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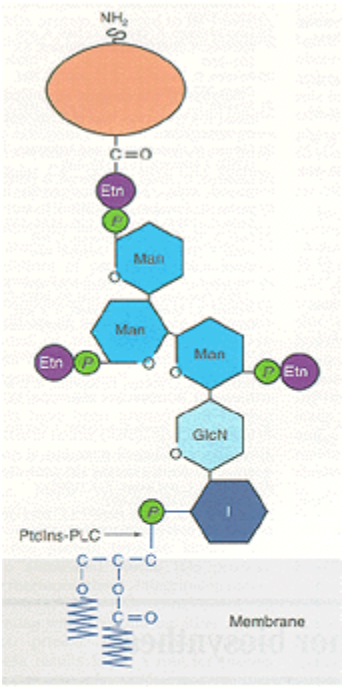
Paroxysmal nocturnal hemoglobinuria



A glycosylphosphatidylinositol (GPI) anchor - people with paroxysmal nocturnal hemoglobinuria (PNH) have a mutation in the first enzyme in the GPI anchor synthesis pathway. [Reproduced with permission from Takeda, J. and Kinoshita, T. (1995) Trends Biochem. Sci. 20, 367-371.]

The distinct and rather peculiar characteristics of paroxysmal nocturnal hemoglobinuria (PNH) have puzzled hematologists for more than a century. PNH is characterized by a decreased number of red blood cells (anemia), and the presence of blood in the urine (hemoglobinuria) and plasma (hemoglobinemia), which is evident after sleeping. PNH is associated with a high risk of major thrombotic events, most commonly thrombosis of large intra-abdominal veins. Most patients who die of their disease die of thrombosis.

PNH blood cells are deficient in an enzyme known as PIG-A, which is required for the biosynthesis of cellular anchors. Proteins that are partly on the outside of cells are often attached to the cell membrane by a glycosylphosphatidylinositol (GPI) anchor, and PIG-A is required for the synthesis of a key anchor component. If PIG-A is defective, surface proteins that protect the cell from destructive components in the blood (complement) are not anchored and therefore absent, so the blood cells are broken down.

The PIG-A gene is found on the X chromosome. Although not an inherited disease, PNH is a genetic disorder, known as an acquired genetic disorder. The affected blood cell clone passes the altered PIG-A to all its descendants—red cells, leukocytes (including lymphocytes), and platelets. The proportion of abnormal red blood cells in the blood determines the severity of the disease.

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