PROPOSALS FOR THE STRATEGIES TO SUCCEED IN CANCER IMMUNOTHERAPY

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GENERAL INTRODUCTION:

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Species Used: Humans

Abbreviations: CCR, CC chemokine receptor; cDC, conventional CD8α+ dendritic cell;

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CTL, cytotoxic T lymphocyte; CXCR, CXC chemokine receptor; HEV, high endothelial venule; LN, lymph node; mDC, myeloid dendritic cell; pDC, plasmacytoid dendritic cell; pre, precursor; TAA, tumor-associated antigen; TCR, T cell receptor; Th, helper T lymphocyte; Tn, naïve T lymphocyte; Tnp, nonpolarized T lymphocyte; Treg, regulatory T lymphocyte.

Numerous clinical as well as preclinical trials for cancer immunotherapy have been conducted for the last several decades, but most of them showed very limited therapeutic potential, excepting a few. Those include adjuvant immunotherapy using microbial components, cell-therapy such as LAK/NK therapy, mini-transplantation, graft vs. leukemia (GVL) reaction and dendritic cell (DC)-based therapy, cytokine therapy such as high dose IL 2, interferons type I and II, and gene therapy expressing cytokines and tumor-associated antigens. In spite of the disappointment with most of the immunotherapy so far, there still exist great expectations for cancer immunotherapy. This is partly due to the reality that the most of cancers are still intractable with poor prognosis and poor quality of life despite development of sophisticated surgical treatment, chemotherapy and radiation therapy. Fortunately, in the last several years there was tremendous advancement of our basic knowledge in immunology, to which studies on chemokines and dendritic cells very much contributed. This is an excellent turning point to reconsider the strategy of cancer immunotherapy. FIGURE 1 (PLEASE SEE THE BEGINNING OF THIS ISSUE FOR THIS FIGURE IN COLOR) illustrates how tumors can be surveyed and regulated by immune system. It has become clear that immune system recognizes tumor-associated antigens (as Dr. Smyth and Dr. Sato et al. discuss in this issue), but unfortunately tumors have mechanisms to evade the immune system. This could be partly due to the production of immuno-suppressive cytokines such as IL 10 and TGF beta by Tr1/Th3/Treg and the loss of MHC-I expression by tumor cells which is critical to be recognized by CTL. In tumor-bearing state, we have recently confirmed that the number of CD4+CD25+CCR4+FoxP3+Treg is significantly increased in the draining lymph nodes of the tumor in mice (unpublished observation). But the main problem of the failure of strong immune response to naturally occurring tumor could be due to the induction of tolerance to self-antigens such as tumor-associated antigens by antigen-captured myeloid DCs migrating from the tumor site to the draining lymph nodes.

Therefore, there are very limited inflammatory and immune responses occurring at tumor sites. Whereas, administration of immuno-adjuvants including microbial
Figure 1: The strategy of cancer immunotherapy

Immunosurveillance for cancer: CCR, CC chemokine receptor; cDC, conventional CD8α+ dendritic cell; CTL, cytotoxic T lymphocyte; CXCR, CXC chemokine receptor; HEV, high endothelial venule; LN, lymph node; mDC, myeloid dendritic cell; pDC, plasmacytoid dendritic cell; pre, precursor; TAA, tumor-associated antigen; TCR, T cell receptor; Th, helper T lymphocyte; Tn, naïve T lymphocyte; Tnp, nonpolarized T lymphocyte; Treg, regulatory T lymphocyte. PLEASE SEE THE BEGINNING OF THIS ISSUE FOR THIS FIGURE IN COLOR (Copyright 2004 © By PJD Publications Ltd.).
components, CpG and cytokines into tumor sites (as we, Dr. Nishimura and Dr. Mukaida discuss), myeloid DCs (resident DCs in the tissue e.g. Langerhans cells as well as inflammation associated, infiltrated DCs) (Yoneyama et al., 2001) capture antigens and are highly activated to be mature CCR7+DCs to be rapidly recruited by a chemokine, SLC/CCL21 expressed on the endothelium of the afferent lymphatics into the draining lymph nodes to induce antigen specific Th1>Th2 response and CTL. Once, those Th and CTL (in other words, effector/memory cells) are induced, they leave the lymph nodes through efferent lymphatics, enter thoracic duct and circulation, and finally infiltrate into tumor to eradicate cancer cells. But in reality, it is rare to induce such effective CTL to eradicate cancer cells by adjuvant therapy. Inflammatory cells, including neutrophils and macrophages as well as cells involved in innate immunity such as NK, NKT and gamma delta T cells may also have an important role in controlling the outcome of cancer, but the contribution of these cells in cancer immunology is not yet well established and generally seems to be limited. To reach successful cancer immunotherapy, we do hope that our following recent observations help the advancement of cancer immunotherapy.

1) How to relieve the tumor-bearing host from immuno-suppression

Tumor cells as well as infiltrating leukocytes produce immuno-suppressive cytokines such as TGF beta and IL 10, which inhibit the effect of immunotherapy. Among leukocytes, regulatory T cells could be the major population to inhibit the proliferation of tumor specific Th1 and CTL by direct contact as well as through cytokine production. At this stage, there is no direct evidence to show the regulation of antigen specific T cell proliferation at the tumor site by Treg. Treg can definitely regulate immune response at the draining lymph nodes of the tumor. Since Treg, Th2, Tr1 and Th3, which probably contribute to the immuno-suppression in the tumor bearing hosts, commonly express a chemokine receptor CCR4, it would be quite interesting to inhibit the recruitment of these cells to the tissue or decrease the number of these cells by humanized antibody before immunotherapy. To do so, our recently generated humanized antibody against human CCR4, which very effectively depletes CCR4+cells in ADCC, is a very promising tool (Niwata et al., 2004).

2) DC-based vaccination

Dendritic cells (DCs) play a central role in initiating T cell immune responses, especially to initiate the primary immune response by presenting antigens to naïve T cells. Our previous study revealed that the F4/80B220CD11c+ DC precursors,
expressing CC chemokine receptor (CCR)1 and CCR5, rapidly appeared in the circulation and migrate into the liver of wild-type C57BL/6 (B6) mice by administering Propionibacterium acnes (P. acnes). Macrophage inflammatory protein (MIP)-1α that acts on CCR1 and CCR5 plays a critical role in recruiting these DC precursor cells into the Disse space of the liver where granuloma are formed. We have recently demonstrated that the interaction of MIP-1α and CCR5/CCR1 is responsible for the mobilization of DC precursor cells into the circulation in mice, and the MIP-1α mobilized B220CD11c+ myeloid DC precursor cells, when cultured with granulocyte/macrophage colony-stimulating factor (GM-CSF) and tumor necrosis factor α (mTNFα) and pulsed with B16 tumor lyzate could induce potent MHC-class I restricted, tumor specific anti-tumor immunity in vivo as well as CTL in vitro (Zhang et al., 2004). This study suggests that the administration of recombinant MIP-1α in humans may provide a way to get a large number of DC precursors from the patient’s blood, which is very useful in DC-based vaccination. Important issue to be clarified on DCs for effective DC-based vaccination is the functional and phenotypic heterogeneity of DCs. There are at least three distinct populations among DCs, which include myeloid DCs (CD11b+CD11c+B220- in mice), lymphoid (CD8α+CD11c+ in mice) and plasmacytoid DCs (B220+CD11c+ in mice). Although CD8α+DCs are now considered to be mature myeloid DCs which migrated from the peripheral tissues in response to inflammatory stimuli, we clearly showed that there are committed CD8α+Lin-progenitor cells which migrate into T cell area of lymphoid tissues and solely differentiate into CD8α+CD11c+DCs under homeostatic conditions and those cells can produce IL 12 by stimulation (Wang et al., 2002). Therefore, we believe these cells represent the so-called lymphoid DCs.

We have also recently established that B220+CD11c+cells, which also appear in the circulation in a large number during systemic inflammation, are plasmacytoid DC precursors (Yoneyama et al., 2004). These cells produce a large quantity of INF α, but lack APC function to naïve T lymphocytes. Very importantly, we observed that those plasmacytoid DC precursors very rapidly migrate into paracortex area of inflamed lymph nodes in a Mig/CXCL9- CXCR3 dependent manner, whereas myeloid DC precursors infiltrate into inflamed tissue to capture invading pathogens in a CCL3-CCR1/5 dependent manner and eventually migrate into the draining lymph nodes to stimulate CD8+ naïve T lymphocytes to convert to CTL. Plasmacytoid DCs can restore the virus-induced impairment of APC function of myeloid DCs in an HSV-infection model. Based on these findings, we propose that plasmacytoid DCs are helper DCs for myeloid DCs in antigen presentation. Therefore, the protocol of the
DC-based cancer vaccination should take into consideration cooperative interaction of myeloid and plasmacytoid DCs through distinct in vivo trafficking pathway, although we should await demonstration that tumor-associated dysfunction of myeloid DCs is also restored by plasmacytoid DCs.

References