

Dendritic cells in cancer immunotherapy from bench to clinic

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Generation of robust immunity against microbial infection and cancers require fine-tuned interaction between the components of innate and adaptive arms of immune system. Dendritic cells (DCs) are the central player of innate immune arm that bridge innate to adaptive immunity. These cells are effective at antigen uptake, killing, processing and presentation of the processed small and large peptides (MHC class-I and class-II proteins) to cytotoxic CD8⁺ and helper CD4⁺ T cells, respectively. Upon recognition of the presented peptides by T cells (signal 1) concomitant interaction of the costimulatory molecules CD80 and CD40 on DCs with their ligands CD28 and CD40L (signal 2) on T cells, DCs and T cells become activated. However, full activation and proliferation of DCs and T cells also require induction of inflammatory cytokines (signal 3) such as IL-1, IL-6, IL-12, IFN- α and TNF- α . Signal 3 is ultimately induced by the interaction of toll like receptors (TLRs) highly expressed on innate immune cells in particular DCs, with different natural or synthetic microbial products (TLR ligands). Due to the morphological features of DCs and extension of thousands of dendrites from their surface, these cells are several fold higher at uptaking, processing, and presenting foreign antigens than macrophages. They are also more capable of interaction with TLR ligands than other innate immune cells. As such, DCs are of paramount significance to generation of effector 1ry immunity upon encountering the 1st antigen exposure and then generation of resting memory cells capable of mounting robust 2nd immunity. DCs, however, are dysfunctional in the presence of cancer due to secretion of several toxic factors by cancer cells. Therefore, ex vivo generation of DCs either from hematopoietic cells or from monocytes is one potential alternative to restore the functions of

these cells and their role in bridging innate and

adaptive immunity. Upon their generation in vitro they are activated by TLR ligands and pulsed with the desired tumor antigens. Then, DCs are injected back to the same patient with the goal to activate endogenous tumor specific T cells. DCs can be pulsed with different forms of antigens, including peptides, proteins, tumor cell lysate, RNA or naked DNA. Both preclinical and clinical studies have demonstrated promising anti-tumor responses after treatment with DC-based vaccination against both hematological and solid tumors. To optimize its clinical applications, recent studies have been focusing on how to: 1) speed up the generation of these cells in vitro, 2) maximize their activation in vitro, 3) using allogenic DCs rather than personalized DCs, 4) their combination with other immunotherapy modalities and 5) how to induce their activation in vivo upon their adoptive transfer. In our own experience, we have been able to generate DCs from mouse and human and to induce their activation in vitro and in vivo with TLR3 ligand. We have also used them to vaccinate against pancreatic cancer and the results showed promising clinical responses with minimal toxicity. We do believe that DC-based vaccination can optimize the effective immunotherapy based on the use checkpoint inhibitors as well as CAR cells. Future studies are needed to address this hypothesis.

