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The Human Platelet and Leucocyte *Antigens*: Locations, Diagnosis and Solutions

Okolo RC[1,2]*, Ufelle SA[1], Ogbuabor AO[1], Peter U[1], Achukwu PU[1], Odugu JA[3], Ozochi JA[1] and Uchejeso OM[4]

[1]*Department of Medical Laboratory Sciences, Faculty of Health Sciences and Technology, University of Nigeria, Nsukka, Nigeria*
[2]*District Hospital Nsukka, Nsukka Enugu State, Nigeria*
[3]*Ahmadu Bello University Teaching Hospital, Zaria Kaduna State, Nigeria*
[4]*Department of Chemical Pathology, Federal School of Medical Laboratory Science, Jos Plateau, Nigeria*

Abstract

Every platelet has natural proteins on its surface. This is well known as human platelet antigen. The human leucocytes antigens are integral to the platelet membrane and next to ABO system which possess chief barrier to transplantation by the presentation of antigenic peptides T cells. Both the human platelet and leucocytes antigens (HPLA) are highly polymorphic glycoprotein encoded on the different arms of the chromosome. The human leucocytes antigen (HLA) expression is especially high on leucocytes because of their easily availability, and lymphocytes are used to identify the types. The most important function of the HLA molecule is in the induction, regulation of immune responses and in the selection of T cell repertoire. Also the HLA are effective stimulators, graft versus host disease (GVHD) and graft rejection. Moreover, subsets of HLA B27 and B57 are strongly associated with slow progression of acquired immunodeficiency syndrome (AIDS). This review highlights the human platelet and leucocytes antigens, its importance in antenatal screening, transfusion and in health and diseases.

Keywords: Platelets; Leucocytes; Antigens; Transfusion; Transplantation

Introduction

Human platelet and leucocytes antigens (HPLA)

Platelets are the smallest and anucleated discoid type of cells that circulate in the blood and have a tripartite functional responses to the system such as adhesion, activation-secretion and aggregation when there is a vessel wall injury in form of chemical stimuli or blood flow alteration [1,2]. Platelets are very important in bleeding prevention and stoppage. The discovery and rediscovery of platelet was the handwork of Bizzozero in 1882 and was later forgotten for many decades respectively [3].

The physiology, metabolism, catabolism and usage of platelets: The platelets as known are anucleate cells derived after breakdown of megakaryocytes (large-nucleus-cells) that occurs in the capillaries of the lung. This represents only about 0.02-0.05% of all nucleated cells in the bone marrow. The megarkaryote breaks into 2000-3000 discoid fragments with the diameter of approximately 1.5-3.3 um. The number of platelets in the peripheral blood is 150-400×10^9/L but in a situation where the value is less than 150 and above 400 we experience thrombocytopenia and thrombocytosis respectively. When platelet is unutilized for its purpose in the system it gets broken down in the spleen after 7-9 days [4]. Platelet has inflammatory attributes in human so also in the lower organism like in caterpillar, the haemocytes act as defense against foreign organism by adhesion and aggregation of the foreign bodies. Platelet also has multifaceted functions: interaction with neutrophils, stimulation of basophils, mediators excretions, cytokines production, production of growth factors, bacteria and parasites interactions. This platelet has immune membranes like Major Histocompactibility Complex (MHC) class 1 molecules. It also possesses ABO antigens [5,6]. Platelet in its activated state interacts with lysosomes and other cellular components in the surface. Kishimoto and Anon [7,8] described 45 distinctive membrane structures of platelet in the resting state and categorized into five groups. They are the adhesion molecules, immune molecules, receptors, blood group antigens and other molecules. Both the human platelet and leucocyte antigens are highly polymorphic glycoprotein encoded on the different arms of the chromosomes. The nomenclature adopted in the HPA goes the same manner as the blood group system following the patients based on antibodies developed during platelet transfusion and pregnancies. The HLA is encoded by a cluster of more than 200 genes [9] on the short arm of chromosome 6 [10]. Human Platelet Antigen (HPA) according to von den Borne and Decary [11] classified it into immunogenetic system following alloimmunisation been triggered by it. This HPA has its polymorphic complexes with several alleles coding for each glycoprotein (GP), alloepitopes and their respective proteins. There are several glycoproteins namely: GP111a, GP IIb/111a (α11bß3) complex, GPIb/V/IX complex, GPIa-IIa complex, GPIV (CD36, also GPIIIb).

GPIIIA carries a set of alloepitopes HPA-1, HPA-4, HPA-6, HPA-7, HPA-8, HPA-10, and HPA-11 with their amino acid residues as 33, 143, 489, 407, 636, 62 and 633 respectively [12].

The GPIIb/IIIa: αIIbß3/complex is also known as heterodimeric integrin. The integrin has an adhesive motif or proteins such as fibrinogen, vitronectin, fibronectin and von Willbran factor. The integrin has α and ß subunits and non-covalent property that binds with amino acid sequence Arg-Gly-Asp (RGD) which portraits the adhesive features. This participates actively in the platelet aggregation when activated in the final stage of the process.

GPIIIa (CD61, ß3): This is a glycosylated 90-kDa single protein consisting of three domains: a large extracellular N-terminal region which is highly cross linked by 28 disulfide bonds: a transmembrane

***Corresponding author:** Chinweike OR, Department of Medical Laboratory Sciences, Faculty of Health Sciences and Technology, University of Nigeria, Nsukka, Nigeria, Tel: +234 80667945063; E-mail: okoloraph@gmail.com

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domain, and a short cytoplasmic c terminal segment. It is situated on the long arm of chromosome 17(bands q21-23) with a single 260 kb segment.

GPIb/V/IX complex: This belongs to the family of leucine-rich repeat proteins. It is called CD42 or von Willbrand's factor receptor and transmembrane components. They are composed of four units - namely GPIbα (CD42b, MW142kDa), GPIbß (CD42cMW 22 kDa). The above two units are covalently linked by s single disulfide bond and non-covalently linked with other two namely GPIX (CD42a, MW20kDa) and GPV (CD42d, MW 83 kDa). The CD42 is involved in the initial stage of platelet adhesion.

GPIa/IIa complex (CD49/CD29 α2ß1): This is known as VLA-2 very late antigen that is platelet membrane integrin. The activated T-lymphocytes are rich in GPIa/IIa complex. The GPIa and GPIIa have the molecular weight of 165-kDa α2 chain and 145-kDa ß1 chain respectively. GPIIa can also be called PECAM-1(Platelet endothelial cell adhesion molecules-CD31). Clemtson and Parise et al. were so fortunate enough to describe the structure of GPIa-IIa.

GPIV (CD36, also GPIIIb): This has MW 88 kDa and resides on the surface of platelets and monocytes. GPIV has similarity with the glycoprotein PAS IV of the globular membrane of the lactic fat. GP IV acts as a stabilizer in the platelet aggregate and adhesion and receptor for thrombospondin (TSP) and collagen. The GPIV (CD36) during the malarial activation of the platelets shows its effect in red blood cells infected with plasmodium. This GPIV deficiency manifests in Japanese population with platelet defects at the range of 3-11% frequencies [13,14]. GPIV has two polymorphs; the first platelet alloantigen is Nak [15-17], and the second is Vis [18] that is of low frequency. Both of them are involved in immunization during pregnancy and after transfusion. The platelets express antigens that can be recognized by auto-antibodies or by antibodies made by recipient of platelet during transfusions. Every platelet has natural proteins on its surface and known as the Human Platelet Antigens (HPA). As of 2013, there are 28 known HPAs for example, HPA-1, HPA-2, and HPA-3 and so on.). But scientists are discovering new ones all the time. The HPAs are similar to, but distinct from, the antigens on the red cells. All HPAs exist in two forms; a high and low frequency form designated 'a' and 'b' respectively such as HPA-1a and HPA-1b. In addition, platelets also possess platelet-specific antigens that are unrelated to erythrocytes or leucocytes isoantigens resulting in immune thrombocytopenia. A dominant platelet antigen recognized by the auto-antibodies by many patients with autoimmune thrombocytopenia is the platelet glycoproteins GPIIb/IIIa (otherwise called aIIbb3 or CD41/CD61), although other platelet glycoproteins also may be targeted by auto-antibodies [19]. Human platelet antigen (HPA) has specific antigens that reside on surface membrane glycoproteins [20]. On the other hand, there are several types of antigens. The platelet specific antigen and antigens shared with other cells (red blood cells, HLA antigens) [21]. HPAs are polymorphisms of platelet surface GPs which result in alloantigen expression, leading to alloimmuniztion mainly after transfusions and pregnancies [22]. Human platelet alloantigens are of importance in neonatal alloimmune thrombocytopenia (NAITP), refractoriness to platelet transfusion therapy, and post transfusion purpura (PTP) [11]. Platelets bind on the surface some erythrocytes specific antigens (ABO, Lewis, LI and P), but lack antigens like Rh, Duffy, Kell, Kedd. Some ABO antigen are part of the platelet membrane, others are adsorbed from the plasma. The density of A or B antigens on platelets surface is about 5% of that on erythrocytes [21] this quantity is enough to produce an immune conflict. In this Platelets specific antigens are targets for antibodies (auto-antibodies, alloantibodies, drug dependent antibodies). Alloantibodies appear following transfusion or post-partum and are involved in refractoriness to platelet transfusion [21]. HLA antigens comprise the major histo-compatibility complex that is next to ABO system, the MHC is the principal barrier to transplantation. The biological function of HLA molecules, however, is the presentation of antigenic peptides T cells. There are six major groups of HLA antigens: HLA-A, HLA-B, HLA-C, HLA-DR, HLA-DQ and HLA-DP. These groups are divided into classes of antigens designated as class I, class II and class III representing the three types of HLA molecules. The class I antigens are HLA –A, HLA –B and HLA –C antigens. They are expressed on essentially all tissues in the body and present small peptides fragments to $CD8^+$ T cells. The antigens are mostly found in tissue distribution, and on nucleated cells of the body. The HLA –DR, HLA –DQ and HLA –DP antigens are the class II antigens present on antigen peptide fragments to $CD4^+$ T cells and limited in expression primarily to B cells monocytes and macrophages. This class I antigens are abundance and easily found on the leucocytes during the antigen and antibody reactions (serological techniques). It serves as an indicator for the intracellular infection, while class II senses the antigens present in the intracellular milieu. [22]. Clinical situations involving platelet-specific antigens and antibodies are autoimmune thrombocytopenia (anti-HPA auto-antibodies). Anti-platelet specific antibodies can be detected in the serum/sera of poly transfuse alloimmunized patient in 20-25% of cases. These patients usually associate post transfusional anti-HLA antibodies too [23]. Platelets bind on their case recipients antibodies bind A or B transfused antigens. In clinical practice, ABO matched platelet transfusions are rarely administered only in selected cases (children, refractory patient). ABO alloimmunization is considered to have less importance than HLA alloimmunization in platelet refractoriness issue [2,24]. HLA antigens are integral to the platelet membrane. Platelet HLA antigens are class I (-A, -B, -C), while class II (DR) is not found on platelets or may be induced on the platelet surface by cytokine stimulation (gamma interferon) [23].

HLA proteins also interact with killer inhibitory receptors (KIR) expressed on the surface of natural killer (NK) cells often leading to inhibition of NK cell activity [25-30]. The role of HLA molecules is to present peptides from invasive organisms and the genes of the MHC are the most polymorphic of the human genome (total HLA alleles 13023, HLA class I alleles 9749 and HLA class II alleles 3274 [31]. As April2015, there are over 3017 HLA-A, 2623 HLA-C, 3887 HLA-B, 1829 HLA-DRB1, 780 HLA-DQB1 and 520 HLA-DPB1 alleles recognized by the World Health Organization (WHO) Nomenclature Committee for factors of the HLA system [31,32]. HLA molecule differs slightly from each other in its amino acid sequence (different HLA antigens) which causes different structure in the peptide binding cleft. The most important function of HLA molecule is in the induction, regulation of immune responses and the selection of the T cell repertoire [33].

Clinical Consequences of HPA Alloantibody Formation

Neonatal alloimmune thrombocytopenia (NAITP)

This often known as feto-maternal alloimmune thrombocytopenia (FMAIT) that occurs as a consequence of maternal immunization against fetal placental alloantigen inherited from the father. Maternal IgG antibodies then cross the placenta and cause immune destruction of platelet in utero, a situation analogue to haemolytic disease of the new born except that approximately 30% of cases occur in the first pregnancy. At present there is no routine antenatal screening, even

though the incidence of the disease is higher than that of severe haemolytic disease of the new born and several pilot studies have demonstrated that routine screening is feasible.

Post-transfusion puerperal (PTP)

PTP is a rare but severe disease that occurs approximately a week after transfusion of any blood product containing platelets or platelet membranes. PTP is a life threatening disease as bleeding is often severe.

The Refractoriness to platelet transfusion is defined as an inadequate increment in the platelet count following transfusion of random ABO identical donor platelets.

Methods used for the detection of platelet specific antibodies are as follows

- The platelet immunofluorescence test (PITF).
- Monoclonal antibody immobilization of platelet antigens (MAIPA).
- The solid –phase red cell adherence assay.
- A variety of ELISA –based techniques.

The class II antigens were originally defined by lymphocytes proliferation assays such as the mixed lymphocyte reaction (MLR) or primed lymphocyte test (PLT), and only later were identified by serological findings.

Class II antigens have a more restricted distribution than class I. These antigens primarily are located on B lymphocytes, monocytes, macrophages, dendritic cells, and endothelial cells. However, class II antigens can be induced on other cell types through activation [25]. HLA antigen expression is especially high on leucocytes because of their easily availability and can detected with the help of lymphocytes.

The HLA class III region's genes encode proteins which differ in both structure and function to the class I and class II loci, including complement components, several inflammatory cytosine, such as human necrosis factor alpha (TNF alpha) or the heat shock proteins.

The HLA are specialized in presentation of short peptides to T cells and play a key role in the body's immune defense [26]. The class I and class II genes are cell-surface glycoprotein that binds intercellular and extracellular peptides respectively [27].

HLA class I proteins are expressed on the surface of all nucleated cells but to varying degrees. They are comprised of one trans-membrane heavy chain with three extra cellular domains (alpha1-3) and B_2 macroglobulin ($B2^{\cdot m}$) light chain.

The normal function of HLA class I proteins is a presentation of peptides from expired or defective intracellular proteins and peptides from invasive viruses from within the cell to the T cell receptor (TCR) on CD8 T cells (often cytotoxic) leading to immune mechanisms which destroy the cell.

HLA disease association: There are common diseases associated with human leucocytes antigens over the years in the human race such as HLA –B alleles (e.g. HLA –B*2702, HLA –B*2705) are associated with ankylosing spondylitis. HLA –DQB1*0602 is associated with narcolepsy. HLA –DRB1*0401, the best known for its association with Rheumatoid Arthritis (RA), associated with type I diabetes (TID) as well [34].

HLA and immune response*:* The HLA molecules have being involved in the regulation and induction of immune responses. This is done by the collaboration of the HLA and the T cells in the foreign antigen complexes of the HLA activated [35].

Deficiency in HLA molecules: Isolated HLA class I deficiency also termed type I bare lymphocyte syndrome (type I BLS), is not usually life threatening, in contrast to the more severe HLA class II deficiency (type II BLS) and combined HLA class I and II deficiencies. The symptoms present in the majority of the patients are rather unexpected, considering the role of HLA class I molecules in the presentation of viral peptides to cytotoxic T lymphocytes (CTL) [36].

Abnormalities of gene linked to the HLA: This known as hemochromatosis: This is iron-overload disorder owing to genetic mis-regulation of iron acquisition and referred to as HH. The most prevalent genetic iron-overload in Caucasian is caused by mutations in the HFE gene, an atypical HLA class I molecule. This is a missense mutation that results in a cytosine to tyrosine substitution at amino acid 282 of human HFE protein (C282Y) was found in vast majority of patients with HH [37,38].

HLA and infectious diseases

Malaria: Not only to genetic disorder, the resistance to severe malaria has been attributed to the HLA class 1 and 11 alleles in Sub-Sahara populations [28,39,40].

HIV/AIDS: This is one of only a few infectious diseases showing a clear-cut and consistent HLA association. The primary influence of HLC loci on HIV disease relative to all other single human genetic variants has now been confirmed by several Genome Wide Association Studies (GWAS). Thus, all available evidence points to HLA as the most significant locus in differential control of HIV across humans [41]. Kaslow et al. [42] assessed the role of HLA class I alleles in HIV infection and found that HLA B27 and B57 were strongly associated with slow progression to AIDS.

Hepatitis C virus: HLA association with respect to hepatitis B virus and HCV infection susceptibility, protection, disease severity, interferon treatment response to vaccination have been intensively investigated across the global populations [43]. Both HLA B*57 and HLA B*27 have been identified as protective in terms of both HIV and HCV infection.

HLA and cancer: Tumor cells do not respond to the regulatory stimuli that normally limit tissue proliferation. As a result of this process, the tumor may no longer be recognized by the immune system [44,45].

The Structural and functional changes in HLA has been possible because of loss of expression of tumor antigens, lack of co-stimulatory molecules and production of immunosuppressive cytokines that cause tumor cells to escape immune surveillance (Paul, 1998). Interestingly, none of the HLA classes I and II alleles have been demonstrated to be associated with an increased incidence parse of any cancer.

HLA and transfusion: There are high tendencies and concentration of leucocytes and platelets, but exist in little amount on the erythrocytes whenever there is transfusion of either platelet or leucocytes that posses a risk to the platelet during immunization, multiple transfusion of whole blood, platelet, and leucocytes concentrates and develop antibodies to HLA antibodies. The Anti HLA antibody has led to two problems, the platelet refractoriness on the course of transfusion, and non-haemolytic transfusion reaction. (*Shankarkumar, 2004*).

HLA and transplantation: The HLA system is the primary immunologic barrier to successful stem cell transplant. Therefore, the clinical outcomes of haemotopoietic stem cell transplant (HSCT) are dependent on optimizing the histo-compatibility matching between the patient and the donor. The HLA antigens are effective stimulators and targets of graft versus host disease (GVHD) and graft rejection.

HLA typing: Tissue typing for HLA antigens can be performed using a number of methods of varying degrees of sophistication and complexity. For example:Mixed Lymphocyte Culture (MLC), Primed Lymphocyte Test, Cytotoxic T lymphocyte (CTL) Clones, 2-dimensional electrophoresis, iso-electric focusing, Molecular assays. The most frequent procedures used in the clinical laboratory have been serological and cellular assays. However, with the advent of the Polymerase Chain Reaction (PCR), DNA-based typing is becoming common for class I and class II.

Microcytotoxicity test (serology): This has been the basic tissue typing method for HLA antigen for the past three decades [46]. In this assay a suspension of lymphocytes is incubated with human alloantisera in a micro liter tray [47]. Rabbit serum is added as a source of complement. Cell death is evaluated microscopically and determined by the uptake of a vital dye or by immunofluoresence. Antibody panels generally consist of two to four sera that recognize the same specificity.

Importance:

- For patients destined to receive repeated platelet transfusions.
- In typing patients and donors for solid organ transplantation.
- In the initial investigation of families of patients desiring marrow or stem cell transplantation.

Cellular assays

Mixed lymphocyte reaction: A mixed lymphocyte reaction involves coculturing for several days the stimulator cells from one individual with the responder lymphocyte from another. Stimulation cells are prevented from proliferating by irradiation or exposure to mitomycin C. The responder cells that recognize alloantigens expressed by stimulator cells are induced to proliferate. Stimulator cells are B cells and monocytes that are antigen presenting cells. T lymphocytes are responding cells. A radioactive nucleotide, usually 3 H thymidine is added during the last 6 to 18 hours of culture to measure newly synthesized DNA. The amount of radioactive thymidine incorporated into the DNA of responder cells is generally proportionate to th degree of HLA D disparity between responder and stimulator cells.

HPA typing

Accurate typing of patients for HPA antigens is required in several different clinical situations and blood services need to maintain panels of HPA-typed apheresis-platelet donors and whole blood donors to support HPA phenotyping is limited as often too few platelets can be obtained from thrombocytopenic patients, and reliable serotyping reagents for HPA antigens, other than HPA-1a and HPA-5b are rare. HPA antisera often contain human leucocyte antigens (HLA) class 1 antibodies, thus limiting their use to GP-specific assays such as the monoclonal immobilization of platelet antigen (MAIPA) assay. Monoclonal antibodies are now routinely used for red cell phenotyping but, with the exception to HPA-1a, no monoclonal antibodies have been developed for HPA typing.

Molecular typing

The most common methods currently in use for HLA typing are sequence specific primer amplification (SSP) and sequence specific oligonucleotide probe hybridization (SSOP).The use of molecular testing has a number of advantages over serologic testing.

- DNA based typing does not require the isolation of viable lymphocyte populations but can be done using any nucleated cell source.
- DNA based assays has increased accuracy and specificity. The clinical applications of HLA include; area of transplantation, immune response regulation and in disease susceptibility.

Conclusion

The HLA and HPA with their relevance in the clinical aspects, transfusion, and in disease susceptibility should be given much concern for wellbeing of the patients. However, due to its involvement in immune reactions and integrations on the membrane glycoprotein where the ABO antigens reside on and the effect it has as protein markers. The platelet antibodies screening should be instituted in our hospitals for routine checks. The neonatal alloimmune thrombocytopenia should be given the same priority as in the case of hemolytic disease of the newborn which occurs in the screening of the antenatal women in the hospital as a result of maternal immunization against fetal placental alloantigen inherited from the father. Also following the diseases caused by missense mutation and other disorders associated with chromosomal aberration and infectious agents, the HPLA should be taken into consideration in disease etiology, diagnosis and treatment.

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