

Can human leukocyte antigen G be widely accepted as a biomarker in cancer clinical practice?

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Tumor markers have a number of clinical uses such as prediction of cancer, indicating prognosis, monitoring treatment, or following-up on cancer recurrence. Currently, some tumor markers have been sensitive enough to be used as targets of cancer therapy.

Human leukocyte antigen G (HLA-G) is a non-classical HLA class I molecule that was first explored in reproductive immune regulation for fetal implantations [1]. Because HLA-G has immune suppressive functions, it has been assumed that HLA-G could play a role in tumor immune escape mechanisms. Thirty years ago, Paul et al. [2] first reported that HLAG expression was specifically observed in melanoma lesions. Since then, numerous subsequent studies with thousands of samples from more than thirty different types of tumors have demonstrated that HLA-G expression in cancers is highly related to immune suppressive microenvironments, advanced tumor stages, and poor therapeutic responses and prognosis [3]. Accordingly, HLA-G has been recommended to be a novel biomarker for the diagnosis, prognosis, and tumor immune escape of human cancers.

A question remains on why HLA-G has not been applied to clinical practices after almost thirty years of extensive pre-clinical research. When used in cancer diagnosis, HLA-G is always found to have elevated levels in cancer patients while having low levels in healthy individuals. However, HLA-G is less predictable because HLA-G is associated with many types of cancer, and thus, lacks tumor specificity. Moreover, alterations in HLA-G expression are found to be associated with non-neoplastic diseases such as infection and autoimmune diseases. Thus, tests for cancer based on HLA-G are not free of false negatives or false positives.

Once a cancer is diagnosed, expressions of HLA-G in cancer tissues or blood circulations can indicate more advanced cancer stages and worse prognosis for various types of cancer. However, not many pre-clinical trials have been conducted to investigate whether cancer therapeutic regimes were chosen based on HLA-G tests or whether HLA-G tests were used to monitor the progress of treatments and to observe for any cancer recurrence after the treatments.

HLA-G tests should be considered during cancer immune therapy since immune suppressive functions of HLA-G through the HLA-G/ILT signaling pathway favor tumor immune evasion and progression. Some studies have demonstrated that the induction of HLA-G expression during immune therapy may impair the therapeutic effects and that HLA-G expression status can dramatically affect therapeutic responses [4,5].

Interestingly, HLA-G was supposed to be used as an effective target for anti-cancer drug delivery to the HLA-G-positive tumor cells for

killing the residual tumor cells and for inhibiting the recurrence [6]. Recently, the HLA-G/ILTs signaling pathway has been touted as a new checkpoint molecule in addition to other checkpoint molecules such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4)/B7 and programmed cell death protein-1 (PD-1)/PD-L1 [7]. In particular, the HLA-G/ILTs signaling pathway is seen as a promising immunotherapy target by applying HLA-G antagonists or anti-HLA-G or anti-ILT antibodies to block the interaction between ILT receptors and HLA-G [7].

However, all the evidences suggesting that the HLA-G/ILTs signaling pathway is a novel checkpoint were obtained from *in vitro* cell experiments or in *vivo* animal models. As such, clinical trials with internationally recommended standardization protocols, larger cohorts, and prospective studies are still needed in order to confirm and validate HLA-G as a target before routine applications in clinical settings.

Similarly, as described above, more clinical trials are required in the future to determine whether HLA-G tests can be used as biomarkers to monitor cancer therapy or watch for cancer recurrence. As a result, HLA-G tests would need to be first recognized by international clinical oncology organizations and approved by the appropriate authorities before HLA-G can be accepted as a valuable biomarker in any clinical practice.

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Received: July 01, 2019; Accepted: July 15, 2019; Published: July 17, 2019

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