The Control of Complement Activation by the Blood Cells in Paroxysmal Nocturnal Hemoglobinuria

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Since the classic studies of Ham and Dingle, it has been known that the red blood cells of patients with paroxysmal nocturnal hemoglobinuria (PNH) are unusually susceptible to the hemolytic action of complement. There are two major types of abnormal cells in this syndrome: the PNH II red blood cells are moderately sensitive to the lytic action of complement (three to six times more sensitive than normal red blood cells), and the PNH III red blood cells are markedly sensitive to complement (15 to 25 times more sensitive than normal cells). The platelets and granulocytes are also more sensitive although the degree of abnormality is less well defined than for red cells.

The reason for this unusual susceptibility has remained elusive. The increased lysis could not be attributed to increased binding of antibody or to increased activation of any of the first three components. It has been demonstrated that when complement is activated on the surface of both varieties of abnormal red cells, platelets, and granulocytes, an abnormally large amount of C3 is deposited on the membrane. For red cells, this component is deposited primarily on the glycoproteins of the membrane, and although these may be abnormal, they do not provide an acceptor surface that attracts activated C3b abnormally.

The activation of complement on the surface of red blood cells is regulated by a series of reactions that tend to inactivate the complexes formed by that activation. One such inactivation reaction is due to the presence of a glycoprotein, decay-accelerating factor (DAF), on the surface of the red cell which either prevents the formation of the C3 convertase complexes (C4b2a and C3bBb) or facilitates their disassembly. Recently, it has been shown that DAF is absent on both PNH II and PNH III red cells as well as platelets and granulocytes in PNH. This defect probably accounts for the increased binding of C3 since inhibition of the activity of DAF by antibody results in a marked increase in binding of C3 as is seen in PNH II and PNH III cells. The deficiency of DAF appears to be acquired during maturation of the red cells since it apparently is not deficient on the surface of early red cell precursors.

But does the deficiency in DAF fully explain the complement sensitivity of the abnormal PNH cells? The answer appears to be both yes and no. When normal red cells are treated with antibodies to DAF, they have the complement lysis sensitivity of PNH II cells (a three- to fivefold increase in sensitivity). When DAF is added back into the membrane of PNH II cells, they are no longer susceptible to the lytic action of complement when activated by acidification of serum. Thus, the deficiency in DAF appears to account fully for the increased susceptibility of PNH II cells to lysis by complement.

PNH III cells appear to bear a second defect. Normal red cells appear to be able to modulate the fixation or insertion of the terminal lytic complex of complement consisting of C5b-9. This appears to be lacking in the markedly abnormal PNH III cells since they readily fix more terminal complexes, particularly when complement is activated in fluid phase (reactive lysis). These complexes are also more effective in lysing these abnormal cells. The defect is not directly related to the deficiency of DAF since both PNH II and PNH III cells lack DAF, but only PNH III cells have this defect.

This latter defect in regulation of the effectiveness of the terminal complex is probably the more important in causing the hemolysis observed in PNH. The life span of PNH II cells measured by diisopropyl fluorophosphate (DFP) is only somewhat shorter than that of normal cells, whereas the life span of the more abnormal PNH III red cells is markedly shortened. Patients with only PNH II cells have little clinical hemolysis. Since PNH III cells are susceptible to lysis by reactive lysis reactions and PNH II cells are not, it is likely that the majority of lysis that is observed clinically is due to activation of complement in the fluid phase or at sites external to the red cell; these reactions can generate C5b-7, which is able to bind more readily to PNH III than to PNH II or normal red cells, but this increased binding is not related to the deficiency of DAF on these cells. Further, the platelets in PNH appear to have the DAF defect but not the terminal complex defect; they appear to have a normal life span both as measured by C3 and by II. Thus, the deficiency of DAF appears to have relatively little effect on the survival of the affected blood cells.

What is the defect in PNH? The answer is that there is no single defect. In addition to the abnormalities outlined before that relate to the activation of complement, the abnormal cells are also known to be deficient in acetylcholinesterase. Glycophorin a, the major glycoprotein of the red cell's surface, is also abnormal. Thus, the defects that result in the unusual susceptibility to complement are part of a constellation of membrane abnormalities that are probably the result of marrow injury and dyserythropoiesis. How they are interrelated will be the subject of considerable research.

REFERENCES

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