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Immune Evasion by B-cell Lymphoma

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Lymphoid malignancies such as lymphoma and leukemia are particularly problematic as the transformation of these cells compromises host defense, and often these tumors evolve mechanisms to evade or escape immune surveillance. Burkitt Lymphoma (BL) is a very aggressive form of non-Hodgkin's lymphoma and has the fastest doubling time among human tumors [1,2]. BL is primarily found in its endemic form which occurs in tropical climates, such as Papua New Guinea and equatorial Africa, having a > 95% degree of association with Epstein-Barr virus (EBV). A sporadic form of BL occurs elsewhere in the world and has only a 5-15% degree of association with EBV. A third form, HIV-associated BL, is associated with EBV in approximately 40% of cases [3]. In addition to its strong association with EBV, BL incidence in tropical climates very closely follows the distribution of malaria, with areas of endemic malaria having the highest incidence of BL [4]. Despite BL's strong associations with EBV and malaria, it has yet to be resolved how these factors may contribute, or even if they contribute, to the development of BL. Due to BL's rapid doubling time, aggressive chemotherapy is required to control its spread and growth [5]. Nearly 100% of BL and 5-8% of diffuse large B-cell lymphoma (DLBCL) harbor a balanced translocation involving c-MYC, which confers an adverse prognosis with chemoresistance and shortened survival. Currently used chemotherapy regimens are quite successful in children and adults, and survival rates exceeding 70% have been reported [6,7]. Unfortunately, these chemotherapy regimens are not as effective in elderly or immunocompromised patients. In addition to inferior responses, these patients are less able to tolerate the aggressive treatment and develop more severe treatment-associated toxicities [1,8,9]. Although the anti-CD20 monoclonal antibody rituximab has been successfully used in conjunction with chemotherapy, the efficacy of its use in immunocompromised patients has been a debated issue [10]. These issues highlight the shortcomings of current BL therapies and make the pursuit of alternative immunotherapies for BL a relevant and valid objective. Immunotherapies which can harness the host's immune system to more specifically target BL cells for clearance could prove invaluable in lessening or eliminating the need for toxic chemotherapies, as well as enhancing responses in all patient groups, most notably the elderly and immunocompromised. Treatment of BL is further complicated by the fact that BL possesses multiple defects which contribute to immune evasion. Studies have found an impaired capacity of the immune system to recognize this malignancy, stemming from defects in antigen (Ag) presentation by BL [11]. These defects offer potentially novel targets for immunotherapeutic treatment. Immunotherapies have generally focused on generating a $CD8^+$ T cell response, but sustained responses are often difficult to achieve. The poor response is compounded in BL due to a well known defect in HLA class I-mediated Ag presentation to $CD8^+$ T cells. This defect results from the poor immunogenicity of the Epstein-Barr virus nuclear Ag 1 (EBNA1), the sole EBV Ag synthesized in BL [3,12]. An internal glycine-alanine repeat in EBNA1 impairs its proteasomal processing which leads to the generation of weakly immunogenic peptides for presentation on HLA class I [13,14]. As a result, $CD8^+$ T cell responses to BL are weak and short-lived. This defect in $CD8^+$ T cell activation by BL has been well-characterized, but only addresses one aspect of the immune response. While the $CD8^+$ T cell response to BL has been very well characterized, the $CD4^+$ T cell response has received much less study. Although $CD8^+$ T cells are capable of directly killing target cells, $CD4^+$ T cell activation has been shown to be necessary for a sustained response [15,16]. Thus, the role of HLA class II-mediated Ag presentation in BL remains to be fully resolved and demands further investigation. BL cells, like normal B cells, express measurable amounts of HLA class II, as well as components of the class II pathway (Ii, CLIP, HLA-DM, and HLA-DO). However, study has revealed that BL are deficient in their ability to stimulate $CD4^+$ T cells through HLA class II-mediated Ag presentation [17]. Investigation has suggested the presence of a BL-associated inhibitory molecule (BLAIM) capable of impairing HLA class II-mediated Ag presentation and resultant $CD4^+$ T cell activation [11]. Due to the drawbacks of using aggressive chemotherapy for treating BL in elderly and immunocompromised patients, there is a need for exploration into the development of less toxic therapies which would enhance responses in these patients, while at the same time reducing treatment-associated toxicities. Immunotherapy represents an ideal area of investigation as it harnesses the patient's own immune system to target transformed cells, potentially lessening, or even eliminating, dependence on chemotherapy. As in the case of rituximab, immunotherapy may also be used in conjunction with chemotherapy to enhance patient responses. BL's defect in HLA class I-mediated Ag presentation results from the poor immunogenicity of the EBV Ag, EBNA1. As this is the lone EBV Ag synthesized in BL, no other options are available for HLA class I presentation. The class II defect, however, appears broader and results from expression of a BL-associated molecule, which impairs the presentation of Ag to $CD4^+$ T cells by HLA class II proteins. BLAIM thus represents a potentially novel target to consider for the development of immunotherapy for BL. Successful identification of BLAIM would allow for the development of mAbs which could be used to block the activity of BLAIM and restore class II-mediated Ag presentation. A sustained $CD4^+$ T cell response could then serve to augment development of immunotherapies aimed at generating $CD8^+$ T cell responses. Additionally, BLAIM itself could also be used to generate a more targeted $CD8^+$ T cell response, and to reduce bystander effects in non-malignant cells. A recent study also suggests a defect in BL, which is related to Ag presentation via the alternative or recycling pathway [18]. Alteration of trafficking molecules, such as the GTPase Rab, may affect MHC/peptide recycling

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and impair immune recognition of B-cell lymphomas [18]. Further characterization of the defects involving these molecules may be important in developing effective immunotherapies for lymphoid malignancies. When considering this evidence, two things become clear. First, it is necessary to pursue the development of improved therapies for BL which demonstrate lower levels of toxicities, especially for patients who are elderly or have compromised immunity. Secondly, further investigation into the numerous defects in Ag processing and presentation displayed by BL could yield novel therapies for BL, as well as other lymphoid malignancies.

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