tumor cells once co-cultured with immune cells [13].

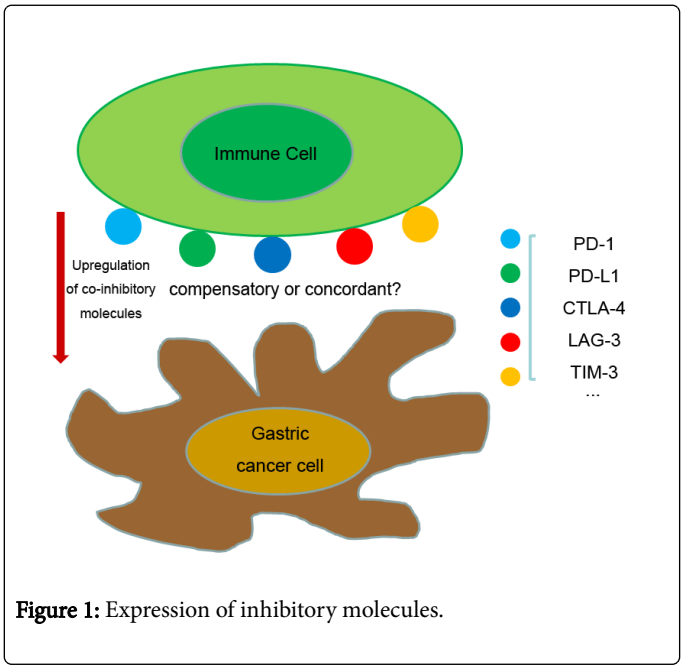

Figure 1: Expression of inhibitory molecules.

Strikingly, in gastric cancer specimens, it was also revealed that, high expression of these inhibitory molecules including PD-L1, PD-1, CTLA-4, T-cell immunoglobulin domain and mucin domain 3 (TIM-3), IDO1, LAG-3, transforming growth factor-β (TGF-β), interleukin-10 (IL-10), and Foxp3 positively correlated with the levels of IFN-gamma, without an exception. In addition, it is interesting to note that higher levels of almost all these molecules showed better outcome tendency in survival curve, although only PD-L1, CTLA-4 and LAG-3 have significant difference. It might be worthy to question whether there is predominant importance among these molecules taking part in a process of anti-tumor immunity, or on the other side, whether these immune checkpoints act in concert or influence one another to achieve immune dynamic regulation, which still remains to be explored (Figure 1). Intriguingly, a recent study reported that in

metastatic ovarian cancer model, there was a compensatory up-regulation among checkpoints: PD-1, LAG-3, and CTLA-4, which limits the efficacy of single-agent blockade [14]. However, the potential molecular mechanism under which they interact with other checkpoints requires more data from future basic research.

Based on the analysis of these immune profiles implicated in gastric tumor microenvironment, especially the finding that higher TIL density exhibited survival benefit and was identified as an independent prognostic factorit is curious to know why just a proportion of patients have higher TILs density, or what is the critical factor that recruits TILs to exert anti-tumor immunity and thus exhibit favorable outcome. In 2014, a comprehensive project from The Cancer Genome Atlas (TCGA) for the classification of gastric tumor molecular subtype has reported that the gastric tumor positive with Epstein-Barr virus (EBV) is one of the four molecular subtypes, apart from microsatellite unstable tumor, genomically stable tumor, and tumor with chromosomal instability [15]. Meanwhile, this type is characterized by PD-L1 amplification and favorable patient outcome [16]. It has been discovered that nearly 10% of gastric samples are positive for EBV infection in our study, and EBV positivity correlates with PD-L1 expression and increased TIL density. The discovery that these three factors were significantly linked with each other provides a hypothesis that EBV infection might recruit effector immune cells into tumor area, later inducing up-regulation of PD-L1 as a negative feedback mechanism, although EBV might not be the only factor inducing immune infiltration in gastric cancer. Consistent with this, Kim et al. reported that EBV infection would recruit more T cells migrated to EBV-infected gastric cancer cells, which might be conducive to longer survival of EBV-positive patients compared with those not associated with EBV infection [16]. Taken together, these studies constructively suggested a dynamic immunity mode in gastric cancer that EBV infection could activate immune response *via* recruiting immune cell infiltration, and the later induce checkpoint up-regulation as a feedback mechanism, and that those EBV-positive patients with activated immunity might be an appropriate subset for the selection of checkpoint blockade therapy.

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