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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; Ndhlovu 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 secretory 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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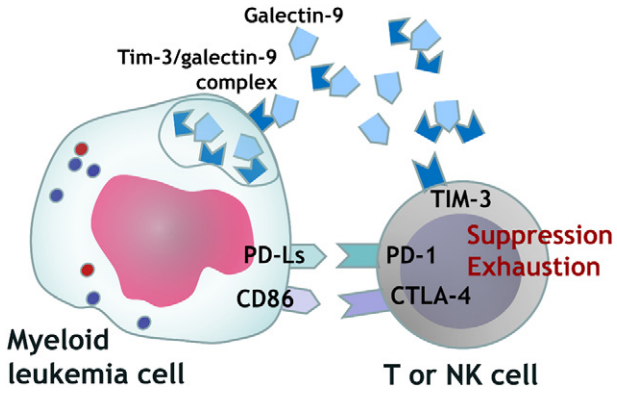

Fig. 1. Immune evasion of myeloid leukemia cells through co-inhibitory molecules. Inhibitory ligands expressed by AML cells contribute to impairment of T cells or NK cells. Interaction of PD-1 ligands (PD-Ls) with PD-1, CD86 with CTLA-4 (on effector T cells), and ligation of galectin-9 or soluble TIM-3/galectin-9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

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 more importantly, identification of other stimuli that induce TIM-3/galectin-9 secretion remain to be addressed in future studies. Critically, the information gathered from the current checkpoint blockade trials in leukemia and especially from an ongoing phase I clinical trial with a combinatory blockade strategy against PD-1 and TIM-3 (NCT03066648) will evidence the importance of "double-hit" for cancer immunotherapy and the redundancy between the co-inhibitory pathways.

Disclosure

The authors declare no competing interests.

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