Lymph node biopsy from a patient with EBV+ LBCL. The cells are pleomorphic including the presence of Hodgkin-like cells. Inset, the neoplastic B cells are positive for PAX5 (red nuclear stain) and strongly express PD-L1 (brown), which may inhibit the host antitumor response. Hematoxylin and eosin, original magnification ×250; inset, double immunostain for Pax5 (red) and PD-L1 (brown).
classical complement system component C3 undergoes a complex cascade of activation steps, generating multiple activation fragments (C3a, C3b, iC3b, C3dg, C3d, etc), each of which interacts with different receptors and has distinct functions. After the discovery of the complement receptors ~35 years ago, CR3 was considered essential for phagocytosis of iC3b opsonized immune complexes and pathogens, without interacting with C3dg. Nevertheless, recent studies have demonstrated that CR3 interacts with C3dg. Lin et al provide evidence for the pathophysiologic relevance of this interaction in the context of the PNH. In this disease, the red blood cells of patients lack 2 membrane-expressed complement regulators, CD55 and CD59, and hence are susceptible to complement-mediated lysis, leading to a life-threatening intravascular hemolysis. The approval for clinical use of the complement C5-blocking antibody eculizumab revolutionized the treatment of these patients, because it prevents complement-mediated intravascular hemolysis. It is noteworthy that eculizumab blocks only the late stages of the complement cascade, thus leading to an accumulation of C3d(g)-opsonized erythrocytes in the circulation of patients with PNH.

Lin et al investigate the role of C3dg opsonization for the phagocytosis of these cells. They confirm that C3dg can interact with the phagocytic receptor CR3 using purified proteins. Further, they demonstrate that this interaction can occur at the phagocytic synapse between patients’ erythrocytes and activated monocytes (see figure). The level of phagocytosis was linearly correlated with the level of C3d opsonization of patients’ purified erythrocytes. These results provide a hint to explain the residual hemolysis that occurs despite treatment with eculizumab in some PNH patients. Further studies are needed, however, to identify the proportion of cells that are lysed by the proposed mechanism in vivo. A recent study correlated the level of hemolysis in PNH patients with the level of free eculizumab present in the circulation. They found that the low levels of circulating eculizumab (measured at the moment before the next injection of the drug) correlated with a detectable complement activity, the presence of hemolysis, and a need for blood transfusion. Moreover, in this study, the level of C3d(g) on patients’ erythrocytes did not correlate with increased hemolysis or a need for blood transfusion. Analysis in 2 additional cohorts (where the level of free eculizumab was not measured) suggested that the opsonization of PNH erythrocytes by C3d(g) leads to extravascular clearance of these cells, and that this type of clearance may contribute to the low level of hemolysis and residual transfusion requirement observed in some patients on...
The expanding spectrum of EBV+ lymphomas

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