HLA-G: A Versatile Biomarker

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Abstract

HLA-G is a non-classical MHC Class I molecule that is usually restricted to cytotrophoblasts and other fetal cells in order to protect the fetus from maternal immune responses. However, HLA-G is expressed during viral infections and cancer. The presence of soluble HLA-G, sHLA-G, in serum is noted in various instances of human diseases. Serum HLA-G can serve as a biomarker, which makes it a unique tool in developing confirmatory diagnostics for infectious diseases and cancer. An accurate and early diagnosis of deadly diseases is really important for an early intervention or treatment. The immunosuppressive capabilities of HLA-G make it not only a biomarker for diagnosis but also an excellent target for developing therapeutics. Here, I discuss HLA-G's potential to be an invaluable tool as a biomarker for diagnostics and a target for therapeutics.

HLA-G

Major histocompatibility class I or MHC class I can be divided into two categories: classical and non-classical MHC class I. The classical MHC class I consists of HLA-A, -B, and -C proteins, while HLA-E and HLA-G are considered non-classical MHC class I proteins. HLA-A, -B, and -C present foreign antigen to CD8+ T-cells and result in subsequent cytotoxicity of infected cells. Thus, the classical HLA-A, -B, and -C are mostly involved in immune responsive pathways; however, HLA-G in contrast is an immunosuppressive protein. HLA-G exists in 7 isoforms (HLA-G1- HLA-G7) as a result of alternative splicing [1]. Of these 7 isoforms, membrane bound HLA-G1 and soluble HLA-G5 is well studied and implicated in immune suppression.

HLA-G induces tolerogenic properties in immune cells of both innate and adaptive immune systems. HLA-G binds to the inhibitory receptors such as ILT-2, ILT-4, KIR2DL4 present on the surface of APCs, NK cells, T-cells and B-cells [2]. ILT2 and ILT4 bind preferentially to HLA-G molecules compared to the classical MHC class I molecules [3]. ILT2 inhibitory receptors are expressed on APCs, NK cells, T- and B- cells, whereas ILT4 was found to be expressed mostly on myeloid APCs. It has also been shown that HLA-G binding to ILT4 of myeloid APCs results in inhibition of APC maturation and converting these cells to regulatory tolerogenic cells incapable to activating T-cells [4,5].

HLA-G exhibits a unique characteristic of incorporating itself into another cell such as NK cell [6] and T-cell [7]. This process is called trogocytosis, where membrane proteins or membrane patches from one cell incorporate themselves to another upon contact. Trogocytosis of HLA-G to NK or T-cell results in inhibition of their activation [8]. The expression of HLA-G results in long term immune suppression via many different ways, thus making HLA-G a very unique MHC class I protein capable of causing not only a localized, but also a global immune suppression when expressed.

sHLA-G is not only detected in pregnant women but also detected during infectious diseases such as hCMV [9], hepatitis [10,11], and HIV [12] infections. HLA-G was reported to be expressed on cells infected with rabies virus [13,14], influenza virus [15], and herpes B virus [16]. In our lab, we have shown that herpes B virus infected human cells induce increased surface expression of HLA-G but HSV-1 infected cells do not show similar HLA-G expression [16]. Preliminary results from our lab also suggested that individuals that are positive for herpes B virus infection but not HSV expressed sHLA-G in their serum (unpublished data). Collectively, these data indicate that serum HLA-G can be an important biomarker in differentiating between HSV-1 and herpes B virus infections in humans. Although HLA-G can be induced during other infectious diseases, it serves as a biomarker for developing confirmatory diagnostics.

Confirmatory diagnosis is especially important in case of early detection of cancer for an appropriate and effective treatment. Expression of sHLA-G was reported in patients with ovarian cancer [17], cervical cancer due to human papilloma virus [18], melanoma [19], and gastric cancer [20] etc. Detailed studies on the expression of HLA-G in relation to the stage of cancer progression can help in developing diagnostic tools for early cancer detection and cancer staging. Early detection of cancer is an invaluable tool in preventing cancer metastasis.

Because of the immunosuppressive nature of HLA-G, the expression of HLA-G can be altered to prevent immune suppression and promote robust immune responses to fight many human diseases making it a potential target for

developing therapeutics. Due to immunosuppressive capability of HLA-G, it can also be induced to suppress an unusually active immune system such as in the case multiple sclerosis, an autoimmune disease. Thus, HLA-G functions as an extremely versatile protein in developing accurate diagnostics and effective therapeutics.

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