Lec 04
Blood Groups

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Introduction

- Red cell membranes have **antigens** (protein / glycoprotein) on their external **surfaces**. The antigens can be **integral proteins** where polymorphisms lie in the variation of **amino acid** sequence (e.g., rhesus [Rh], Kell), **glycoproteins** or **glycolipids** (e.g., ABO).

- These antigens are
  - **unique** to the individual
  - **recognized** as foreign if **transfused** into another individual
  - promote **agglutination** of red cells if combine with **antibody**
  - more than **30** such antigen systems discovered → complex
• **Presence** or **absence** of these antigens is used to classify blood groups
• **Major** blood groups – ABO & Rh
• **Minor** blood groups – Kell, Kidd, Duffy etc
• One of the most complex of all RBC blood group systems with more than **50 different Rh antigens**.
• The term “blood group” refers to the entire blood group system comprising red blood cell **antigens** whose specificity is controlled by a series of **genes** which can be **allelic** or **linked** very closely on the same chromosome.

• “Blood type” refers to a specific pattern of **reaction** to testing **antisera** within a given system.

• At present, **33** blood group systems representing over **300 antigens** are listed by the International Society of Blood Transfusion.

• Most of them have been **cloned** and **sequenced**. The genes of these blood group systems are **autosomal**, except **XG** and **XK** which are **X-borne**, and **MIC2** which is present on both **X and Y** chromosomes.
<table>
<thead>
<tr>
<th>Name</th>
<th>Symbol</th>
<th>Number of antigens</th>
<th>Gene name</th>
<th>Chromosome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABO</td>
<td>ABO</td>
<td>4</td>
<td>ABO</td>
<td>9</td>
</tr>
<tr>
<td>MNS</td>
<td>MNS</td>
<td>43</td>
<td>GYP A, GYP B, GYP E</td>
<td>4</td>
</tr>
<tr>
<td>P</td>
<td>P1</td>
<td>1</td>
<td>P1</td>
<td>22</td>
</tr>
<tr>
<td>Rhesus</td>
<td>Rh</td>
<td>49</td>
<td>RhD, RhCE</td>
<td>1</td>
</tr>
<tr>
<td>Lutheran</td>
<td>LU</td>
<td>20</td>
<td>LU</td>
<td>19</td>
</tr>
<tr>
<td>Kell</td>
<td>KEL</td>
<td>25</td>
<td>KEL</td>
<td>7</td>
</tr>
<tr>
<td>Lewis</td>
<td>LE</td>
<td>6</td>
<td>FUT3</td>
<td>19</td>
</tr>
<tr>
<td>Duffy</td>
<td>FY</td>
<td>6</td>
<td>FY</td>
<td>1</td>
</tr>
<tr>
<td>Kidd</td>
<td>Jk</td>
<td>3</td>
<td>SLC14A1</td>
<td>18</td>
</tr>
</tbody>
</table>
BLOOD GROUPING SYSTEM.

- **Major blood group system** – based on Agglutinogens on cell membrane, present widely & causes **severe** transfusion reaction
  - ABO
  - Rh system
- **Minor blood group system** – based on Agglutinogens but present in few populations & causes **mild transfusion reaction**
  - MNS
  - P
- **Familial blood group system** – found in few families KELL. DUFFY, LUTHERAN, BOMBAY LEWIS, DEIGO, KIDD
Blood groups on the RBC

- Lutheran
- Knops
- Kell
- Lutheran
- Gerbich
- Diego
- ABO
- Ii
- Rh
- Indian
- Cromer
- LW
- Duffy
- MNS
- Yt
ABO Blood Groups

- Most **well known** & **clinically** important blood group system.
- Discovered by Karl Landsteiner in 1901
- He discovered major blood groups such as O, A, and B types, compatibility testing, and subsequent transfusion practices. He was awarded Noble Prize in **1930**
- It is the **ONLY** system that the **reciprocal antibodies** are consistently and predictably present in the **sera** of people who have had no exposure to human red cells
- ABO blood group consist of
  - two antigens (A & B) on the surface of the RBCs
  - two antibodies in the plasma (anti-A & anti-B)
ABO system

- ABO remains the most important in **transfusion** and **transplantation** since any person above the age of 6 **months** possess clinically significant anti-A and/or anti-B antibodies in their serum.

- Blood group **A** contains **antibody** against blood group **B** in serum and vice-versa, while blood group **O** contains no A/B antigen but both their antibodies in serum.

<table>
<thead>
<tr>
<th>Antigens on RBCs</th>
<th>Antibody in plasma / serum</th>
<th>Blood group</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Anti-B</td>
<td>A</td>
</tr>
<tr>
<td>B</td>
<td>Anti-A</td>
<td>B</td>
</tr>
<tr>
<td>AB</td>
<td>None</td>
<td>AB</td>
</tr>
<tr>
<td>None</td>
<td>Anti-A, Anti-B</td>
<td>O</td>
</tr>
</tbody>
</table>
Development at birth

- All the ABH antigens develop as early as day 37 of fetal life but do not increase very much in strength during gestational period.

- Red cell of newborn carry 25-50% of number of antigenic sites present on adult RBC.

- Although cord red cells can be ABO grouped, the reactions may be a little weaker than expected.

- A or B antigen expression fully developed at 2-4 yrs of age and remain constant throughout life.
Expression of ABO Antigens

- Although the ABO blood group antigens are regarded as RBC antigens, they are actually expressed on a wide variety of human tissues and are present on most epithelial and endothelial cells.

- ABH antigens are not only found in humans, but also in various organisms such as bacteria, plants, and animals.
**ABO and H Antigen Genetics**

- Genes at **three** separate **loci** control the occurrence and location of ABO antigens.
- The presence or absence of the A, B, and H antigens is controlled by the H and ABO genes.
- The presence or absence of the ABH antigens on the **red blood cell** membrane is controlled by the **H gene**.

![Diagram of red blood cell antigens](image)
ABO Antigen Genetics

• *H* gene – *H* and *h* alleles (h is an *amorph*)

• *ABO* genes – A, B and O alleles
H Antigen

• The $H$ gene codes for an enzyme that adds the sugar **fucose** to the terminal sugar of a **precursor substance** (PS)

• The precursor substance (proteins and lipids) is formed on an **oligosaccharide chain**
H antigen

- The H antigen is the foundation upon which A and B antigens are built
- A and B genes code for enzymes that add a sugar to the H antigen
  - Immunodominant sugars are present at the terminal ends of the chains and confer the ABO antigen specificity
A and B Antigen

• The “A” gene codes for an enzyme (transferase) that adds **N-acetylgalactosamaine** to the terminal sugar of the H antigen
  • N-acetylgalactosaminyltransferase

• The “B” gene codes for an enzyme that adds **D-galactose** to the terminal sugar of the H antigen
  • D-galactosyltransferase
Formation of the A antigen

Formation of the B antigen

- Glucose
- Galactose
- N-acetylglucosamine
- Galactose
- Fucose

- Glucose
- Galactose
- N-acetylglucosamine
- Galactose
- Fucose

- Glucose
- Galactose
- N-acetylglucosamine
- N-acetylgalactosamine

- Glucose
- Galactose
- N-acetylglucosamine
- N-acetylgalactosamine

- Glucose
- Galactose
- N-acetylglucosamine
- N-acetylgalactosamine

- Glucose
- Galactose
- N-acetylglucosamine
- N-acetylgalactosamine
Anti-A and anti-B antibodies

- **Not present in the newborn**, appear in the first years of life (4-6 months), reach adult level at 5-10 years of age, decreases in elderly
- Naturally occurring as they **do not need any antigenic stimulus**
- However, some **food & environmental antigens** (bacterial, viral or plant antigens) are similar enough to A and B glycoprotein antigens and **may** stimulate **antibody development**
- Usually **IgM**, which are **not able** to pass through the **placenta** to the fetal blood circulation
### ABO Antigens & Corresponding Antibodies

<table>
<thead>
<tr>
<th>Red Blood Cell Type</th>
<th>Group A</th>
<th>Group B</th>
<th>Group AB</th>
<th>Group O</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Antigens Present</strong></td>
<td>A antigen</td>
<td>B antigen</td>
<td>A and B antigens</td>
<td>None</td>
</tr>
<tr>
<td><strong>Antibodies Present</strong></td>
<td>Anti-B</td>
<td>Anti-A</td>
<td>None</td>
<td>Anti-A and Anti-B</td>
</tr>
</tbody>
</table>

Legend:
- **A** antigen
- **B** antigen
- **AB** antigens
- **O** antigens
The Rh(D) Antigen

- Rh is the most complex system, with over 50 antigens.
- The complexity of the Rh blood group Ags is due to the highly polymorphic genes that encode them.
- Discovered in 1940 after work on Rhesus monkeys.
- The 2nd most important after ABO in the crossmatch test.
- The genes that control the system are autosomal codominant located on the short arm of chromosome 1.
**Rh blood group antigens are proteins**

- The antigens of the Rh blood group are proteins (12 transmembrane).
- The RhD gene encodes the D antigen, which is a large protein on the red blood cell membrane, & the most important.
Rh Antigen Frequency

- D antigen – 85%
- d antigen (or no D) – 15%
- C antigen – 70%
- c antigen – 80%
- E antigen – 30%
- e antigen – 98%

The presence or absence of D Ag determines if the person is Rh+ or Rh-
MNS antigen system

- MNS antigen system, first described by Landsteiner and Levine in 1927 is based on two genes: Glycophorin A and Glycophorin B. The blood group is under control of an autosomal locus on chromosome 4 and also under control of a pair of co-dominant alleles LM and LN. Anti-M and anti-N antibodies are usually IgM types and rarely, associated with transfusion reactions.

![Diagram of MNS system]

- M & N only differ in their amino acid sequence at positions 1 and 5
- S & s only differ in their amino acid sequence at position 29
Lutheran system

• Lutheran system comprised of **four pairs of allelic antigens** representing **single amino acid** substitution in the Lutheran glycoprotein at **chromosome 19**. Antibodies against this blood group are **rare** and generally not considered clinically significant.
Kell system

• These erythrocyte antigens are the third most potent immunogenic antigen after ABO and Rh system, and are defined by an immune antibody, anti-K. It was first noticed in the serum of Mrs. Kellacher. She reacted to the erythrocytes of her newborn infant resulting in hemolytic reactions. Since then 25 Kell antigens have been discovered. Anti-K antibody causes severe hemolytic disease of the fetus and newborn (HDFN) and haemolytic transfusion reactions (HTR).
Duffy system

- Duffy-antigen was first isolated in a patient called Duffy who had haemophilia. It is also known as Fy glycoprotein and is present in the surface of RBCs. It is a nonspecific receptor for several chemokines and acts as a receptor for human malarial parasite, *Plasmodium vivax*. Antigens Fya and Fyb on the Duffy glycoprotein can result in four possible phenotypes, namely Fy(a+b−), Fy(a+b+), Fy(a−b+), and Fy(a−b−). The antibodies are IgG subtypes and can cause HTR.
Kidd system

- Kidd antigen (known as $Jk$ antigen) is a **glycoprotein**, present on the membrane of RBCs and acts as a **urea transporter** in RBCs and **renal endothelial cells**. Kidd antibodies are **rare** but can cause severe **transfusion reactions**. These antigens are defined by reactions to an antibody designated as **anti-$Jk^a$**, discovered in the serum of **Mrs. Kidd** who delivered a baby with HDFN. $Jk^a$ was the first antigen to be discovered by Kidd blood group system, subsequently, two other antigens $Jk^b$ and $Jk^3$ were found.

- Located Chromosome 18

- Glycoprotein with 10 membrane spanning domains