Dendritic cells
in cancer immunotherapy

Aimin Jiang

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Dendritic cells at the interface of innate and adaptive immune responses
Dendritic cells: initiators of adaptive immune responses

Dendritic cell

MHC-II

TCR

Naive T cell

immunity

tolerance
DC cancer vaccine

A vaccine is a biological preparation that improves immunity to a particular disease. A vaccine typically contains a small amount of an agent that resembles a microorganism. The agent stimulates the body's immune system to recognize the agent as foreign, destroy it, and "remember" it, so that the immune system can more easily recognize and destroy any of these microorganisms that it later encounters.

It often contains an adjuvant that activate DCs.

Could be preventive (humoral) or therapeutic (cellular, cancer vaccine)
Why do we need cancer vaccine?

Immune responses against cancer cells were not strong enough.

Immune system can reject tumors!!!

Passive Immunotherapy: Transfer of T cells or antibodies
    ---- no memory T cells

Active immunotherapy: DC vaccine
    ------tumor-specific effector and memory T cells
Three approaches of DC-based cancer vaccine

Advantage: safe, some clinical responses, potential

Dendreon’s Provenge (DCs) was approved for prostate cancer treatment.
Dendritic Cells as Therapeutic Vaccines: Original Concept (circa 1992)

- **Goal**: Induce antitumor (or antiviral) immunity using autologous DC pulsed with tumor Ag

- **Methods**
  - Generate DC in vitro from circulating precursors
  - Load DC with Ag
  - Return DC to patients

Edgar Engleman
Dendritic Cell Based Vaccines in Cancer Treatment

Leukapheresis

DC Generation (GM-CSF, IL-4)

Tumor Antigen

DC Maturation (TNF, CD40-L)

Vaccination (Intratumoral)

Ag loading

Immune & Clinical Monitoring

Vaccination (systemic)

Antigen-Pulsed DC
Problems with Customized DC Vaccines

- Poor efficacy -- most tumor bearing patients do not respond
- Best tumor Ags, DC activation method, route of delivery all unknown
- Cost and complexity are high
A New Approach to Vaccination

1. Receptor-mediated antigen targeting to dendritic cells in peripheral lymphoid tissues.

2. Simultaneous maturation of the antigen-capturing dendritic cells.
DEC-205, a Homologue of the Macrophage Mannose Receptor, with 10 vs 8 External, Contiguous, C-type Lectin Domains

1. Available mAb to DEC-205
2. High expression by lymph node DCs of DEC-205
3. Rapid targeting of mAb to DCs in lymph nodes including distal tissues.
4. Access to MHC class I & II

DEC-205 on Dendritic Cells in the T Cell Areas of Mouse Lymph Nodes
Rapid, Efficient and Durable Targeting of αDEC-205 Antibodies to DCs, systemically, *in situ*

C57BL/6

10 µg αDEC-205:Alexa<sub>488</sub> or isotype control (s.c.)

30 minutes to 3 days

Harvest draining/distal nodes and spleen

Enrich for CD11c<sup>+</sup>

Evaluate:

- αDEC-205 targeting kinetics
- Subset targeting

Spleen

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<td>3 days</td>
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Targeting Dendritic Cells with $\alpha$-DEC-205:OVA Markedly Enhances Presentation to CD4$^+$ and CD8$^+$ T cells (CFSE-labeled) in vivo in the Steady State
A Single Vaccination with $\alpha$-DEC-205:OVA + $\alpha$-CD40 Induces CD8$^+$ T Cell Immunity of Greater Magnitude (and Duration) than Current “Gold Standards”
Vaccination with $\alpha$-DEC-205:OVA + $\alpha$-CD40, but not DC-OVA or OVA / CFA, Exerts a Therapeutic Effect on 7 Day Tumors
β-catenin signaling in determining DC function

β-catenin activation leads to DC maturation without the production of cytokines

β-catenin activation in DCs leads to CD4⁺ T cell tolerance in models of autoimmune disease.
Targeted deletion/activation of $\beta$-catenin in DCs

*Pathway inactivation:* $\beta$-cat$^{-/-}$ (CD11c-Cre $\beta$-cat$^{FL/FL}$)

*Pathway activation:* $\beta$-cat$^{\text{active}}$ (CD11c-Cre $\beta$-catExon3$^{FL/FL}$)
Whether tumors activate $\beta$-catenin in DCs?

Splenic DCs of tumor-bearing mice
β-catenin activation and tumor-bearing mice exhibited suppressed CD8 recall responses.
How activation of $\beta$-catenin in DCs affects anti-tumor CD8 T cell immunity?

αDEC-OVA (CpG) 3, 5, 8 days Naïve CFSE$^+$ OT1 3 days In vitro restimulation

3

68±12

5

77±17

8 (days)

26±1

WT

β-catenin$^{\text{active}}$

3

41±4

5

34±5

8

23±1

CFSE

IFN-γ
Tumor-mediated inhibition of cross-priming is $\beta$-catenin-dependent.

$\alpha$DEC-OVA (CpG) 3 days $\rightarrow$ Naïve CFSE$^+$ OT1 3 days $\rightarrow$ In vitro restimulation

![Flow cytometry plots](image)

WT  60±2  
WT-T  40±10  
$\beta$-catenin$^{-/-}$  86±5  
$\beta$-catenin$^{-/-}$ -T  84±9
Tumor-bearing β-catenin<sup>-/-</sup> mice exhibited normal CD8 memory responses when transferred into WT mice.
Blocking β-catenin reversed tumor-induced inhibition of cross-priming
β-catenin\textsuperscript{active} DCs exhibited increased FOXO3 expression and reduced NF-κB activation upon TLR signaling.