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Mechanisms of Paroxysmal Nocturnal Hemoglobinuria clonal expansion

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Paroxysmal Nocturnal Hemoglobinuria (PNH) is a rare, acquired clonal disease of bone marrow stem-cells, genetically characterized by the somatic mutation of the phosphatidylinositol glycan class A (PIG-A) gene. That leads to defective synthesis of glycosylphosphatidylinositol (GPI) responsible for anchorage and fixation of surface proteins like complement decay-accelerating factor (DAF/CD55) and membrane inhibitor of reactive lysis (MIRL/CD59). These proteins protect red blood cells from lysis by activated complement, leading to intravascular hemolysis.

Despite basis hemolysis in PNH is already explained, mechanisms promoting expansion of the PNH clone have yet to be elucidated. PIG-A mutation is essential, but not sufficient, to cause PNH: rare PIG-A mutations have been found in a very small proportion in healthy individuals. It seems that clonal dominance in PNH occurs due to an intrinsic growth advantage and/or to a imune escape ability of PIG-A mutant cells. PNH clones with multiple mutations are present at substantially higher frequencies than those of clones with only mutations in PIG-A. Decrease of PNH clone expression can also occur concomitantely with spontaneous remission of the disease in 15% of the cases.

The aim of this project is to discover mechanisms of clonal expansion and remission that may be useful in revealing the possible mechanisms of proliferation of PNH clones and developing therapeutic strategies for PNH.

Keywords: Paroxysmal nocturnal hemoglobinuria; PIG-A gene; clonal expansion