

Complement and inflammasome overactivation mediates paroxysmal nocturnal hemoglobinuria with autoinflammation.

Yoshiko Murakami, Taroh Kinoshita and their research group report the mechanistic basis of atypical paroxysmal nocturnal hemoglobinuria (PNH) caused by germline mutation plus somatic loss of *PIGT* gene on chromosome 20q, termed PIGT-PNH. PIGT-PNH is characterized by relapsing autoinflammatory symptoms as well as hemolysis. Anti-C5 eculizumab prevented hemolysis and autoinflammation. Because PIGT is required for transfer of synthesized glycosylphosphatidylinositol (GPI) to proteins, *PIGT*-defective PNH cells lost GPI-anchored complement regulators similar to *PIGA*-defective PNH cells but also expressed non-protein-linked free GPIs on the cell surface, which does not occur in *PIGA*-defective cells. Blood leukocytes from a PIGT-PNH patient secreted much higher levels of IL-1 β than those from PNH patients after stimulation with inflammasome activators. Studies with *PIGT*-knockout and *PIGA*-knockout THP-1 cells demonstrated that complement activation is enhanced on *PIGT*-knockout cells and higher levels of IL-1 β was secreted dependent upon C5b-9 membrane attack complexes. These results suggest a causal role of high free GPIs in increased generation of C5b-9 complexes and IL-1 β secretion. Furthermore, a region containing maternally imprinted genes implicated in clonal expansion in 20q- myeloproliferative syndromes was somatically lost together with normal copy of *PIGT*. Therefore, the mechanism of clonal expansion in PIGT-PNH seems different from that in PNH.

