The αVβ3 Integrin Molecule

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Abstract

The αVβ3 integrin molecule consists of several domains. Only three domains were built: the propeller domain from chain A, the βA, and deadbolt domain fibrinogen. These three domains are significant due to their roles in activating the molecule, binding to ligands to initiate clotting.

What happens when something goes wrong?

- Platelets are unable to aggregate due to a lack of integrins or defects within them because the portion of the integrin that binds with coagulants is associated with a variety of disorders, including Glanzmann’s Thrombasthenia and other clotting disorders. The Drs. Newman were interested in learning more about the structure and function of αVβ3 in hopes that such information could lead to more effective treatments dealing with generating and dissolving blood clots. This could provide relief for millions of heart attack victims each year.

The Integrin Model

- The αVβ3 integrin molecule contains several domains. Only three domains were built: the propeller domain from chain A, the βA, and deadbolt domain fibrinogen. These three domains are significant due to their roles in activating the molecule, binding to ligands to initiate clotting.

What are the available treatments?

- At the moment, treating these clotting diseases involves complex and often uncomfortable procedures, due to the complex nature of the problem.

Propeller Domain

- Contains Two Ligand Binding Sites
  - 3rd Propeller “Blade”
  - Between 2nd and 3rd Propeller “Blades”
- Has a very peculiar structure with seven α-helices around a β-sheet
- Has a “MIDAS” site
- Has a binding site for fibrinogen and drugs that affect clotting
- Site for fibrinogen bound to the clotting drugs
- The propeller’s action one cannot easily look at the roles of the other domains as well.

Deadbolt

- This domain is associated with fibrinogen and drugs that affect clotting.
- Highlighted in green are the sidechains that bind to the propeller, the βA domain, and the deadbolt. The magenta sidechains connect to the deadbolt domain fibrinogen.
- The deadbolt is supposedly the key to activating the integrin molecule. If this domain holds the βA and propeller domain close to the “leg” of the molecule, then once the “leg” is separated from inside the platelets the deadbolt would release the two domains, thus activating them.

Conclusion

- A model of the molecule is useful for seeing three dimensionally how integrin interacts with the platelets, the fibrinogen, and how the domains interact with each other. Going forward, more knowledge about integrin structure could lead to more effective treatments dealing with either generating or destroying blood clots.

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