Immunological (side) effects to blood transfusions

Anne Husebekk
Professor, UiT

040612
Disposition

- Compatible blood components?
  - Donor
  - Product
    - Focus on platelets as immune cells
  - Patients
- Immune related complications to blood transfusion
  - Haemolytic transfusion reactions
  - Transfusion induced acute lung injury (TRALI)
  - Transfusion associated graft versus host disease (TA-GVHD)
  - Immunomodulation
  - Allergic reactions
  - Febrile non-haemolytic transfusion reactions
- Summary
Blood components
1. Beside from transfusions between monozygotic twins, all transfusions are incompatible.
2. We crossmatch for ABO.
3. We take into consideration the most immunogenic antigens:
   1. RhD
   2. c, Kell
   3. HLA class I
   4. HPA 1a, 5b
What is the risk of immune complications to transfusion of blood components?

1. Donor related factors
2. Product related factors
3. Patient related factors
Donor related factors

- HLA constitution of donor
- HLA class I antibodies
- Amount of anti-A and anti-B
- Other blood cell antigens
Product related factors
Platelets and the immune continuum
John W. Semple, Joseph E. Italiano, Jr & John Freedman
Nature Reviews Immunology 11, 264-274 (April 2011)
Platelets and innate immunity

Human platelets alone  Platelets with *E. coli*  Platelets with *S. aureus*
Platelets have several types of TLR in the surface
Platelets as active immune cells

Platelets activate neutrophil granulocytes

Activated platelets produce cytokines and chemokines and promote neutrophil activation.

Platelet-expressed selectins promote neutrophil tethering.

Damage to the endothelium facilitates neutrophil activation.

Platelet-Neutrophil Interaction:
- CD154 (CD40L) on platelets interacts with CD40 on neutrophils.
- Cytokines and chemokines are released, promoting neutrophil activation.
- Selectins on platelets interact with selectin ligands on neutrophils, facilitating adherence.
- Fibrin deposition and damaged endothelium contribute to the activation process.

Neutrophil Activation Pathways:
- Selectins and selectin ligands play a crucial role in neutrophil tethering and activation.
- Cytokines and chemokines secreted by activated platelets attract and activate neutrophils.

Diagram illustrates the interaction between platelets and neutrophils, highlighting key molecules and pathways involved in neutrophil activation.
Semin Immunopathol

**Intercellular Adhesion, Signaling**
- Monocyte
- Soluble agonists
- PSGL-1
- P-selectin
- Activated Platelet

**Nuclear Signaling, Transcriptional Regulation**
- mRNA
- Analysis of transcriptome by microarray, PCR, and RNA-seq

**Post-transcriptional Regulation, Translation and Expression of Key Proteins**
- MCP-1, IL-8, TNF-α, MIP-1, MMP-9, UPAR, IL-1β, COX-2
- Polysome analysis, proteomics, detection of specific proteins, functional assays

Semin Immunopathol
Platelet and adaptive immunity

(a) Cell-cell interactions
- Activated Platelets
- Platelet-neutrophil
- Platelet-monocyte
- Platelet-lymphocyte

(b) Immature dendritic cell
- Activated Platelets
- B-lymphocyte
- T-lymphocyte
- Mature dendritic cell
Platelets induce DC maturation

Activated platelets promote DC activation, which increases antigen presentation to T cells

T cell

Activation of adaptive immune responses

Nature Reviews | Immunology
Stimulated platelets make CD40 L (membrane bound and secreted) inducing strong interactions with immune cells

a

- Thrombin, ADP, collagen, TXA2, other endogenous agonists; bacteria, toxins
- Activation of circulating, quiescent platelets
- Activation of integrin $\alpha_{II}\beta_3$, binding of fibrinogen
- Platelet-platelet aggregation
- Surface display of P-selectin
- Display and release of CD4OL
- Secretion of PMPs, chemokines, cytokines
- Signal-dependent translation; synthetic responses
Platelets inhibit Treg recruitment

- Platelets inhibit T_{reg} cell recruitment
- Platelets activate endothelial cells and promote inflammation
- TGFB from T_{reg} cells promotes anti-inflammatory responses that stabilize the thrombus
- Increased thrombus stability
- Reduced thrombus fragility
- Increased thrombus size
- Increased thrombus fragility

Smooth muscle cells

Nature Reviews Immunology
Summary

• Platelets have no nucleus, but an advanced system for signal induced protein synthesis based on mRNA from the megacaryocytes.

• Platelets have a variety of surface receptors making them interact with a variety of cells both in hemostasis, the innate and adaptive immune response.

• The activities of the platelets are both beneficial and detrimental in hemostasis and the immune response.
Patient related factors

- Immunocompetence
- Earlier sensitisation
- HLA class II constitution
- The presence of inflammation
Haemolytic transfusion reactions

- Intravascular acute haemolytic transfusion reaction – passive transfer of anti-A and anti-B of IgM class

- Delayed haemolytic transfusion reaction (active immunization, antibodies of IgG class)
  - 0.007% after 1 transfusion
  - 10% after 10 transfusions
  - 30% after 100 transfusions
TRALI

- Number one cause of transfusion related death in Europe and US
- Definition: New acute lung injury that develops within 6 hr after receiving any blood transfusion
- Pathophysiology:
  1. Inflammation in patients
  2. Blood product transfused containing anti-HLA class I and/or anti-neutrophil antibodies antibodies and/or bioactive lipids
  3. Neutrophil accumulation must take place
  4. Platelets seems to have a role
TA-GVHD

- Immunocompetent recipient:
  - Homozygous donor, haploidentical with the donor

- Immunodeficient recipient:
  - Vital T cell in the transfused blood, non-functioning T-cells in recipient

Donor T cells are activated and destroy recipient cells:
- Gut
- Liver
- Skin
Immunomodulation

- **T cells can be**
  - Activated (TA-GVHD, Graft versus tumor cells?)
  - Destroyed by donor alloreactive T cells (normal)
  - Tolerized (microchimerism)
## Blood transfusion and cancer

<table>
<thead>
<tr>
<th>Tumor site</th>
<th>Significant association (no. of studies)</th>
<th>No significant association (no. of studies)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colorectal</td>
<td>5</td>
<td>13</td>
</tr>
<tr>
<td>Head and neck</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Breast</td>
<td>3</td>
<td>7</td>
</tr>
<tr>
<td>Stomach</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Lung</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Cervix</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Prostate</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>
Blood transfusion and infections

- Blood transfusions seem to suppress the innate immune response and to skew the immune response in Th2 direction.

- This has shown to influence the infection rate in patients who have been transfused perioperatively.

- The effect seems to be related to leukocytes in the transfused products; the same tendency cannot be found when filtered products are used.
Blood transfusion and decreased survival after cardiac surgery

- 3 RCTs comparing non-filtered versus WBC reduced/filtered blood products

- 60 days death risk decreased from 7.8% to 3.5% with WBC reduction
Allergic reactions

Pathophysiology:
- Passive transfer of IgE to allergens in recipient
- IgG anti-IgA

Symptoms
- Urticaria and chills
- Anaphylactic reactions

Treatment
- Anti-histamins/corticosteroids/adrenalin
- In case of IgA deficiency: use IgA deficient donor or wash the blood product extensively
- Fever less than 2ºC increment
- Symptoms caused by WBC lysis (direct alloreactivity by donor alloreactive T-cells) and release of cytokines
Summary

1. Transfusion of blood components induce immune responses
2. The consequences of the immune responses are related to donor, product and recipient factor
3. Serious transfusion adverse event can be explained by immunological mechanisms:
   - TRALI
   - Haemolytic transfusion reactions
   - TA-GVHD
   - Allergic reaction
   - Immunomodulation
4. Immune competent platelets may enhance immune reactions