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Novel mechanism of immune evasion involving PD-L1 in various cancers

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In their editorial, skillfully summarizing major recent findings in the relevant field, Chae's *et al.* (1) have made insightful remarks on our article, which demonstrated a unique genetic mechanism for cancer immune evasion through aberrant PD-L1 expression caused by 3'-UTR disruption (2). Initially identified through integrated genetic analysis of adult T-cell leukemia/lymphoma (ATL, 27% of cases) (3), the mechanism was found to operate in a wide variety of common cancer types, including 8% of diffuse large B-cell lymphomas and 2% of stomach adenocarcinomas (2). Resulting from different types of structural variations (SVs), such as deletions, inversions, tandem duplications, and translocations, 3'-UTR disruption invariably induces PD-L1 overexpression in cancer cells, which is known to be relevant to promote immune escape by rendering T cells unresponsive or exhausted (4). The role of SVs involving *PD-L1* 3'-UTR was confirmed by *in vivo* murine experiments using CRISPR/Cas9 genome editing system to disrupt the same untranslated regulatory sequence of the *Pd-l1* gene, which showed that these SVs enhance immune escape of the tumor cells (2).

One of the critical points raised by Chae and colleagues is the direct association between PD-L1 overexpression and oncogenic viral infection (1). Accumulating evidence has suggested that PD-L1 is frequently overexpressed in a variety of cancers associated with oncogenic viruses (5,6). In contrast to most epitopes newly generated by somatic mutations in cancer genomes, which are closely related to endogenous peptides and may or may not induce T cell-mediated immune responses, virtually all viral products are thought to act as potential T cell epitopes causing strong immune reactions. In our study, *PD-L1* 3'-UTR disruption was recurrently observed in virus-driven cancers, such as ATL, cervical and head and neck cancers, as well as diffuse large B-cell lymphoma and stomach adenocarcinoma, which are associated with human T-cell leukemia virus type-1 (HTLV-1), human papillomavirus (HPV), and Epstein-Barr virus (EBV), respectively (2). In some cases with cervical and head and neck cancers, the viral genome was integrated into or in the vicinity of the *PD-L1* locus, causing the aberrant *PD-L1* transcription through gene amplification and/or 3'-UTR truncation. Therefore, in these cases, the viral integration is thought to enable the infected cells to evade not only anti-viral immunity but also anti-tumor immunity at the same time. Despite the limited number of cases, our findings substantiate the relevance of PD-L1 overexpression in virus-related cancers. By contrast, no ATL cases in which HTLV-1 is integrated into the *PD-L1* locus have been thus far identified (3). Given the difference of host-virus interaction and virus-specific features between HPV/EBV and HTLV-1 retrovirus, the mechanism in which oncogenic virus can induce PD-L1 activation might be different, depending on the virus type. Further genetic and biological studies should be warranted to investigate the role of *PD-L1* genomic alterations and their underlying mechanisms in numerous other tumor histologies, especially virus-associated cancers.

Another important implication from our study is that *PD-L1* 3'-UTR disruption could be exploited as a potential genetic biomarker to identify those patients most likely to benefit from immune checkpoint blockade therapy. The surprisingly high efficacy of anti-PD-1 therapy in

Hodgkin lymphoma, in which *PD-L1* and/or *PD-L2* genetic alterations are present in almost all cases, strongly supports this possibility (7-9). To examine the significance of *PD-L1* 3'-UTR disruption as a genetic marker, a phase II clinical trial of anti-PD-1 antibody for relapsed/refractory ATL is ongoing in Japan. These efforts will contribute towards the development of mechanism-driven biomarkers to better guide immune checkpoint blockade in cancer therapy.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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