

## Potential Roles of HLA-G and MDSCs in Virus Infection

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### Editorial

Myeloid-derived suppressor cells (MDSCs) are a heterogeneous population of granulocytic or monocytic cells that could inhibit both innate and adaptive immune response [1]. Suppressive factors expressed by MDSCs, such as arginase-1, reactive oxygen species, inducible nitric oxide synthase and program death ligand 1, play critical roles in inhibition of T cell, B cell and NK cell mediated immune responses, and in induction of tolerogenic Tregs and regulatory DCs [2]. Other than extensive investigations have been carried out for the suppressive function and clinical significance of MDSCs among cancer patients and animal tumor models, increasing findings have demonstrated its relevance to virus infection [3].

As a subset of myeloid progenitors and immature myeloid cells, previous studies revealed that MDSCs could be generated in the presence of various cytokines and growth factors, including G-CSF, GM-CSF, PGE<sub>2</sub>, VEGF, IL-6, IL-1 $\beta$  and TNF- $\alpha$  [4]. To be noted, through binding to the murine receptor paired immunoglobulin like receptor-B (PIR-B) expressed on MDSCs, human leukocyte antigen-G (HLA-G) has been found with the capability to contribute the expansion and suppressive functions of MDSCs [5].

HLA-G is a member of the non-classical HLA class I antigen which generates four membrane-bound (HLA-G1, -G4) and three soluble isoforms (HLA-G5, -G7) [6]. In the context of virus infection, significance of HLA-G expression was addressed in amounts of previous studies, where HLA-G was markedly increased during various virus infection such as human immunodeficiency virus (HIV) [7], Human papillomavirus (HPV) [8], human cytomegalovirus virus (HCMV) [9], influenza A virus [10], hepatitis B and C virus [11,12], herpes simplex virus and rabies virus [13], etc. Among these infectious diseases, increased HLA-G expression was observed to be associated with virus replication and/or disease progression.

HLA-G exerts important tolerogenic functions through interaction with its receptors expressed on a various immune cells which includes immunoglobulin-like transcript-2 (ILT-2)/CD85j, ILT-4/CD85d, and killer immunoglobulin-like receptor (KIR) 2DL4/CD158d [14]. The murine receptor PIR-B, expressed by murine myeloid and lymphoid lineage cells, shares sequence homology with the human ILTs and can bind to HLA-G. In this scenario, previous findings had recognized that HLA-G and PIR-B signal pathway could impair DC maturation and function, inhibit NK and T cell cytotoxicity and prolong allogeneic graft survival [15-17].

PIR-B was addressed to play a critical role in regulation of the suppressive function and fate of myeloid derived suppressor cells [18]. Recent studies showed that interaction between HLA-G and PIR-B could expand the population of CD11b<sup>+</sup>Gr1<sup>+</sup>PIR-B<sup>+</sup> MDSCs in an immunocompetent HLA-G1<sup>+</sup> M8 (a human melanoma cell line) tumor-bearing mouse model, which could decrease NK cytotoxic activity [5]. In another study, in a mouse model with murine mammary 4T1 cell line, HLA-G5 was observed to favor the CD11b<sup>+</sup>Ly6G<sup>+</sup> mice G-MDSC expansion with binding to PIR-B [19]. Moreover, in ILT-2 transgenic mice, HLA-G has been found to induce the emergence of CD11b<sup>+</sup>Gr1<sup>+</sup> MDSCs with an enhanced suppressive activity and

directly involved in the prolongation of allogeneic skin graft survival [20].

Given the fact that both HLA-G expression and MDSCs expansion was commonly observed and strongly associated with the progression of infectious diseases, we speculate that the cross-talk between HLA-G and its receptors expressed on MDSCs, and that its consequent biological functions could have clinical significance during infection; however, more studies are necessary to be carried out to make it clear.

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