



Versatile effects of epigenetic reprogramming in immune restoration and tumor therapy

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Local immune environment is a crucial factor that regulates the progression of tumor and efficacy of immunotherapy. The immune microenvironment differs from one individual to another, with T cell-infiltrated, inflamed tissues identified as “hot” tumor, non-infiltrated and non-inflamed tissues as “cold” tumor, and a broad spectrum of intermediate stage between them (1). The immunogenicity of a tumor to trigger antigen presentation is the initial step of an effective anti-tumor response and immune microenvironment formation. Recent studies focusing on host intrinsic factors have identified multiple mechanisms that affect tumor immunogenicity, including genetic antigen presentation machinery defects in tumor. Generating immune response is a direct effect of virus infection. However, to what extent virus infection affects immunogenicity remains unclear yet.

Viral infection has long been recognized as determinant factors in tumor formation and progression. The Epstein Barr virus (EBV), the first described onco-virus, contributes to the development of a variety of lympho-proliferative disorders, including B-cell lymphoma. EBV infection may lead to expression of virus related antigens EBNA, LMP, and LP in cancer cells, which constitutes an important aspect of tumor immunogenicity and promotes further tumor elimination by antigen specific T cells. Still, the prognosis and the responsiveness to immunotherapy in EBV⁺ B-cell lymphoma patients are quite different. This might have been due to the heterogeneous immune microenvironment derived by different latency patterns

of EBV infection. EBV⁺ B-cell lymphoma shows three different latency patterns according to the immunogenicity. Latency I tumors hardly express virus antigens except the less immunogenic Epstein-Barr nuclear antigen (EBNA1), EBV-encoded small RNAs, and some microRNAs, so that the host immune system can be easily blinded. In contrast, latency III tumors express all EBV encoded latent nuclear antigens (EBNA1, EBNA2, EBNA3A-C, and LP) and latent membrane proteins (LMP1, LMP2A, and LMP2B), so that they can often be eliminated by the host immune response. Latency II is intermediate stage with modest immunogenicity between latency I and III. However, how EBV infection shapes distinct tumor microenvironment formation in different individuals with B-cell lymphoma is yet undefined. Identification of the approach to regulate the immunogenicity of EBV⁺ B-cell lymphoma, and to transform latency I tumor into latency III tumor is important for the clinical treatment for patients with B-cell lymphoma.

A brief article published in *Blood* reported that epigenetic reprogramming was a potential switch of EBV related tumor immunogenicity (2). Utilizing a high-throughput screen, the author identified a series of small molecules that could induce the expression of latency III viral genes in EBV⁺ B-cell lymphoma. Among them, a DNA methylation inhibitor decitabine was the most potent. The induction of latency III antigen LMP1 and EBNA3 by decitabine was independent of hypomethylating agent-induced cell

death and was uncouple with lytic viral replication. Of note, the induction occurred at low doses and persisted after removal of decitabine. Mechanistically, decitabine induced hypomethylation at key viral promoters and promoted virus antigen expression, which finally sensitized tumors to T-cell-mediated lysis. Most importantly, in an adopted EBV-CTL transfer xenograft mouse model, decitabine pretreatment reshaped local immune environment, resulting in T-cell homing and further tumor inhibition *in vivo*.

Epigenetic dysregulation represents an important tumorigenic mechanism. Tumor cells often express methyltransferase with high level of methylation modification on promoters of multiple genes. In addition to manipulating tumor hallmarks directly, methylation modification might also exert essential roles in regulating local immune status. An effective antitumor T cell response is dominated by multiple layers of complicated factors, many of which are usually disturbed in tumors. Fortunately, recent studies leveraging pre-clinical models point out that epigenetic reprogramming may help rescue T cell response in several aspects. First, the methylation status of genes in tumor cells controls the expression of tumor antigens, which account for the initial priming of T cells. DNA hypomethylation in melanoma and esophageal carcinoma up-regulates tumor antigen expression and enhances tumor recognition by T cells (3,4). Second, it has been proved that EZH2-mediated histone modifications and DNA methyltransferase 1 (DNMT)-mediated DNA methylation limits T_H1-type chemokines CXCL9 and CXCL10 expression, and thus blocks the infiltration of T cells and favors immunosuppressive microenvironment formation. Abrogating methylation methyltransferase activities by inhibitors improves the therapeutic efficacy of PD-L1 blockade in ovarian cancer (5). Third, in addition to malignant cells, immune cell can be an important target for epigenetic reprogramming. Recent study focusing on the epigenetic modulation of T cell lineages shows that post-effector *de novo* DNA methylation programming accompanies memory CD8⁺ T cell exhaustion. The highly methylated status of gene loci concerning T cell proliferation, differentiation and functions accounts for the intrinsic failure of anti-tumor T cell response in primary tumor and immunotherapy conditions. Application of DNA demethylating agents promotes the rejuvenation of effector T cells in tumors and augments the efficacy of PD-L1 antibody treatment (6). Fourth, epigenetic modulation controls tumor intrinsic type I interferon production, which has been proved to enhance antigen presenting process and

maintain T cell functions. Endogenous retrovirus (ERV) in human genome may transcribe and fold into a secondary dsRNA structure, which activates MDA5/MAVS/IRF7 pathway and promotes type I interferon production. The activation of ERV is often restricted by DNA methylation on cytosine residues at regulatory elements as a systemic immune homeostasis mechanism. Removal of the aberrant DNA methylation by agents such as 5-azacitidine and decitabine inhibits tumor growth by reactivation of silenced tumor suppressor programs and potentially synergizes with immune checkpoint therapies (7). Thus, epigenetic reprogramming has been an emerging approach in tumor treatment. Although the mechanism by which epigenetic modulation regulates host immune status and related intervention have been clearly demonstrated in non-viral tumors, it's yet unclear whether and how epigenetic programming works in the context of virus related tumors. Virus infection often endows tumor cells with unique antigen characterization, and thus exerts a regulatory role in local immune microenvironment formation. Dalton and colleagues demonstrated that hypomethylating reagent decitabine could also interfere with the epigenetic modulation of EBV genome in virus related B-cell lymphoma. This led to the immunogenic EBV antigens LMP1, EBNA3A, and EBNA3C expression and a reversion from latency I to latency III in tumors in EBV⁺ B-cell lymphoma, which further resulted in T cell homing and inhibition of tumor growth in mouse xenograft model. It's possible that epigenetic reagents can also be applied in other virus related tumors such as HBV related hepatoma, EBV-related nasopharyngeal carcinoma, HPV-related cervical carcinoma and so on, to increase the expression of viral antigens and tumor immunogenicity despite the lack of evidence to date. This study provides a new angle in understanding the immuno-editing role of DNA demethylating agents in virus related tumors and indicates a promising therapeutic strategy combining epigenetic modulators and immune therapies.

Although immunotherapy has accomplished great success in tumor treatment, the response rate remains low with unclear cause. How to predict the clinical response, broaden its application and improve its efficacy has become a central theme in the field of cancer immunology and cancer therapy. Heterogeneity across the tumors, including cancer types, heritage background, and local immune composition, holds key to the efficacy of cancer therapy. In this article, the authors have made a good attempt to reveal the regulating mechanism of immune activation/silencing in

B-cell lymphoma in the angle of virus infection and raised a possible therapeutic regimen combining immunotherapy and epigenetic reprogramming. More studies collecting every facet of tumor characteristics and the underlying regulating mechanism are still in need to shed light on future tumor therapy.

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Footnote

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