When Amino Acids Don’t Get Along: Neonatal Alloimmune Thrombocytopenia

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Abstract

Platelets, also called thrombocytes, are required to control bleeding. Alloimmune thrombocytopenia is a disease that results when an individual makes antibodies that bind to proteins on another individual’s platelets. Neonatal Alloimmune Thrombocytopenia (NATP) occurs when a mother makes antibodies that bind to her baby’s platelets. In this disease, the mother’s antibodies on the fetal platelets can cause them to be cleared by the immune system or prevent them from working properly, resulting in severe bruising and hemorrhaging. Once the antibodies are gone, the baby’s platelets will then function properly and initiate clotting. The baby is in danger when the antibodies are present at or before birth because of the possibility of intracranial bleeding can lead to severe brain damage.

A major target for antibodies in NATP is the glycoprotein IIb-IIIa (GPIIb-IIIa), which is made up of two subunits, GPIIb and GPIIIa, and is expressed only on platelets. NATP most commonly occurs when a mother has the amino acid proline (Pro or P) and her baby has a leucine (Leu or L) at position 33 of the GPIIIa subunit.

Scientists have struggled for years to solve the structure of the region within the GPIIIa subunit that contains the L33 polymorphism. They have recently determined that it folds into a structure called a PSI domain. We have built a model of the PSI domain of GPIIIa, which possesses a leucine at position 33. The ability to visualize the structure adopted by the PSI domain of GPIIIa will hopefully enable scientists to use their knowledge of that structure to find successful treatments for NATP.

3D Structure of the GPIIa PSI Domain

The Molecule as Associated with the Disease

The PSI domain of the GPIIIa subunit of GPIIb-IIIa can adopt two different structures. One structure occurs when there is a proline at position 33 and the other occurs when there is a leucine at that position. Antibodies can recognize the structural difference, causing platelets to be cleared by the immune system, but this recognition occurs in only one direction. For example, in NATP, if a mother (♀) has only prolines and the father (♂) donates a proline to the fetus, there will be no problem. The shape of the molecule will be the same in the mother and fetus. Therefore, the mother’s immune system will accept it. However, if a mother has only prolines and the father donates a leucine to the fetus, the fetus will have a proline-leucine dimorphism. The platelets in the fetus may not be able to survive, as the mother may make antibodies against the leucine-containing forms of GPIIIa, causing the fetal platelets to be cleared or inactivated.

Statistics:

- 100,000 platelets/mL of blood
- 80,000 GPIIb-IIIa receptors per platelet
- Proline/leucine &- proline/proline = could result in disease if father donates
- Proline/leucine &- leucine/leucine &- proline/proline = could result in disease if other conditions are present in the mother
- Leucine has a 15% frequency, proline has a 85% frequency

Conclusion

For many decades, scientists had sought the structure of the region within the platelet glycoprotein GPIIb-IIIa responsible for NATP. With the new discovery of the PSI domain structure of GPIIIa, scientists can now design drugs that could impair the antibody’s ability to attack foreign platelets, thereby reducing the negative side effects of NATP. Our model also helped clarify some structural ideas that had been previously unexplained. In one instance, our mentors observed that the leucine on the bottom kink turned inward instead of outward, an observation unclear in the 2-D models on the computer. To model something that was so new to the scientific community was a truly inspiring experience and we hope that scientists will be able to use our model to better understand the structural translation of the disease Neonatal Alloimmune Thrombocytopenia.

The Disease

Neonatal Alloimmune Thrombocytopenia occurs with a frequency of 1 in 5000 to 1 in 1200 live births. An infant is diagnosed with NATP if it has less than 100,000 platelets per microliter of blood. In about 10% of the cases the disease is classified as severe, in which there are less than 50,000 platelets per microliter of blood. About 60% of infants with NATP are firstborns. Symptoms that the affected infants may suffer include:

- Petechiae, purpura, or overt bleeding at birth
- Central nervous system hemorrhage
- Intrauterine hemorrhages characterized by severe neurologic sequelae, preeclampsia, and optic hypoplasia

To treat an infant with NATP requires increasing its platelet count. In severe cases, a platelet transfusion is needed. These platelets can come from various sources:

- The mother’s platelets that, by a saline solution, are washed free of antibody-containing plasma
- Mother’s siblings’ platelets
- Regional blood centers

To prevent birth trauma in subsequent pregnancies, the mother should have a Cesarean section. Furthermore, on the day before delivery, maternal platelets can be obtained to transfuse to the neonate.

Bibliography