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Review

$CD4^+HLA\text{-}G^+$ regulatory T cells: Molecular signature and pathophysiological relevance

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ABSTRACT

The regulation of potentially harmful immune responses by regulatory T (T_{reg}) cells is essential for maintaining peripheral immune tolerance and homeostasis. Especially $CD4^+$ T_{reg} cells have been regarded as pivotal regulators of autoreactive and inflammatory responses as well as inducers of immune tolerance by using a variety of immune suppressive mechanisms.

Besides the well-known classical $CD4^+CD25^+FoxP3^+$ T_{reg} cells, $CD4^+$ T cells expressing the immune tolerizing molecule human leukocyte antigen G (HLA-G) have been recently described as another potent thymus-derived T_{reg} (tT_{reg}) cell subset. Albeit both tT_{reg} subsets share common molecular characteristics, the mechanisms of their immunosuppressive function differ fundamentally. Dysfunction and numerical abnormalities of classical $CD4^+$ tT_{reg} cells have been implicated in the pathogenesis of several immune-mediated diseases such as multiple sclerosis (MS). Clearly, a deeper understanding of the various $CD4^+$ tT_{reg} subsets and also the underlying mechanisms of impaired immune tolerance in these disorders are essential for the development of potential therapeutic strategies.

This review focuses on the current knowledge on defining features and functioning of $HLA\text{-}G^+CD4^+$ tT_{reg} cells as well as their emerging role in various pathologies with special emphasis on the pathogenesis of MS. Furthermore, future research possibilities together with potential therapeutic applications are discussed.

Contents

Abbreviations: cAMP, cyclic adenosine monophosphate; CCR5, chemokine (C–C motif) receptor 5; CNS, central nervous system; FoxP3, forkhead box protein P3; GvHD, graft-versus-host disease; MS, multiple sclerosis; TCR, T-cell receptor; T_{eff}, effector T cells; tT_{reg}, thymus-derived regulatory T cells.

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1. Introduction

The immune system comprises a highly-regulated network of cellular and humoral components. Its physiologic function is dependent on the balance between an optimal protection against a broad spectrum of foreign pathogens and tolerance towards self- and innocuous antigens.

Central tolerance is established while T-cell maturation and selection in the thymus by clonal deletion of developing lymphocytes recognizing self-antigens [1]. However, under certain conditions even in state of health, a part of autoreactive T cells can escape clonal deletion and enter the periphery with potential to cause autoimmune disorders and uncontrolled chronic inflammation [2]. Additional mechanisms of peripheral tolerance within the immune system exist to ensure protective immunity in the absence of immune pathology. Here, $CD4^+$ regulatory T (T_{reg}) cells are critical players in immune regulation due to their ability to control and limit potentially inappropriate immune responses.

Over the past two decades, diverse subpopulations of $CD4^+$ T_{reg} cells have been described and analyzed. They are either induced in the periphery (e.g. T regulatory type 1 (T_r1) and T-helper 3 (T_h3) cells) or are naturally occurring originating from the thymus. Up to now, $CD4^+CD25^+$ forkhead box protein P3 (FoxP3) expressing T_{reg} cells represent the most prominent subtype of thymus-derived T_{reg} (tT_{reg}) cells which were initially described by Sakaguchi and coworkers in 2001 [3]. Since 2007 $CD4^+$ T cells expressing the immune tolerizing molecule human leukocyte antigen G (HLA-G) have been demonstrated as another distinct, immune suppressive tT_{reg} cell subset [4–7]. The growing knowledge on their defining features and mechanisms of action over the past decade recognizes the importance of $CD4^+HLA\text{-}G^+$ tT_{reg} cells in peripheral immune regulation and in parenchymal immune homeostasis with important implications for various (neuro)inflammatory disorders such as multiple sclerosis (MS). Therefore, this review focuses on the role of $CD4^+HLA\text{-}G^+$ tT_{reg} cells in adaptive immune responses and provides a comparison of their cellular and molecular characteristics to classical $CD4^+CD25^+FoxP3^+$ tT_{reg} cells. The most recent insights from experimental (animal) models and human studies are summarized. Moreover, an outlook on future research opportunities and clinical applications is given.

2. $HLA\text{-}G^+CD4^+$ tT_{reg} cells: a subset of HLA-G expressing T cells

The expression of HLA-G, a nonclassical major histocompatibility complex (MHC) class Ib molecule, was originally described on fetal trophoblast cells during pregnancy [8]. In adults, different tissues including thymic epithelium [9], cornea [10], pancreatic islets [11] and skeletal muscles [12] have been shown to express HLA-G in membrane-bound and/or soluble manner under physiologic conditions. In addition to this restricted tissue distribution, HLA-G proteins were also detected on different immune cell subsets such as macrophages [13], monocytes [14–16] and dendritic cells [17] in the peripheral blood of healthy adults. Recently direct regulatory properties have been shown for HLA-G expressing monocytes [18]. Besides these reports on myeloid cells, in 2007, our group discovered HLA-G expressing T cells with regulatory capacity in the peripheral blood of healthy individuals [4].

2.1. HLA-G: an immune tolerizing molecule

The nonclassical MHC class Ib molecule HLA-G occurs in seven isoforms as a result of alternative splicing yielding membrane-bound (HLA-G1 to -G4) and soluble isoforms (HLA-G5 to -G7) [19]. Notably, due to metalloproteinase-dependent proteolytic cleavage, membrane-bound isoform HLA-G1 can be released as soluble molecule called shed HLA-G1 [20]. HLA-G molecules are immune tolerogenic by themselves and can mediate their functions by interacting with CD8 [21] and CD160 [22] as well as with the inhibitory receptors immunoglobulin(Ig)-like transcript (ILT)-2, ILT-4 and killer Ig-like (KIR)2DL4 [23,24]. These receptors/molecules except ILT-4 are widely expressed on lymphoid immune cells such as T cells and natural killer (NK) cells, while expression of CD8, ILT-2 and -4 have also been described for immune cells of the myeloid lineage such as macrophages and monocytes [25,26]. Monomeric HLA-G molecules can spontaneously arise in dimeric form considered as the more biologically active form of HLA-G [27].

Most of the immunosuppressive functions described for HLA-G are related to the membrane-bound/shed HLA-G1 and its soluble counterpart HLA-G5 [27]. HLA-G derived from myeloid cells has been shown to inhibit the activation/proliferation of autologous $CD4^+$ T lymphocytes [16,28] and to induce the differentiation of immunosuppressive $CD4^+$ T cells such as interleukin (IL)-10 producing T_r1 cells [17,28]. HLA-G expressing monocytes [18] and $CD4^+$ tT_{reg} cells [4,6] demonstrated effective suppression of T-cell proliferation.

2.2. Phenotype

$HLA\text{-}G^+$ tT_{reg} cells have been detected within the single positive cell compartment of the human thymus implying a thymus-derived origin as demonstrated for classical $CD4^+CD25^+FoxP3^+$ tT_{reg} cells [3,29] (see Fig. 1).

In the peripheral blood, 0.1–8.3% of $CD4^+$ T lymphocytes express HLA-G1 on their cell surface [4], while about 5–10% of $CD4^+$ T cells co-express CD25 and FoxP3 identifying classical $CD4^+$ tT_{reg} [29,30]. Besides the constitutive expression of membrane-bound HLA-G1, $CD4^+HLA\text{-}G^+$ tT_{reg} cells are characterized by secretion of soluble HLA-G5 and the lack of FoxP3 and CD25 expression [4]. Thus, $CD4^+HLA\text{-}G^+$ tT_{reg} cells can be clearly distinguished from classical $CD4^+CD25^+FoxP3^+$ tT_{reg} cells based on their unique immunological phenotype (see Table 1).

Naïve, central memory and effector memory $CD4^+$ T cells can be distinguished by their unique immunological phenotypes (effector molecule, chemokine receptor, adhesion molecule expression, proliferative potential, cytokine production etc.). In addition it was recently shown that also characteristic membrane potentials can be attributed to the different $CD4^+$ T-cell subsets [31,32]. Of note, our group was able to identify a specific, hyperpolarized membrane potential for both $CD4^+HLA\text{-}G^+$ (-71.0 ± 3.0 mV) and $CD4^+CD25^+FoxP3^+$ tT_{reg} cells (-70.2 ± 3.2 mV) compared to non-regulatory T-cell control (-46.6 ± 1.4 mV) [7] arguing for comparable molecular signatures and functional pathways (see Table 1).

2.3. Mechanism of action

In vitro suppression assays revealed that $CD4^+HLA\text{-}G^+$ tT_{reg} cells inhibit T-cell responses mainly by cell–cell contact independent