Commentary

A Co-Inhibitory Alliance in Myeloid Leukemia: TIM-3/Galectin-9 Complex as a New Target for Checkpoint Blockade Therapy

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As a pressure applied on the transformed cells, anti-tumor immunity leads to the selection of the most successful clones to evade and/or to suppress the immune responses. These cells need to develop capacities to adapt to the harsh milieu established by the immune responses. Therefore, cancer cells are commonly accepted to be non-immunogenic; nevertheless, tumors such as melanoma, prostate cancer, and acute myeloid leukemia (AML) challenge this concept. Under inflammatory conditions, myeloid cells are responsible of triggering adaptive immunity, mainly T cells, through antigen presentation and costimulation. Correspondingly, myeloid leukemia cells need to employ elaborate strategies to cope with cytotoxic T cells (CTLs), natural killer (NK) cells, and type-1 helper T (Th1) cells, which are the most critical effectors in anti-tumor immunity. Intriguingly, the costimulatory molecules are not vanished on leukemic blasts, thus, they promote T cell activities as an unconventional way that yields immunogenicity. Influenced by myeloid leukemia cells, the immune responses can become dysregulated through two potent mechanisms that rely on co-inhibitory molecules; the adaptive resistance and the T cell exhaustion (Dolen and Esendagli, 2013; Ozkazanc et al., 2016). When exposed to the mediators of anti-tumor immunity, i.e. interferon-γ (IFN-γ), leukemia cells rapidly downregulate costimulatory molecules such as the inducible T-cell co-stimulator ligand (ICOS-LG) and upregulate co-inhibitory molecules, especially the ligands for programmed death-1 receptor (PD-L1 and PD-L2) (Dolen and Esendagli, 2013). The continuous stimuli from costimulatory molecules CD86 and ICOS-LG found on leukemia cells are responsible for inducing the inhibitory receptors, PD-1, cytotoxic T-lymphocyte antigen 4 (CTLA-4), lymphocyte activation gene 3 (LAG3), and T-cell immunoglobulin and mucin-domain-containing protein 3 (TIM-3), the four leading actors of T cells’ dysfunction (Ozkazanc et al., 2016). Of note, under the control of these multiple inhibitory receptors, the effector T cells easily become exhausted and anti-tumor immunity is diminished. Moreover, modulation of costimulatory molecules has been shown to substantially contribute to evasion from NK cell-mediated anti-leukemia immunity. The presence of PD-1 and TIM-3 indicates a fully responsive activated phenotype in NK cells (Guo et al., 2016; Ndhlouvu et al., 2012). However, myeloid leukemia derived PD-L1 and ligation of TIM-3 can significantly impair NK cell responses. Therefore, it may be plausible that myeloid leukemia cells would benefit from cooperation of these inhibitory pathways (Fig. 1).

In this issue of EBioMedicine, Gonçalves Silva et al. show the capacity of a myeloid leukemia cell line to secrete TIM-3 (sTIM-3) and its ligand galectin-9 as a complex through latrophilin 1 (LPHN1)-induced mechanism. Moreover, the TIM-3/galectin-9 complex was able to suppress NK cell cytotoxicity (Goncalves Silva et al., 2017). A similar influence on T cell effector functions can be anticipated as well. Accordingly, TIM-3 not only functions as an inhibitor receptor on effector T cells but also can be directly utilized by the tumor cells to traffic and exocytose its cognate ligand (Goncalves Silva et al., 2017; Dempke et al., 2017). Secreted together with galectin-9, sTIM-3 contributed to diminution of immune responses (Goncalves Silva et al., 2017) (Fig. 1). Alternatively, galectin-9 production by myeloid leukemia cells has been previously shown to act as an autocrine factor that maintains growth/self-renewal of TIM-3+ leukemic blasts (Kikushige et al., 2015). Therefore, this pathway can be implicated both in the immune modulation and the persistence of the disease.

Following the exceptional success of PD-1, PD-L1, and CTLA-4 checkpoint blockade therapies in oncology, a wide range of co-inhibitory molecules including TIM-3, VISTA, and LAG3 has been tested as novel targets (Dempke et al., 2017). Furthermore, the need for additional checkpoint blockade therapeutics emerged following the loss of sensitivity to anti-PD-1 therapy in a lung cancer model wherein TIM-3 was responsible of this therapy resistance (Koyama et al., 2016). TIM-3 collaborates with PD-1 and maintains T cell hypo-responsiveness (Li et al., 2016). Initial reports from several anti-PD-1 clinical phase studies demonstrated the necessity for a combinatory immunotherapy approach since the upregulation of alternative co-inhibitory receptors, e.g. CTLA-4, was evidenced (Albring et al., 2017). Here, the findings of Gonçalves Silva et al. imply the TIM-3/galectin-9 secretary pathway as a potential target in myeloid leukemia. In addition to PD-1 ligands and CD86 expressed on leukemic blasts, the abundance of secreted galectin-9 is

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another indicator of TIM-3-mediated immune evasion in AML patients (Goncalves Silva et al., 2017).

Nonetheless, as observed on THP-1 myeloid leukemia cell line in vitro and in primary AML samples, the relationship between LPHN1 expression and immune modulation in AML, the effect of TIM-3/galectin-9 complex on T cell dysfunction, and ligation of galectin-9 or soluble TIM-3/galectin-9 complexes with TIM-3 represents an allied mechanism to suppress and exhaust anti-leukemia immunity.

Fig. 1. Immune evasion of myeloid leukemia cells through co-inhibitory molecules. Inhibitory ligands expressed by AML cells contribute to impairment of T cells or NK cells. Interaction of PD-1 ligands (PD-Ls) with PD-1, CD86 with CTLA-4 (on effector T cells), and ligation of galectin-9 or soluble TIM-3/galectin-9 complexes with TIM-3 represents an allied mechanism to suppress and exhaust anti-leukemia immunity.

Disclosure

The authors declare no competing interests.

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