Dendritic Cell Based Immunotherapy of Cancer with Cell Penetrating Domains

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Received: 18 October 2013 / Accepted: 3 December 2013 / Published online: 12 December 2013
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Immunotherapy has always been an attractive therapeutic modality for cancer compared with chemotherapy and radiotherapy due to its non-toxicity. An effective vaccine-based immunotherapy, also known as therapeutic cancer vaccine, may last a lifetime with negligible side-effects. Immune system has the ability to detect and eliminate tumor cells by generating tumor-specific killer Cytotoxic T Lymphocytes (CTLs) by a process called immune surveillance. However, tumor cells induce deleterious effects on the host immune system, which are more pronounced in advanced malignancy leading to inefficient generation of CTLs. The limited ability of cancer cells to mount an immune response coupled with

their propensity to evade immune detection tips the balance towards growth of tumor. In our lab, we have been working on various gene and protein-based approaches for cancer immunotherapy addressing the hurdles in the development of therapeutic cancer vaccine using Cell Penetrating Domains (CPDs), Dendritic Cells (DCs), and a Tumor Specific Antigen (TSA) called MAGE-A3.

DCs are professional Antigen Presenting Cells (APCs) which endocytose exogenous antigens (Ags) and play a central role in both initiating and modulating the immune response leading to stimulation of naive T cells. DCs evolve from hematopoietic bone marrow progenitor cells and embed in all peripheral tissues. Captured Ags are processed into peptides that bind to both HLA class I and class II molecules in the cytosol of the cell. DCs then migrate to lymph nodes where they interact with both CD8⁺ and CD4⁺ T cells to generate CTLs and Helper T Lymphocytes (HTLs), respectively, to shape the adaptive immune response. Cytosolic bioavailability of the tumor Ag is important in order to access HLA class I peptide with which it forms a complex to express on the cell surface and activate CTLs that lyse cancer cells. But since DCs captures Ag by a process called endocytosis, where Ag is retained in the endosomes, the Ag's access to cytosol is limited.

DC cell membrane is impermeable to hydrophilic substances and cytosolic entry of proteins requires delivery vehicle. Various natural and synthetic CPDs are capable of delivering therapeutic proteins into cellular compartments. MAGE-A3 is a tumor specific antigen, which belongs to a family of Cancer-Testes (CT) Ags. Although MAGE-A3 can generate tumor specific killer CTLs, its effectiveness is limited unless it can cross plasma membrane of DCs for cytosolic bioavailability to HLA class I molecules.

We sought to address the problem of inadequate cytoplasmic TSA expression by using synthetic CPD to create fusion protein, CPD-MAGE-A3, that penetrates through the plasma

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membrane. CPD (Tyr-Ala-Arg-Ala-Ala-Ala-Arg-Gln-Ala-Arg-Ala)-MAGE-A3 fusion protein efficiently entered the DC cytosol without altering DC cell surface markers. In addition, we found that DC transduction with CPD-MAGE-A3 did not alter functional activity of DCs. Thus, CPD-MAGE-A3 entry through plasma membrane into cytoplasm, a process often known as protein transduction, solves the problem of inefficient entry of MAGE-A3 into cytoplasm of DCs.

The recent success of DC vaccine therapy in complementing chemotherapy is illustrated by the first ever FDA approved, APC 8015 (Sipuleucel-T), for the treatment of prostate cancer, moves DC based vaccines from bench to bedside. GlaxoSmithKline Biologicals S.A. have undertaken MAGE-A3 protein-based tumor vaccine to treat non-small cell lung cancer patients and prevented tumor relapse.

Although the work has generated pre-clinical data, we are determined to establish infrastructure to accomplish the translation of this basic science research into translational research

in a systematic and coherent way leading to advanced clinical trials. For this purpose, we created surgical oncology and developmental therapeutics program essentially to use the sum of the data generated by the basic science enterprise to translate into clinical trials for a tangible public benefit. For clinical applications, we will essentially follow established eligibility criteria. Patients between the ages of 18 and 65 without any active uncontrolled infection, who are positive for MAGE-A3 expression, will be selected. Patients will sign a written informed consent and will be informed about the investigational nature of the study.

In conclusion, we cloned full length MAGE-A3 in the expression vector in frame with CPD and successfully demonstrated that the recombinant CPD-MAGE-A3 fusion proteins efficiently entered into cytosol of DCs without affecting the phenotype of the cells. We are in the process of generating CTLs to show tumor cell killing. We believe that this method will generate efficient tumor lysing CTLs and pave way for better therapeutic cancer vaccine generation.