CHAPTER 11

NASOPHARYNGEAL CARCINOMA
IMMUNOTHERAPY:
Current Strategies and Perspectives

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Abstract: Recent success in treating Epstein-Barr virus (EBV)-associated posttransplant lymphoproliferative disorder (PTLD) using cytotoxic T-cell (CTL) based immunotherapy has led to interest in the development of CTL-based immunotherapy to treat other EBV-associated malignancies, including Nasopharyngeal carcinoma (NPC). However unlike PTLD, which arises in immunosuppressed individuals following transplant, NPC can arise in immunocompetent individuals, expresses a limited array of EBV antigens that are poorly immunogenic, and appear to suppress the function of these T cells either directly or through the expansion of regulatory T cells. There is therefore a unique set of problems that need to be addressed in order to optimise CTL-therapy for the effective treatment of NPC.

INTRODUCTION

The primary function of CTL is to recognise and clear both intracellular pathogens and malignant cells.1,2 Following T-cell receptor engagement of a peptide-major histocompatibility (MHC) class I complex on the surface of an infected or malignant cells, CTL function by inducing lysis of the target cell via a number of molecular pathways.3 The potential development of CTL-based immunotherapy offers an attractive, low-toxicity alternative to the use of current therapies employed to treat a number of human malignancies, including NPC. The consistent detection of EBV in NPC offers a potential target for CTL-based therapeutic treatment of NPC.


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Following the control of primary lytic infection in B cells, EBV causes a persistent life-long latent infection, characterised by the expression of the EBV nuclear antigens (EBNA1-3) and the latent membrane proteins (LMP 1 and 2). It is now evident that latent infection is controlled by a population of CTL that recognise epitopes derived from these antigens. Furthermore, dysfunction in this CTL population, either through immunosuppression, which can lead to PTLD in transplant patients following immunosuppressive therapy, or via loss of function, which appears evident in EBV-associated Hodgkin’s lymphoma (HL) and NPC, can result in the uncontrolled growth of EBV-transformed malignant cells. Conversely, augmentation of the CTL response against the latent antigens offers a potential therapy to treat EBV-associated malignancies. CTL-based therapy has thus far been successfully employed to treat PTLD and a number of strategies are currently being investigated as an alternative treatment for NPC, particularly for the treatment of patients who are unresponsive to current therapies.

IMMUNOLOGICAL TARGETS IN NPC

NPC cells do not express the full array of latent antigens, as typically occurs in PTLD. Together with EBV-associated HL, NPC represents a Type II latency malignancy, whereby antigen expression is limited to LMP 1 and 2 and EBNA1. Therefore immunotherapeutic approaches employed to treat EBV-associated NPC are dependent upon the capacity to generate an immunological response against these antigens, which play a significant role in EBV latency and have evolved to evade immune recognition.

LMP 1 and 2 play a role in activating and transforming cells following infection, allowing proliferation and survival of latently infected cells. The LMP antigens are thus oncogenic by nature. Furthermore, the LMP antigens, particularly LMP1, are poorly immunogenic, likely due to poor antigen processing in infected cells and the subsequent limited amount of antigen available for presentation by MHC class I molecules. As a consequence, the LMP antigens, particularly LMP1, generate a subdominant CTL response when compared to the responses generated against lytic cycle antigens and other latent antigens, such as EBNA3. Evasion of the immune response and the subsequent minimalisation of the LMP-specific CTL response may play some role in the capacity of LMP1 and 2 bearing malignancies to occur. Accordingly, amplification of the LMP-specific CTL response offers an obvious choice when developing an immunotherapeutic treatment for NPC.

In contrast to the LMP antigens, which are not detectable in all EBV-associated malignancies, EBNA1 can be detected in all EBV-associated malignancies. EBNA1 has been shown to be highly stable and contains a glycine-alanine repeat sequence near its N-terminus that inhibit translation and subsequent self-replication. Consequently, EBNA1 is processed poorly via the MHC class I pathway. However, since the discovery of EBNA1-specific CD8+ CTL, which were thought to be induced via cross-presentation by professional antigen presentation cells rather than via direct recognition of infected cells, it has been clearly established that endogenously processed EBNA1 can be detected by CD8+ T cells. This has lead to the realisation that in addition to the LMP proteins, EBNA1 may be a viable target for CTL-based immunotherapy of NPC.