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Significance of soluble PD-L1 for malignant tumors

Asanuma K*, Nakamura T, Hagi T, Kita K and Sudo A

Department of Orthopedic Surgery, Mie University School of Medicine, Tsu City, Mie, Japan

The tumor immune microenvironment has drawn attention as a therapeutic target. One immune suppressive protein, PD-L1 (B7-H1 or CD274), a 40-kDa transmembrane glycoprotein, is known as a primary ligand of PD-1. PD-L1 expression has been observed in active T cells, B cells, NK cells, DCs, monocytes, macrophages, activated vascular endothelial cells, mesenchymal stem cells, and tumor cells [1]. The interaction of PD-L1 and PD-1 can induce T cell tolerance [2], T cell apoptosis [3], and T cell exhaustion [4]. The enhancement of this immune suppressive protein leads to evasion of the host immune response and tumor aggravation. A relationship between high PD-L1 expression in tumor tissues and poor prognosis in various malignant tumors such as non-small cell lung cancer [5], ovarian cancer [6], renal cell carcinoma [7], melanoma [8], breast cancer [9], and soft tissue sarcoma [10] has been reported. Thus, it is recognized that PD-L1 expression affects tumor behavior and prognosis.

The circulating soluble form of PD-L1 (sPD-L1) in blood has attracted much attention. In addition to poor prognosis related to high PD-L1 expression in tumors, high sPD-L1 is related to poor prognosis in various cancers such as renal cell carcinoma [11], hepatocellular carcinoma [12], lung cancer [13], gastric cancer [14], and B cell lymphoma [15]. The link between elevated sPD-L1 and poor prognosis indicates that sPD-L1 probably has functional activity. However, its roles have not been fully elucidated. Here, we review the sources and functions of sPD-L1.

Speculated sources of sPD-L1:

1. Cleavage and release from membrane PD-L1
2. Spliced variants
3. Release by cytokines, cell stress, cell injury, or cell death

Chen, *et al.* reported that sPD-L1 is released into the culture supernatant and could be decreased by a metalloproteinase (MMP) inhibitor [16]. This means that MMP can release the extracellular domain of membrane PD-L1, leading to sPD-L1. The cleavage site of PD-L1 and the function of cleaved PD-L1 by MMP are still unknown and need further study. Zhou, *et al.* found four splice variants, PD-L1-1, PD-L1-3, PD-L1-9, and PD-L1-12. It is easy to consider that the variants that lack the transmembrane domain (PD-L1-3, PD-L1-9) are released in the culture medium. However, the variant with a transmembrane domain is also secreted and detected in the culture medium (PD-L1-1). These variants are also observed in the plasma of melanoma patients [17]. In addition, cytokines such as interferon gamma, interferon alpha, and TNF-alpha increase the release of these variants into culture medium [17]. At this time, the possible induction of PD-L1 release by cell stress, cell injury, or cell death cannot be excluded.

Functional assessment of sPD-L1

Functional assessment of sPD-L1 is extremely important. Chen [16]. and Takeuchi [18]. Developed a unique ELISA to detect sPD-L1. They used a PD-1-Ig fusion protein to capture sPD-L1, which possesses binding capacity to PD-1, instead of a capture antibody. This ELISA detected 29 out of 75 plasma samples from patients with non-small cell lung cancer, and detected sPD-L1 with much higher sensitivity and frequency than conventional ELISA. This sPD-L1 can probably transduce signals into cells by binding membrane PD-1. PD-L1 glycosylation is also important. As deglycosylation of PD-L1 reduces the absorbance of the ELISA, deglycosylated PD-L1 probably cannot bind PD-1. Glycosylation is therefore a critical factor for their interaction [18]. Additionally, spliced variants have also had their functions assessed. The variants reduce the number of activated $CD4^+$ and $CD8^+$ T cells [17]., and one variant induces apoptosis of $CD4^+$ T cells more than $CD8^+$ [11]. The variants possess inhibitory functions against T-cell activation and proliferation [17].

We believe that high PD-L1 in tissues and sPD-L1 are involved in poor prognosis. However, regardless of PD-L1 expression, clinical data indicate that patients receive benefits from checkpoint inhibitor therapy [19-24]. For that reason, we need to develop predictive biomarkers to establish which patients are most likely to benefit from checkpoint blockade. From what we know, released sPD-L1 (at least except for deglycosylated PD-L1) can affect T cell biological activity, and this means that circulating sPD-L1 has the potential to induce systemic immune suppression. sPD-L1 may be a biomarker for determining the use of checkpoint inhibitors. However, there are many things about sPD-L1 left to be clarified, and these need further study.

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Correspondence to: Kunihiro Asanuma, Mie University, Orthopedic Surgery, 2-174, Edobashi, Tsu City, Mie 514-8507, Japan, E-mail: kasanum@gmail.com

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