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(REVIEW ARTICLE)

Monocytic HLA-DR expression in type 2 diabetes mellitus: Impact on disease susceptibility

Dyahati Wahyurini [1,*] and Heri Wibowo [2]

[1] *Master Programme in Biomedical Sciences, Faculty of Medicine, Universitas Indonesia, Jakarta, 10440, Indonesia.*
[2] *Department of Parasitology, Faculty of Medicine, Universitas Indonesia, Jakarta, 10440, Indonesia.*

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Abstract

Monocytes are innate immune cells that act as antigen-presenting cells. HLA-DR is a cell surface protein that plays a crucial role in the immune system by presenting antigens to CD4 T Cells (T helper). Based on surface expression, monocytes can differentiate into three subsets; classical monocytes ($CD14^+CD16^-$), intermediates monocytes ($CD14^+$ $CD16^+$), and non-classical monocytes ($CD14^{dim}$ $CD16^+$). Among these subsets, classical monocytes have the lowest, and intermediate monocytes have the highest expression of HLA-DR. Monocytes are very sensitive to environmental changes, like hyperglycemia in Type 2 Diabetes Mellitus (T2DM). Metabolic changes in T2DM conditions trigger changes in immune cells including monocytes. Chronic low-grade inflammation in T2DM decreased HLA-DR expression in all monocyte subsets. Monocytes that do not express or lose HLA-DR expression are known as $CD14^+HLA\text{-}DR^{-/low}$ monocyte and is immunosuppressive. This increase in monocytes in T2DM conditions is related to the ability of monocytes as antigen-presenting cells. Decreased HLA-DR expression increased the risk of severity and susceptibility to several diseases such as COVID-19 infection, TB, cancer, or sepsis. The alterations in HLA-DR expression are one of the factors that make T2DM a comorbid disease. This literature review aims to explore monocytic HLA-DR in T2DM conditions hence increasing the risk of severity and susceptibility to disease. This literature is expected to be the basis for research on the potential of HLA-DR as a prevention or treatment for T2DM patients.

Keywords: HLA-DR; Monocyte; Type 2 Diabetes Mellitus; Susceptibility

1. Introduction

The major histocompatibility complex (MHC) plays a pivotal role in the immune system by presenting antigens. This gene expresses many polymorphisms and has a specific function. MHC is classified into MHC class I and II which encode surface glycoproteins resulting from intracellular or extracellular peptide binding [1]. The polypeptide chain of the MHC class I molecule is composed of a heavy chain (α) and a small protein called β2-microglobulin whereas MHC class II consists of α and β chains. The binding site for T cells on the MHC class I is CD8 bound to α3 domain and the MHC class II domain is CD4 bound to the pocket formed from α2 and β2 [2]. MHC class I produces 8-11 residues while MHC class 2 produces 10-30 residues or more. Differences in the structure and characteristics of both MHC contribute to their functions and antigen presentation capabilities. MHC class I present intracellular antigens to CD^{8+} T Cells or cytotoxic T cells (CTL), while MHC class II molecules present extracellular antigens to CD^{4+} T Cells or helper T cells (Th). These interactions are critical for humoral adaptive or cell-mediated immune response [3].

The short arm of chromosome 6 is where the MHC can be found in humans [2]. MHC class I nomenclature is HLA-A, HLA-B, and HLA-C. Then, HLA-DP, HLA-DR, and HLA-DQ are the names given to MHC class II [3]. Previous studies state that HLA is involved in several conditions such as inflammation, infection, autoimmune, transplantation, cancer, and

* Corresponding author: Dyahati Wahyurini

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others [1]. In the immune system, HLA plays a role in presenting antigens. It is expressed on antigen-presenting cells (APCs) such as monocytes, macrophages, dendritic, and B cells. Therefore, HLA can be a marker of the antigen presentation capabilities of each APC [2].

Monocytes are mononuclear phagocytic cells that are easily affected by environmental changes, such as hyperglycemia, hypercholesterolemia, and obesity [4]. Hyperglycemia can be found in Type 2 Diabetes Mellitus (T2DM). T2DM is followed by dysregulation and dysfunction of immune cells, including monocytes, and affects metabolic changes. This condition occurs chronically and becomes a chronic low-grade inflammation or metaflammation in T2DM patients [5][6]. The changing expression of HLA-DR affects the activation of T and B lymphocytes. Decreased activity of adaptive immune cell play a role in increasing the risk of infection, risk of susceptibility, and comorbid disease such as coronary heart disease, cancer [2][7], Lung infections such as tuberculosis, pneumonia[8], influenza and including COVID-19 infection [4][9][10].

Therefore, changes in HLA-DR expression are expected to have a role in the susceptibility of type 2 DM to infectious diseases and manifest in an increase in the frequency, duration, or severity of an infection. The purpose of this literature review is to discuss the role of HLA-DR in T2DM conditions so that it can increase susceptibility to an infectious disease. Knowing the role and changes in HLA-DR expression in T2DM conditions can be used as a basis for research on the potential of HLA-DR as a prevention or treatment in T2DM patients. This review will explain the role of HLA-DR in T2DM conditions against infection susceptibility [1].

2. Methodology

This review is a narrative literature review. The method used is to find and discuss several references using search engines and databases from PubMed, ScienceDirect, Scopus, and Google Scholar. The search strategy included keywords: HLA-DR, monocyte, Type 2 Diabetes Mellitus, and susceptibility. References are relevant studies published within the past ten years and limited to journals published in English or Indonesian language. The total reference is 34 references (including textbooks and journals).

3. Results and discussion

3.1. HLA-DR Expression in Monocyte

The immune system is a complex interconnected system of molecules, cells, and tissues that work together in the body's defense against antigenic threats. The immune system consists of two main systems; innate and adaptive immune system. The innate immune system serves as the body's first line of defense mechanism that is less specific than the adaptive immune response [2]. The innate immune system includes various types of cells such as monocytes, macrophages, dendritic, neutrophil, NK, and mast cells. Monocytes are innate immune cells whose role is to defend the body from pathogens, and phagocytosis, helping the process of efficient inflammatory resolution, recognition of antigens against adaptive immune cells, formation of memory cells, and formation of antibodies [11][12].

Based on their surface receptor expression, circulating monocytes are divided into three subtests. They are classical monocytes ($CD14^+$ $CD16^-$), non-classic ($CD14^{dim}$, $CD16^+$), and intermediates ($CD14^+$ $CD16^+$)[13][14][15]. Classical monocytes play a role in the process of phagocytosis, *innate sensing*, and the migration process [13]. Non-classical monocytes are involved in complement, adhesion, and phagocytosis by Fc-γ mediation [14]. Intermediate monocytes function to present antigens, secrete cytokines, regulate apoptosis, and differentiate [16]. Monocyte plays a role as an antigen-presenting cell (APC) which is important for linking innate and adaptive immune responses [9]. Expression of HLA on its surface is a marker of antigen-presenting function. According to previous research, intermediate monocytes have the highest expression of HLA-DR, whereas classical monocytes exhibit the lowest level of HLA-DR expression [17]**.** HLA will bind to peptides from microbes and then present them to T cells, and T cells will be activated and lead an adaptive immune system followed by the humoral immune system [1]. HLA-DR is a part of the MHC class II genes, which are responsible for presenting antigens to T-cell receptors (TCR) on $CD4^+$T Cells [18].

In septic conditions, the function of monocytes as APCs changes. In the early stages, an inflammatory process will occur then the monocyte function as an APC will decrease and enter an immunosuppressive state. The process continues until it enters a state of immune paralysis or is deactivated. The "immune paralysis" is defined when HLA-DR expression in monocytes decreases in sepsis [18]. Therefore, monocytes that have low or absent HLA expression are known as $CD14^+HLA\text{-}DR^{-/low}$, are immunosuppressive, and play a crucial role as a mediator for tumor-induced immunosuppression [17].

Downregulation of HLA-DR can occur through various mechanisms. The regulation of HLA-DR expression is a complex process from multiple factors. In normal conditions, HLA-DR is managed by CIITA, a protein for MHC Class II Transactivator [17]. IFN-γ activates CIITA and then induces HLA-DR expression. In addition, GM-CSF can also contribute to HLA-DR upregulation through a post-transcriptional mechanism. IL-1β and TGF-β cytokines inhibit HLA-DR transcription through CIITA. Conversely, IL-10 cytokines increase intracellular sequestration through a process called ubiquitination, where the membrane-associated RING-CH (MARCH) protein tags it with ubiquitin molecules. Glucocorticoids and steroid hormones can reduce CIITA mRNA levels, affecting HLA-DR transcription[17].

3.2. Monocyte Changes and Dysregulation in Type 2 Diabetes Mellitus

T2DM is caused by multifactorial. Its etiology is associated with the combined action of genes, environment, and immune cells [19]. Age, obesity, and lack of physical activity can increase the risk of developing T2DM. Usually, T2DM patients are obese or overweight, and this correlate with the degree of insulin resistance [20]. T2DM is characterized by hyperglycemia which leads to the formation of *Advanced glycation end products* (AGEs) and then an active protein called *nuclear factor kappa-light chain-enhancer of activated B cell* (NF-κB) [21]. ROS increases in hyperglycemia due to increased sorbitol and protein kinase C activation. NF-κB activation and increased ROS result in increased production of inflammatory cytokines and triggers a chronic inflammatory process [18].

T2DM is characterized by hyperglycemia with metabolic changes such as carbohydrates, fats, and proteins resulting in insulin resistance or defects in insulin secretion. Hyperglycemia and increased inflammation will increase microvascular and macrovascular complications [22]. This change in immune response causes the patient to become more susceptible to infection. Poor glycemic control has more to do with the severity of the infectious disease. Alterations that occur also affect immune cells (phenotype and function of monocytes) [23].

Metabolic changes in T2DM result in the dysregulation of monocytes and macrophages as well as increased cytokines (IL-2, IL-7, IL-6, IL-10, TNFα, and others) [18]. Monocyte function has decreased so that monocyte migration is disrupted as the function of monocytes as antigen-presenting cells to T and B lymphocyte cells [7]. A varied population of immature cells with immunosuppressive abilities known as myeloid-derived suppressor cells (MDSCs) originate in the bone marrow. In T2DM conditions, there are changes in the quantity, activity, and role of the MDSC. MDSC is associated with the incidence and complications and organ damage in T2DM. On the other hand, MDSC has the potential as an immunotherapy according to the immunopathology that occurs in T2DM conditions [19]. The number of MDSCs increased in T1DM and T2DM individuals, in humans, it is called M-MDSC and is characterized by increased levels of S100A8/A9 and decreased levels of HLA-DR [19]. Downregulation of monocytic HLA-DR expression is associated with the decreased capability of monocyte as antigen-presenting cells to CD4 T Cells [24]. This expression can be a marker of monocyte function as an antigen-presenting immune cell signaling through TLR-2, cell proliferation and maturation, cytokine production, and apoptosis [9].

Research [9] confirms a decline in monocytic HLA-DR expression in all subsets, consequently affecting the ability to present antigens. This condition is correlated with both hyperglycemia and dyslipidemia. In individuals with T2DM, lower monocytic HLA-DR expression is observed, which is linked to a decrease in antigen presentation to T cells, thereby increasing the risk of developing diseases [9]. In T2DM there is a decrease in the total number of monocytes. The levels of IL-6 and IL-10 are inversely related to the monocytic HLA-DR expression [25]. Decreased mRNA for HLA-DR was found in obese individuals with insulin resistance compared to healthy obese individuals. $CD14^{+}HLA\text{-}DR^{-/low}$ monocytes are known to suppress/suppress the proliferation of T lymphocyte cells in T2DM patients. This study [26] shows that in T2DM there is a decrease in monocytic HLA-DR expression. Research [27] found that individuals with obesity had higher monocytes than overweight or healthy individuals. Another study [28] reported that individuals with T2DM had elevated IL-10 and TGF-β levels due to an increase in $CD33{+}HLA\text{-}DR^{-/low}$.

Research [23] evaluating the relationship between low $CD14^{+}HLA\text{-}DR$ expression and glycemic control in T2DM patients. This study shows that $CD14^{+}HLA\text{-}DR^{-/low}$ monocytes increase in T2DM. T2DM with uncontrolled blood sugar levels (HbA1c> 9%) had a higher frequency of monocytic HLA-DR low expression compared to patients with controlled blood sugar levels (HbA1c <9%). It is also associated with a longer duration of T2DM, older age, higher glycemic index, and control blood sugar levels This condition correlated positively with the disease susceptibility of T2DM patients [23].

3.3. Impact changes of HLA-DR expression in Type 2 Diabetes Mellitus on disease susceptibility

In diabetic conditions, hyperglycemia cause immune response dysfunction that affects unsuccessful pathogen control, and invasion can continue. Susceptibility to infection will increase in T2DM conditions. There is a possibility that the increasing prevalence of T2DM as a comorbid will also increase the prevalence of infectious diseases [22]. Susceptibility to infection in T2DM patients is related to abnormalities in chemotaxis, phagocytosis, adhesion, and other immune

functions [29]. Several studies have proven that T2DM is a comorbid factor that influences the susceptibility and clinical severity of many diseases like infections (*SARS-CoV-2* and *Mycobacterium tuberculosis*, sepsis, and cancer [8]. Disturbances in populations and immune cell activity that do not regularly play a role in maintaining this condition.

In healthy people, the number of classic monocytes is the highest in the circulation. In individuals with T2DM and or COVID-19, the monocyte profile is changing. In severe COVID-19 with comorbid type 2 DM, total monocyte is decreasing, especially in classic monocytes [11]. This study [11] reported that subset change and monocyte activation are related to the transcription factor IRF-5, and found a positive correlation between IRF5 and HLA-DR. In moderate COVID-19, cellular dysfunction occurs and is marked by reduced expression of HLA-DR on monocyte. This condition can be used as a marker of immunosuppression in severe degrees of COVID-19 patients and related to COVID-19 severity [12][30].

T2DM is linked to higher severity and mortality of COVID-19 [31]. In COVID-19 patients with T2DM, increased $CD14^{+}HLA\text{-}DR^{-/low}$ monocytes are observed, which is associated with a higher viral load in the oropharyngeal and longer durations of hospital stay [31]. The patients also get an elevated risk of severe infection, hospitalization, and mortality, particularly when they have uncontrolled blood sugar levels [31]. In addition to its role in presenting antigens to T cells, decreased monocytic HLA-DR expression may contribute to immunosuppression and impact the progression and susceptibility of disease in patients with T2DM [23]**.** This increase in comorbidity is due to decreased immune system function in T2DM [9]. Obesity, smoking, and lack of physical activity are comorbid risk factors. This is because being overweight and smoking play a role in reducing monocytic HLA-DR expression [32]. Body mass index (BMI) has a contrary correlation with HLA-DR expression specific in classical monocyte. Higher levels of HLA-DR were observed in association with total cholesterol, HDL, and LDL levels. On the other hand, patients with high triglyceride levels showed a decrease in monocytic HLA-DR expression, although these differences were not considered statistically significant [9].

T2DM patients are also more susceptible to *Mycobacterium tuberculosis* infection. T2DM conditions affect monocyte differentiation and macrophage activation during *Mycobacterium tuberculosis* infection. Research [33] reported there is a decrease in HLA-DR expression in T2DM and *Mycobacterium tuberculosis* infection so it interferes with the antigen presentation process accompanied by changes in proinflammatory and anti-inflammatory signals that occur [33]. Low BMI is related to the outcome of TB treatment [34]. Decreased MHC class II expression in T2DM is also associated with clinical symptoms of sepsis. That is in line with research [29] states that T2DM patients with sepsis experienced increased phagocytic activity in monocytes and neutrophils which occurred at the start of acute infection and was followed by decreased expression of MHC class II.

Loss or reduced expression of HLA-DR can also be a hallmark of deactivation of monocyte function and is associated with poor clinical symptoms. Apart from the COVID-19 condition, the frequency of $CD14^{+}HLA\text{-}DR^{-/low}$ was also reported to be relevant to T2DM conditions which increase the risk of infection and cancer [23]. In cancer patients, there is a low expression of HLA-DR on monocyte and similar to sepsis condition. Furthermore, cytokines such as IL-1B, TNF-α, and CD86 are significantly downregulated in cancer than in normal conditions. This is because monocytes are converted to immunosuppressive (in sepsis and malignant conditions) [21]. $CD14^{+}HLA\text{-}DR^{-/low}$ serves as a biomarker for immune suppression and disease progression and can be potentially developed as a therapeutic target [17]**.**

4. Conclusion

In summary, monocytic HLA-DR expression is correlated to the function of presenting antigen to T lymphocyte cells and B cell activation. Chronic Low-grade inflammation in T2DM patients results in changes in monocyte cells followed by reduced monocytic HLA-DR expression, or an increase in the $CD14^{+}HLA\text{-}DR^{-/low}$. The low expression of HLA-DR affects an individual's susceptibility to disease. Further research is still needed to find the molecular mechanism of reduced HLA-DR expression in monocytes, especially in T2DM.

Compliance with ethical standards

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Disclosure of conflict of interest

Authors declare that there is no conflict of interest.

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