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LETTERS AND COMMENTS

Tumor-derived HLA-G1 acquisition by monocytes through trogocytosis: possible functional consequences

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We read the article recently published in the April 2010 issue by HoWangYin et al. [1] with an interest in understanding the functional consequences of tumor-derived HLA-G1 on monocytes. The authors demonstrated that HLA-G1 in tumors is rapidly acquired by monocytes through trogocytosis as acquired by antigen-presenting cells (APC), NK cells and T cells. Surprisingly, although trogocytosis is commonly observed in activated immune cells, the authors demonstrated this phenomenon in both resting and activated monocytes. Furthermore, they showed that HLA-G1 acquisition is transient and quickly disappears in LPS-activated monocytes, but found no evidence of the functional roles of these molecules.

Intercellular communication through the transfer of cell-surface membrane proteins is a widespread phenomenon in multicellular organisms. It can occur through various mechanisms (reviewed in references [2, 3]), including removal of part of the membrane of the target cell by strong ligand-receptor affinity, enzymatic cleavage and transfer of the cell-surface protein ectodomains, transfer in the form of exosomes and membrane nanotubules, and transfer after formation of membrane bridges, such as T cell receptor-mediated acquisition of APC's antigen-presenting machineries by T lymphocytes following immunological synapse formation via the internalization and recycling pathway [4]. The latter mechanism, popularly known as 'trogocytosis', is most commonly observed in various immune cells and their target cells. In the immune system, the functional consequences of trogocytosis vary with the type of antigens involved, differences in the nature of the immune cells, and the microenvironment in which the immune interaction occurs, which in turn direct the developmental path of the different immune cell subsets with distinct functions [5–7]. In addition to producing various tolerance-inducing factors such as IL-10 and TGF-β, and downregulating MHC-class I molecules, it is increasingly evident that tumors transfer cell-surface, membrane-immunoregulatory proteins, such as HLA-G1, to immune cells through secretion of exosomes, and/or trogocytosis, facilitating the escape of tumors from immunosurveillance mechanisms.

HLA-G1 is a nonclassical HLA class I molecule, expressed pathologically in various cancers, and infectious and autoimmune diseases [7]. Its expression endows tumor cells with a multitude of functions (reviewed in references [2, 3, 8, 9]), including inhibition of proliferative, cytokine secreting and cytolytic properties of innate (NK cells) and adaptive immune cells [$CD8^+$ cytotoxic T cells and $CD4^+$ Th cells], induction of regulatory cells and drug resistance, and inhibition of dendritic cell (DC) maturation. As APCs form bridge between innate and adaptive immune responses, tolerization of APCs could profoundly affect both innate and adaptive antitumor responses. It has been shown that tumor-infiltrating, splenic, bone marrow-derived and circulating APCs from cancer patients express HLA-G1 and exhibit

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potent immunosuppressive properties although mechanism by which they acquire HLA-G1 have not been fully established [10, 11]. Such tolerized APCs, in particular monocytes, have been shown to inhibit both innate responses such as inhibiting proliferation and production of IFN-γ by activated NK cells [11] and adaptive responses such as T-cell response to alloantigens [10], enabling the ability of tumors to escape immunosurveillance mechanisms.

Given the regulatory roles of tumor-expressed HLA-G1 in immune tolerance [7, 9], this study, which showed monocytic acquisition of HLA-G1 from both ectodermal (melanoma) and mesodermal (lymphoblastoid) tumors, could provide another explanation as to why tumors induce tolerance. HoWangYin et al. [1] used LPS-activated monocytes in the assessment of the functionality of acquired HLA-G1. As LPS is known to induce differentiation of resting human monocytes into mature DCs through TLR-4 signaling [12], we suggest that LPS treatment of monocytes might have partly inhibited the regulatory role of HLA-G1 in peripheral blood mononuclear cell (PBMC) proliferation and even caused the downregulation of acquired HLA-G1 in an attempt to enhance immunity. It is interesting to note that, through trogocytosis, even resting monocytes acquired HLA-G1 from tumors although the functionality of these cells was not tested in this study. Because resting monocytes express ILT2 receptors for HLA-G1 ligands [1], the interaction among monocytes with acquired HLA-G1 might lead to immune tolerance, inhibiting their tumor antigen-presenting ability [13].

As monocytes act as circulating sentinels against tumors and infectious agents, future studies focusing on the functional consequences of HLA-G1 on resting monocytes, the effect of LPS on HLA-G1-induced tolerance, and phenotypic changes in the monocytes with acquired HLA-G1 could lead to a greater understanding of immunoregulatory roles played by tumors and pathogens. Furthermore, the study involving antigen-specific interactions among target cells, monocytes and T lymphocytes, rather than relying on nonspecifically-stimulated PBMC, would help us understand the regulatory roles of HLA-G1 on monocytes in various infectious and autoimmune disorders, which often provide proinflammatory signals for resting monocytes to undergo differentiation and maturation of DCs.

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