The human neutrophil antigen system: structure, function, and disease implications

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A B S T R A C T

Antibodies directed against human neutrophil granulocytes can cause immune neutropenias such as neonatal immune neutropenia, autoimmune neutropenia, drug-induced immune neutropenia, and stem cell transplantation-associated immune neutropenias, as well as transfusion reactions such as transfusion-related acute lung injury (TRALI) and febrile transfusion reactions. Regarding neutrophil-reactive alloantibodies, 5 alloantigen groups comprising 9 alloantigens have been defined. Antibodies directed against the neutrophil-specific Fcγ receptor IIIb (FcγRIIIb), which bears the HNA-1 antigens, are most frequently implicated in neonatal immune neutropenia and autoimmune neutropenia. HNA-3a alloantibodies are responsible for many severe and fatal TRALI reactions. HNA-2-specific antibodies, which are termed isoantibodies (as HNA-2-negative individuals do not express the glycoprotein despite possessing the encoding gene), can also cause TRALI reactions as well as comparatively long-lasting neonatal immune neutropenia and immune neutropenia after stem cell transplantation, as these antibodies also bind to granulopoietic precursors. HNA-2 is also unique in being expressed in a neutrophil subpopulation with greater antigen expression after G-CSF administration, during bacterial infection, or in patients with polycythemia vera. Alloimmunization against the HNA-4 and -5 alloantigens is rare and only occasionally responsible for neonatal immune neutropenia.

Learning goals

At the conclusion of this activity, participants should:
- know the composition and content of the human neutrophil antigen (HNA) system;
- understand the molecular basis of the HNA antigens;
- understand the clinical significance of the HNA antigens.

Introduction

Most work with blood cell antigens has involved erythrocytes, because most transfusions (and associated immune reactions) involved red blood cells. However, even in the early years of the 20th century, some investigators directed their attention to leukocytes. In 1926, Doan observed that the sera from some patients caused agglutination of leukocytes from other individuals.[1] With the development of the lymphocytotoxicity assay, much of the leukocyte antibody work shifted to the lymphocyte, leading to the definition of the human leukocyte antigen (HLA) system. Comparatively few investigators worked on granulocyte immunology. However, in the 1960s, Lalezari and co-workers discovered two antigen groups that are limited to neutrophils.[2,3] Subsequent studies of granulocyte antigens and antibodies led to the establishment of the human neutrophil alloantigen (HNA) system in 1999[4,5] (Table 1). Currently, nine HNA antigens are assigned to five antigen groups (a 10th antigen has been proposed but has not been officially accepted). The antigen frequencies differ between populations (Table 2). While two HNA groups are restricted to neutrophil granulocytes (HNA-1, HNA-2), the others are expressed on a variety of other blood and tissue cells. Nevertheless, these latter antigens were included in the HNA system because their clinical relevance results from their expression on neutrophils. HNA antibodies have been implicated in neonatal immune neutropenia, autoimmune neutropenia, and drug-dependent immune neutropenia, as well as in febrile and pulmonary transfusion reactions (Table 3). Assays for the detection and identification of HNA antigens and the corresponding antibodies, as well as molecular methods for HNA typing, have been established. This allows for screening for immunized blood donors, as well as for diagnosing HNA antibody-mediated immune diseases. International workshops[6] and national proficiency testing programs (e.g. INSTAND in Germany) have improved the quality of laboratory diagnostics. In this report, the molecular basis of the HNAs and their clinical implications are presented.

HNA-1

The HNA-1 alloantigens are neutrophil-specific and expressed in significant numbers on more mature granulocytes (segmented, bands, metamyelocytes) rather than on their immature precursors. The HNA-1 antigens are expressed on Fcγ receptor IIIb (FcγRIIIb, CD16b),[7] a glycoprotein which binds with low affinity the Fc part of IgG1 and IgG3 antibod-

ies.[8] There exists a highly homologous FcγR, known as Fcγ receptor IIIa (FcγRIIIa; CD16a), with medium affinity for IgG1 and IgG3. However, FcγRIIIa is found on monocytes (subset), macrophages, T cells (subset) and natural killer cells,[9] but notably is lacking on neutrophils. In addition, unlike (transmembranous) FcγRIIIa, FcγRIIIb is linked to the cell membrane via a glycosylphosphatidylinositol (GPI) anchor, which is the result of a phenyalanine to serine exchange at amino acid position 203 of FcγRIIIb.[9] Upon stimulation with the bacterial chemotaxin f-met-leu-phe (fMLP) or with granulocyte-colony stimulating factor (G-CSF), FcγRIIIb molecules are released from granulocytes into the plasma and so the plasma will contain soluble FcγRIIIb showing the same HNA-1 polymorphisms. The highly glycosylated FcγRIIIb exhibits two immunoglobulin G (IgG)-like domains, of which the membrane-proximal domain contains the IgG-binding segments. Crosslinking of FcγRIIIb leads to phagocytosis of small particles and immune complexes, probably with CD11b/CD18 complexes in lipid rafts acting as a signaling partner for the GPI-linked FcγRIIIb.[8] Co-crosslinking of FcγRIIa, also expressed by neutrophils, and FcγRIIIb by larger particles and immune complexes, results in synergestically-enhanced phagocytosis, respiratory burst, and CD11b/CD18 expression/activation.[8] It is thought that the neutrophil FcγRIIIb contributes to the clearance from blood of small immune complexes, an event, facilitated by the high copy number (100,000-300,000 per cell) and the high lateral mobility of FcγRIIIb in the outer part of the neutrophil plasma membrane due to its GPI-anchoring. The gene encoding the FcγRIIIb (*FCGR3B*) is located on the long arm of chromosome 1 (1q23) and consists of five exons.[10] The mRNA transcript codes for 233 amino acids but the mature glycoprotein consists only of 188 amino acids. It was found that the alleles *FCGR3B*01* and *FCGR3B*02* coding for the antigens HNA-1a and -1b, respectively, differ in five nucleotide substitutions within exon three resulting in the replacement of four amino acids at positions 36, 65, 82, and 106 in the membrane-distal domain.[10] Of those, Asp82 and Ser65 seem crucial for the formation of the HNA-1a and -1b epitopes.[11] The third antigen, HNA-1c, presumably evolved from the HNA-1b-antigen by a single nucleotide polymorphism (SNP) in the *FCGR3B*02* allele, resulting in an Ala78Asp exchange.[12] In some Africans and most Europeans typed HNA-1c-positive, a gene duplication is present so that the encoding *FCGR3B*03* allele is located in close proximity to the *FCGR3B*01* allele (encoding the HNA-1a antigen) in *cis*-position because both alleles segregate together.[13] This means that *FCGR3B*03* positive individuals can have up to six *FCGR3B* alleles. It is of note that the glycoprotein encoded by the *FCGR3B*03* allele carries both the HNA-1c and HNA-1b epitopes, leading to occasional confusion and misinterpretation of genotyping results. The HNA-1d epitope is formed by the Ala78 and the Asn82 amino acids of the HNA-1b antigen[14] (Table 4). Anti-HNA-1d alloantibodies can be found in the blood of HNA-1c-positive individuals who do not possess the *FCGR3B*02* allele. Some individuals completely lack the *FCGR3B* gene, so that they do not express the FcγRIIIb at all, resulting in the so-called "HNA-1null" phenotype.[15] This FcγRIIIb deficiency seems not to be associated with increased frequency of infection or autoimmune disease indicating that this lack of FcγRIIIb can be compensated, at least to a significant degree, by the neutrophil FcγRIIa.[8,16] However, FcγRIIIb-deficient individuals can form so-called "isoantibodies" against the FcγRIIIb, which bind to FcγRIIIb independently of any polymorphism.

The frequencies of the HNA-1-antigens vary between different populations (Table 2). In Europeans, the HNA-1b and HNA-1d antigens are more frequent than HNA-1a, whereas in Chinese and Japanese the reverse is seen.[13] HNA-1c is a low frequency antigen in Europeans and Africans, and appears to be absent in East Asians (Chinese, Japanese, Koreans). The HNAnull phenotype is rare among Europeans (Whites, <1%), more frequent in African Blacks (1%-7%) and nearly absent in East Asians. However, in some small populations (frequent examples are indigenous tribes), FcγRIIIb deficiency can be frequent. A number of additional SNPs resulting in amino acid exchanges have been described, but alloimmunization to these protein polymorphisms has not been reported.

Table 1. Human neutrophil alloantigens.

Antigen group	Carrier glycoprotein	CD	Antigens	Previous names	Gene (chromosome)	Alleles	Molecular basis
HNA-1	FcγRIIIb	CD16b	HNA-1a HNA-1b	NA1 NA2	*FCGR3B* (1q23)	*FCGR3B*01* *FCGR3B*02* *FCGR3B*03*	Multiple SNPs
			HNA-1c HNA-1d	SH --		*FCGR3B*03* *FCGR3B*02*	SNP
HNA-2	(NB1 glycoprotein)	CD177	HNA-2	NB1	*nn* (19q13.2)	no glycoprotein expression by HNA-2 neg. individuals	
HNA-3	CTL2	no designation so far	HNA-3a HNA-3b	5b 5a	*SLC44A2* (19q13.1)	*SLC44A2*01* *SLC44A2*02*	SNP
HNA-4	MAC-1 $\alpha_M\beta_2$-integrin	CD11b	HNA-4a HNA-4bw+	MART --	*ITGAM* (16p11.2)	*ITGAM*01* *ITGAM*02*	SNP
HNA-5	LFA-1 $\alpha_L\beta_2$-integrin	CD11a	HNA-5a	OND	*ITGAL* (16p11.2)	*ITGAL*01*	SNP

Shaded areas indicate expression only on granulocytes. SNP: single nucleotide polymorphism. +Currently under investigation but not yet officially accepted.

The HNA-1 antigens are implicated in several diseases (Table 3). HNA-1a and HNA-1b alloantibodies are most often implicated in neonatal immune neutropenia, whereas HNA-1c and HNA-1d alloantibodies, as well as FcγRIIIb isoantibodies, are only rarely implicated in NIN. Transfusion-related acute lung injury (TRALI) due to HNA-1a and -1b alloantibodies has been reported.[17] The FcγRIIIb has been implicated in drug-induced immune neutropenia;[18] here, drug-dependent antibodies recognize a neoantigen formed by both FcγRIIIb and drug (or drug metabolites). The FcγRIIIb, especially its HNA-1a polymorphism, is the most frequent target of neutrophil autoantibodies.[19] The autoantibodies often show a more or less pronounced HNA-1a specificity that can vary over time. Interestingly, autoimmune neutropenia is the most frequent cause of chronic neutropenia in infancy. Neutrophils homozygous for the *FCGR3B*01* allele encoding HNA-1a have a higher affinity for IgG3 than neutrophils from *FCGR3B*02*-homozygous (HNA-1a-, HNA-1b+) individuals.[8] Accordingly, several reports have indicated that HNA-1a-positive individuals have a higher susceptibility for inflammatory diseases, whereas HNA-1b-positive individuals are more susceptible to infection. Since the few HNA-1null individuals examined so far have not been found to exhibit any striking disease association,[16] the clinical relevance of the HNA-1a/-1b polymorphism for disease susceptibility remains unclear.

Table 2. HNA antigen and allele frequencies within different populations.[47,48,58-61]

HNA antigen Allele	Europeans (Whites)	Turkish	Chinese, Japanese	Black African and Afro-American
-1a	56%-63%	68%	88%-91%	66%
*FCGR3B*01*	0.33-0.39	0.42	0.56-0.68	0.40-0.44
-1b	84%-89%	82%	52%-54%	78%
*FCGR3B*02*	0.60-0.66	0.56	0.30-0.43	0.55-0.59
-1c	3%-5%	3%	0%	23%-31%
*FCGR3B*03*	0.02-0.03	0.03	0.00	0.11-0.16
-1d	84%-88%	82%	52%-54%	78%
FCGR3B*02	0.60-0.63	0.56	0.30-0.43	0.55-0.59
HNA-1null	0,2%-0,8%	1.7%	0%-0.5%	1%-7 %
FCGR3B-deficiency	0.03			
-2	87-97%	n.t.	89%-99%	98%
nn				
-2null	3%-13%	n.t.	1%-11%	2%
(gene expression failure)				
-3a	93%-96%	92%	84%	93%-100%
*SLC44A2*01*	0.74-0.96	0.74	0.62-0.74	0.93-0.97
-3b	45%-33%	44%	61%	5%-14%
*SLC44A2*02*	0.21 -0.33	0.26	0.26-0.38	0.05-0.07
-4a	98%-99%	100%	100%	98%
*ITGAM*01*	0.88-0.90	0.88	0.996	0.89
-4bw	17%-22%	24%	1%	19%
*ITGAM*02*	0.10-0.12	0.12	0.004	0.11
-5a	88%-92%	90%	97%-98%	78%
*ITGAL*01*	0.66-0.73	0.75	0.84-0.85	0.5
(-5b, not yet reported)	(45%-47%)	(44%)	(27%)	(78%)
*ITGAL*02*	0.27-0.34	0.25	0.15-0.16	0.5

Table 3. Clinical implications of HNA antigens and their carrier proteins.

Antigens (carrier protein)	Neonatal immune neutropenia	Autoimmune neutropenia	Drug-induced immune neutropenia	TRALI
HNA-1a,-1b,-1c,-1d (FcγRIIIb)	+++ (-1a/-1b >> -1c, -1d)	+++ (-1a, FcγRIIIb)	+ (FcγRIIIb)	(+)
HNA-2 (CD177)	++	+	+	++
HNA-3a (CTL2)	+	nd	nd	+++
HNA-4a ($\alpha_M\beta_2$-integrin)	+	nd	+ (CD11b/CD18)	+ nd
HNA-5a ($\alpha_L\beta_2$-integrin)	+	nd	nd	nd

nd: not described.

HNA-2

In all populations typed so far, HNA-2 is a highly frequent antigen (Table 2). Like the HNA-1 antigen group, HNA-2 is restricted to granulocytes and linked to the plasma membrane via a GPI anchor.[20] HNA-2 is also expressed on neutrophilic myelocytes and metamyelocytes and can be found in the membrane of the secondary/specific granules. In contrast to GPI-linked FcγRIIIb, which is shed by neutrophils after stimulation, soluble HNA-2 is not found in the plasma.[20] The antigen is a glycoprotein (three N-linked glycosylation sites) that by reason of its two cysteine-rich domains is considered a member of the Ly-6/uPAR/snake-toxin family of proteins, for which repetitive cystein-rich domains are typical.[21] Monoclonal antibodies reacting with the NB1 (previous name of HNA-2) glycoprotein have been designated as CD177. HNA-2-negative individuals do not express the glycoprotein at all, representing, therefore, an HNA-2null phenotype. The glycoprotein is expressed in most HNA-2-positive individuals only on a granulocyte subset of varying proportion.[20] Ethnic variation does not seem to influence the proportion of antigen-positive neutrophils but a hormonal influence seems probable, as the expression increases in pregnancy and is higher in women than in men.[22] The HNA-2-negative granulocyte subset is probably the result of a gene transcription failure,[23] whereas the HNA-2null (HNA-2-negative) phenotype is presumably caused by a translation failure due to incorrect splicing resulting in mRNA strands containing intron sequences with stop codons.[24]

Like HNA-1null individuals, individuals with the HNA-2null, i.e. HNA-2-negative, phenotype can form isoantibodies against the CD177. Observations suggesting that "alloantibodies" formed by HNA-2-positive individuals recognizing a CD177 polymorphism, i.e. a single epitope on the CD177 glycoprotein, have not been confirmed. HNA-2-isoantibodies can cause long-lasting neonatal immune neutropenia, prolonged neutropenia after stem cell transplantation, as well as TRALI.[25,26,27] The triggering of TRALI by HNA-2- isoantibodies could be demonstrated in an *ex vivo* rat lung model.[28] Long-lasting neonatal immune neutropenia is probably the result of the isoantibodies binding not only to mature but also to immature granulopoietic cells. This would also explain the failure of G-CSF administration to raise neutrophil counts in neonatal immune neutropenia attributable to HNA-2 isoantibodies.[29] Binding of the isoantibodies to myeloid precursors, as well as HNA-2 upregulation following G-CSF administration (see below), may have contributed to the repeatedly reported prolonged neutropenia in patients with HNA-2 antibodies after stem cell transplantation.[26,30] Like the FcγRIIIb, the CD177 glycoprotein can bind to drugs generating neoantigens, which can trigger formation of drug-dependent autoantibodies.[31]

The gene encoding CD177 /HNA-2 is located on chromosome 19q13.31 and consists of 9 exons. The *CD177 cDNA* has 1614 base pairs coding for an open reading frame of 437 amino acids, of which 416 residues form an NH2-terminal extracellular protein.[21] *CD177 mRNA* overexpression was found in patients with myeloproliferative disorders, especially polycythemia vera, and in patients with essential thrombocythemia who are at risk of thromboembolic complications, so that it can function as a biomarker for these diseases.[32,33] In patients with myeloproliferative disorders, *CD177 mRNA* overexpression is secondary to a gain-of-function mutation in the JAK2 (V617F).[34] A significant upregulation of the HNA-2 expression was observed in patients with severe bacterial infections and in stem cell donors after treatment with G-CSF, indicating a possible role of the complex in the acute neutrophil response to an infection.[32] Functionally, CD177 acts as a counter-receptor for the platelet endothelial cell adhesion molecule 1 (PECAM-1, CD31) suggesting a role in neutrophil transmigration from the blood vessels into the surrounding tissue.[35] Recently, it was demonstrated that CD177 co-localizes with membrane Proteinase 3 and that its membrane expression is affected by presence of CD177.[36] Proteinase 3 was shown to contribute to transendothelial migration of HNA-2-positive neutrophils[37] by re-establishing vascular integrity after neutrophil transmigration.[38] Proteinase 3 is also known as the target of the antineutrophil cytoplasmatic antibodies (ANCA) and it was reported that the CD177/Proteinase-3

Table 4. Molecular basis of the *FCGR3B alleles* and HNA antigens in comparison with FcγRIIIa. *Numbering according to Ravetch and Perussia.[10]

	Nucleotide position*					
Gene/Allele	141	147	227	266	277	349
*FCGR3B*01*	AG**G**	CT**C**	A**A**C	G**C**T	**G**AC	**G**TC
*FCGR3B*02*	AG**C**	CT**T**	A**G**C	G**C**T	**A**AC	**A**TC
*FCGR3B*03*	AG**C**	CT**T**	A**G**C	G**A**T	**A**AC	**A**TC
FCGR3A	AG**G**	CT**C**	A**G**C	G**C**T	**G**AC	**A**TC
	Amino acid position					
Protein/Antigen	36	38	65	78	82	106
HNA-1a	Arg	Leu	Asn	Ala	Asp	Val
HNA-1b; **HNA-1d**	Ser	Leu	Ser	**Ala**	**Asn**	Ile
HNA-1c	Ser	Leu	Ser	Asp	Asn	Ile
FcγRIIIa	Arg	Leu	Ser	Ala	Asp	Ile

*Shaded areas indicate amino acid substitutions considered to be responsible for antigen polymorphism. Bold type indicates amino acid substitutions considered to be responsible for generation of anti-HNA-1d antibodies by HNA-1c -positive individuals who do not have the FCGR3B*02 allele.*

complex interacts with Mac-1 (CD11b/CD18) in lipid rafts, forming a signaling complex that possibly mediates neutrophil activation by ANCA.[39]

HNA-3

The biallelic HNA-3 antigen group (HNA-3a and -3b) is not granulocyte-specific, as HNA-3 antibodies bind also to lymphocytes, platelets and several tissues, including the inner ear.[40] Approximately 95% of Europeans are HNA-3a-positive; 36% are typed positive for HNA-3b.[41] Recently, the HNA-3 antigen group could be localized on the choline transporter-like protein 2 (CTL2), a glycoprotein that passes ten times through the plasma membrane resulting in 5 extracellular and 6 intracellular loops and with intracellular N- and C-termini.[42,43] Despite its name, the exact function of CTL2 is unknown. The HNA-3 epitopes are located on the first extracellular loop and are the result of a non-synonymous single nucleotide polymorphism leading to an amino acid exchange of Arg154 (HNA-3a) to Gln154 (HNA-3b).[42] However, the tertiary structure, i.e. a specific conformation, is critical for antibody binding.[44]

The gene *SLC44A2* encoding the CTL-2 glycoprotein is located on the long arm of chromsome 19q13.1. and consists of 22 exons. Due to alternative splicing, cells can generate either a shorter or a 6-nucleotide longer transcript variant so that CTL2 exists in two isoforms. Human peripheral blood cells express only the shorter variant, also called P1 or TV2.[45] Since the amino acid differences are close to the intracellular N-terminus, it is assumed that they do not affect antibody binding. In each population tested so far, the *SLC44A2*01* allele encoding HNA-3a is more frequent than the *SLC44A2*02* allele coding for HNA-3b. Additional genetic variation of the *SLC44A2* gene has been reported, but alloimmunization against the corresponding polymorphisms has not been observed.

HNA-3a alloantibodies are of major clinical relevance as they have been frequently associated with severe and fatal TRALI.[46] According to the varying frequencies of HNA-3a-negative individuals in different populations, East Asians (Chinese, Japanese) have the highest risk for alloimmunization (6%-19% HNA-3a-negative), Europeans (Whites) should have a medium risk (4%-5%), and Black Africans and Afro-Americans should be at no risk (near absence of HNA-3a-negative).[47,48] TRALI triggering could be shown in an *ex vivo* rabbit lung model as well as in a mouse model.[49,50] Interestingly, TRALI due to the antithetical anti-HNA-3b antibodies has not been oberved so far and, in addition, could not be shown in the mouse model.[50] *In vitro*, HNA-3a antibodies strongly agglutinate neutrophils that might correspond to the neutrophil aggregates described in autopsies of fatal TRALI reactions.[51] Upon activation, the primed neutrophils release reactive oxygen species (ROS) and cytokines leading to leakage of the lung capillaries and the characteristic lung edema. Furthermore, binding of HNA-3a antibodies directly to the endothelium of the lung capillaries may support the detrimental effect.[50] In contrast to TRALI, febrile transfusion reactions and neonatal immune neutropenia have been observed only occasionally.[51,52]

HNA-4

The biallelic HNA-4 group (HNA-4a and -4b) has been localized on the α_M (CD11b) subunit of the leukocyte α_M β_2 integrin (Mac-1, CD11/CD18, CR3).[53] Antibodies defining the HNA-4b antigen are currently undergoing confirmatory testing by reference laboratories. HNA-4a discriminates from its antithetical HNA-4b by an Arg61His exchange which is caused by a single nucleotidem polymorphism in the *ITGAM* (integrin αM) gene on chromosome 16p11.2.[53,54] In most populations tested so far, the frequency of the *ITGAM*01* allele coding for HNA-4a is over 88% whereas only approximately 20% of Europeans bear the *ITGAM*02* allele encoding HNA-4b, and in the Chinese and Japanese populations the *ITGAM*02* allele seems to be very rare. The leukocyte adhesion molecule CD11b/CD18 is expressed on neutrophils, monocytes and natural killer cells. Whether its function is influenced by the HNA-4 polymorphism is unknown. It is interesting that the α_M β_2 integrin, which expresses the HNA-4 polymorphism, can interact with the GPI-linked CD177 (HNA-2) or with the GPI-linked FcγRIIIb (HNA-1 group), and thus form potential signaling complexes.

Neonatal immune neutropenia due to HNA-4a antibodies has been described.[54] Interestingly, these alloantibodies interfere with CD11b/CD18-dependent leukocyte adhesion. In rare cases, the CD11b/CD18 complex is the target of granulocyte autoantibodies that can induce autoimmune neutropenia.[55]

HNA-5a

The original serum "OND" originated from a patient with aplastic anemia and who, therefore, received long-term platelet transfusions. This serum contained at least three different antibodies, one directed against the HNA-5a antigen.[56] This epitope is located on the α_L (CD11a) chain of the $\alpha_L\beta_2$ integrin (LFA-1, CD11a/CD18) complex, which is encoded by the *ITGAL* (integrin αL) gene on chromosome 16p11.2.[53] HNA-5a is the result of a single nucleotide polymorphism in the *ITGAL* gene resulting in an Arg766Thr exchange.[53] In Europeans, HNA-5a (like HNA-4a) is a frequent antigen (expressed in 90%), whereas the antigen is seen more often (98%) in East Asians and less often (78%) in Black Africans. Antibodies directed against the antithetical HNA-5b antigen have not yet been reported.

The CD11a/CD18 complex is expressed on neutrophils, B and T lymphocytes and monocytes. Maternal HNA-5a alloantibodies can elicit immune neutropenia in the neonate.[57] Interestingly, the patient of the original serum showed a notably prolonged survival of an HLA mismatched skin graft indicating that the HNA-5a antibodies possibly interfered with leukocyte interaction, resulting in a delayed graft rejection.

Summary

The human neutrophil antigens (HNA) are defined by granulocyte alloantibodies mainly formed by women who became alloimmunized during pregnancy. The HNA rep-

resent polymorphisms of glycoproteins, except for HNA-2, as HNA-2-negative individuals do not express this glycoprotein at all (HNA-2null phenotype). Only two of the five HNA groups (the GPI-linked HNA-1 and HNA-2) are restricted to neutrophils and cannot be found on other blood cells. The polymorphic glycoproteins, as well as the polymorphisms themselves, can also be targets of granulocyte autoantibodies. Allo- and autoantibodies can cause a number of different forms of immune neutropenias as well as transfusion reactions. Physicians should be aware of these diseases to avoid unnecessary diagnostic procedures and to initiate the right treatment early in patients who are neutropenic due to neutrophil allo- and autoantibodies.

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