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# HLA-G: a look back, a look forward

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HLA-G is best known as a nonclassical HLA Class I molecule of low polymorphism with an expression restricted to fetal tissues at the maternal-fetal interface. This is true, but there is so much more…

The first function to be characterized for HLA-G was that of the inhibition of decidual (maternal) NK cell cytolysis by HLA-G-expressing fetal cytotrophoblast cells [1]. These findings were the basis for a substantial proportion of the HLA-G research because they proved that the expression of HLA-G by a cell, in this case a trophoblast cell, protected it from destruction by killers of the immune system, in this case NK cells. Further studies showed that HLA-G played a crucial role in the tolerance of the fetus by its mother, i.e., in the maternal-fetal tolerance, which is the only example of physiological tolerance to semi-allogeneic tissues. From this point, HLA-G was named "tolerogenic," and a precise characterization of HLA-G, its tolerogenic properties, and its clinical uses was sought.

The review by Rizzo et al. summarizes the key findings concerning HLA-G and pregnancy and particularly focuses on (1) HLA-G expression throughout embryo development, starting from the embryonic stem cells, (2) the structural diversity of HLA-G and the methods used to detect its structures, and (3) the clinical uses that can be or are already made of HLA-G detection in the context of pregnancy.

Rejection is a strong immune defense-like mechanism that involves multiple cell subsets, including NK cells, T cells, B cells, and antigen-presenting cells. Therefore, to counter rejection, tolerance mechanisms have to be at least as complex as and must target all rejection mechanisms and effectors. Studies have revealed that HLA-G inhibitory functions are broad and target multiple immune cell subsets, acting directly or indirectly on effector cell subsets.

Indeed, it has been shown that HLA-G inhibits the cytolytic functions of NK cells [1], the antigen-specific cytolytic functions of $CD8^+$ T cells [2], the allo-proliferative responses of $CD4^+$ T cells [3], and the differentiation of dendritic cells [4]. Furthermore, HLA-G is capable of stopping the ongoing proliferation of T cell and NK cells [5, 6].These results proved that HLA-G is capable of directly acting on all actors of an immune response such as a graft rejection or an anti-tumoral response. Recent results showed that in addition to a direct inhibition of cell function, HLA-G had less direct, but possibly deeper functions through the generation of suppressor/regulatory cells [7]. These results imply that HLA-G may participate in the general re-shaping of the immune system to ignore specific antigens, a mechanism also called specific tolerance.

The immunological functions and the mechanisms of action of HLA-G, including a particular focus on HLA-G-related regulatory cells, are detailed in the review by Carosella et al. Nonimmunological functions have also been reported for HLA-G, and this review also focuses on its role in hematopoiesis.

HLA molecules are highly polymorphic, and it is well known that associations exist between particular alleles and disease. Studies on HLA-G polymorphism were amongst the first to be performed after the gene was discovered [8]

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and continue to this day. In the review by Donadi et al., the extensive work that has been done on topics related to HLA-G polymorphism is reviewed. This exhaustive article particularly focuses on (1) a precise description of HLA-G polymorphism within the coding and the noncoding regions, (2) how the polymorphisms impact the regulation of the gene, (3) evolutionary aspects of HLA-G, and (4) polymorphism–disease associations.

HLA-G was first characterized at the fetal-maternal interface, where its endogenous expression is readily observable, and in the context of the fetal-maternal tolerance, where its role as natural tolerogenic molecule is most easily perceived. However, expression studies have demonstrated that HLA-G expression is not terminally restricted to a few fetal and adult tissues but may be re-activated in pathological contexts. Furthermore, investigations on the immunological functions of HLA-G have proven beyond doubt that this molecule can act on adult, peripheral immune effectors. Hence, it was found that HLA-G plays a critical role not only in the context of pregnancy, but also in other conditions that involve similar immune function inhibitions, such as cancer [9], transplantation [10], auto-immune diseases [11], and viral pathologies [12].

Allogeneic transplantation is the clinical situation that resembles pregnancy the most, and this includes the use of the properties of HLA-G as tolerogenic strategy. Indeed, it was first shown in the context of heart transplantation that HLA-G could be expressed by cardiomyocytes and that this expression was associated with a reduced number of acute rejection episodes and an absence of chronic rejection [10]. Since then, the involvement of HLA-G in allogeneic transplantation has been studied in more than 1,000 patients. In the review by Deschaseaux et al., the main characteristics of HLA-G expression in transplantation are detailed. This review more specifically focuses on the factors that influence HLA-G expression in this context, the mechanisms of action of HLA-G in the allogeneic response, and the use of HLA-G as a potential tool for transplantation.

The maternal-fetal interface is a special, immune-privileged environment that abides by its own immunologic rules. The central nervous system (CNS) is also considered an immune-privileged organ that maintains an adaptable immune surveillance and possesses its own set of immune effectors. Yet, as in the periphery, dysregulated immune responses within the CNS system contribute to tumour growth, inflammation, and auto-immunity. In their review, Huang et al. recapitulate the key findings that show the involvement of HLA-G in the CNS under physiological and pathological conditions, focusing particularly on multiple sclerosis. Looking at the immune homeostasis of the CNS, the authors highlight how, by tilting the immune balance of the CNS, HLA-G may constitute a double-edged sword with respect to pathology and therapeutic strategies.

The fetal tissue that expresses HLA-G the most is the extravillous cytotrophoblast (EVT), which invades the maternal decidua. This tissue shares features with tumors, such as its behavior as an invading tissue, its capacity to resist immune destruction, and its expression of oncogenic factors [13]. For these reasons, the expression of HLA-G in the context of cancers, and its contribution to the immune escape of tumors was investigated as early as 1998 [9]. Despite early controversies, it is now well accepted that HLA-G may be neoexpressed by tumors and that it constitutes one of their immune escape strategies. In their article, Amiot et al. review the wealth of evidence that concerns HLA-G expression in cancers of distinct histology and focus on the mechanisms of HLA-G neoexpression, its association with the clinical course of diseases, and its possible uses as a diagnosis tool.

Maternal-fetal tolerance, tolerance to allogeneic transplants, cancer, auto-immune diseases: these are contexts that have been extensively investigated in association with HLA-G. There are other contexts, however, that are less prominent, either because they are new, or because they have just generated fewer reports in association with HLA-G. Nevertheless, some of these reports suggest future trends in HLA-G research. In their review, Fainardi et al. set their sights on certain exciting emerging topics that yield new perspectives for HLA-G, above all the role of HLA-G in inflammation. The involvement of HLA-G in inflammatory diseases was noted in 2001 in the contexts of psoriasis [14] and atopic dermatitis [15]. Since then, HLA-G has been repeatedly associated with inflammatory pathologies, including multiple sclerosis in 2003 [16], Crohn's disease in 2004 [17], asthma in 2005 [18], rheumatoid arthritis and celiac disease in 2006 [19, 20]…through to spontaneous intracerebral hemorrhage in 2010 [21]. Yet, the possible role of HLA-G in inflammation as an immune process is seldom remembered. In their article, Fainardi et al. review the body of evidence on this topic and make the case for basic studies on the role of HLA-G in the general mechanisms of inflammation.

In a similar fashion, the expression of HLA-G following virus infection has been shown repeatedly, including for HCMV in 2000 [12], HIV in 2002 [22], RABV and HSV in 2005 [23]…through to IAV in 2010 [24]. The data accumulated on the capability of viruses to re-activate HLA-G expression and use it as an immune escape strategy are now compelling. Yet, basic studies on the mechanism by which viruses are able to regulate HLA-G expression are lacking, and so are the downstream possible uses of such knowledge. In their review, Fainardi et al. promote the notion that the critical mass of data concerning HLA-G and virus

infections has now been attained, laying the groundwork for more fundamental studies to take place.

The relation between HLA-G and cytokines/chemokines was first documented in 1996 when it was shown that IFN-$\gamma$ upregulated HLA-G expression in monocytic cell lines [25]. Since then, as reviewed by Fainardi et al., the HLA-G vs. cytokines relationship has been studied both ways: in terms of the capability of cytokines to modulate HLA-G and the role of HLA-G in modulating cytokine expression profiles. These studies mainly concerned pro- vs. anti-inflammatory cytokines and their role in effector function modulation. Recently a third way has emerged with the demonstration that HLA-G modulates chemokine receptor expression [26]. This discovery, combined with the knowledge previously accumulated, makes the case for a role of HLA-G in the modulation of chemotaxis and immune cell trafficking.

The expression of HLA-G by preimplantation embryos was reported in 1996 [27], and this is now the focus of intense clinical research, as reviewed earlier by Rizzo et al. Yet HLA-G expression by embryonic stem cell is still inconclusive. On the other hand, it was recently shown that HLA-G is expressed by mesenchymal stem cells (MSC) and that it significantly contributed to their immunosuppressive properties [28], introducing HLA-G at the heart of the field of regenerative medicine. In their review, Fainardi et al. summarize the current knowledge on HLA-G and stem cells and argue the importance of HLA-G in regenerative medicine.

HLA-G research started at the maternal-fetal interface, and this context is still heavily investigated. From there, branching ideas and investigations placed the notions and hypotheses that had been developed in the context of the maternal-fetal tolerance in other physiopathological contexts, and we are now at the point where diagnosis and therapy are within reach. It seems fair to say that great work has been done. Still, the topic of HLA-G is far from being fully exhausted. In particular, the understanding of HLA-G regulation remains unclear, as do the precise mechanisms of HLA-G-mediated tolerance. But also, new fields open with the demonstration that HLA-G has non-immunological functions or that HLA-G may regulate cell trafficking; the elucidation of these will, no doubt, constitute our next challenges.

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