Abstract

Fifteen to forty percent of intensive care infants have Neonatal Alloimmune Thrombocytopenia (NAIT). This disorder may result in intracranial hemorrhaging, potentially causing death. NAIT is commonly associated with depletion of fetal platelets due to maternal antibodies against a specific glycoprotein located on the platelet cell surface. Glycoprotein IIb/IIIa has a region known as HPA1, which has a specific dimorphism linked to NAIT. If the mother’s platelet has a proline residue in position 33 (HPA1b), and the baby has leucine at this same position (HPA1a), the mother will mount an immune response against the baby’s platelets, as she sees them as foreign. Maternal B cells produce antibodies anti-HPA1a. The antibodies bind to the platelets and these antibody-coated platelets are then marked for destruction, leading to clotting disorder. Interestingly, mother responders are characterized by the expression of class II HLA DRB3*0101 (also known as DRw52a with other nomenclature) on the surface of Antigen Presenting Cells. Class II HLA molecules play an important role in the initiation of the immune response presenting antigenic peptides and stimulating helper T cells. This high HLA association may suggest that the B cells require T cell help. Thus, under the hypothesis that the same dimorphism may control both the B cell target and constitute the HLA-bound peptide, T cells specific for the HPA1 antigen have been identified, supporting the existence of a HLA II/HPA1a complex. Here we present the crystal structure of HLA DRB3*0101 in complex with HPA1a antigen, whose exploration may provide insights as to the understanding of this and other allele-associated diseases.

Neonatal Alloimmune Thrombocytopenia

- Neonatal Alloimmune Thrombocytopenia (NAIT) is a disease where an infant has a lower than normal amount of platelets in his/her blood.
- Platelets are necessary for blood clotting.
- 10% of cases are considered severe: There are less than 50,000 platelets per microliter of blood.
- 60% of infants diagnosed with NAIT are firstborns.

Symptoms

- Tiny red spots on the skin called purpura or petechiae
- Hemorrhaging

Key

- Platelets: Activates blood clotting
- B-cell: Makes antibodies
- Activated by Antigen Presenting Cell (APC), produces interleukines to rev up immune response and B-cell antibody production
- T-cell: Activated by Antigen Presenting Cell (APC), shows the foreign antigen to the T-cell
- APC: Antigen Presenting Cell (APC) shows the foreign antigen to the T-cell
- Macrophage: Destroys foreign antigens

5. The mother’s T-cells are activated and promote B-cells proliferation
6. Antibody production increases
7. The mother’s antibodies enter the baby’s blood
8. The antibodies stick to the baby’s platelets
9. The baby’s macrophages destroy the baby’s platelets
1. Baby’s platelets enter mother’s blood
2. Mother identifies the baby’s platelets as foreign
3. The mother’s B-cells make antibodies against an antigen of the baby’s platelets
4. The Antigen Presenting Cell (APC) presents the same antigen recognized by the B cell to the maternal T-cells

HLA DRB3*0101/HPA1a complex

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