



DCs AS CANCER VACCINES . MATURE DCs AS A TOOL TO SUSTAIN MINIMAL RESIDUAL DISEASE STATUS IN MALIGNANCIES .

E. Ioannou¹, M. Chatziioannou¹, M. Toloudi¹, P. Apostolou¹, I. Papasotiriou¹

¹R.G.C.C. Ltd. (Research Genetic Cancer Centre Ltd.), 115 M. Alexandrou Str, 53070 Filotas, Florina, Greece

INTRODUCTION:

The successful treatment of malignant diseases by the enhancement of antitumor immunity has been a long-standing aim of immunological research. Since the discovery of dendritic cells (DCs), there have been an increasing number of studies conducted on these cells to understand their immunobiology and their role in the immune system. These studies demonstrated that tumor-specific cytotoxic T-lymphocytes can be activated by DC vaccines, and this property of DCs has enabled these cells to be the most suitable candidates for cancer immunotherapy.

A DC vaccine is defined as DCs loaded with antigen, such as a tumor associated antigen (TAA). Upon administration into patients, the vaccine is thought to induce an antigen-specific T-cell response against the tumor. Studies have confirmed that DC-based vaccines can successfully elicit antitumor immune responses and, in some cases, generate objective clinical responses.

The identification and molecular characterization of TAAs in the last 10-15 years has allowed the development of tumor-specific immunotherapy. Tumor antigen-derived peptides have the advantage that many peptides are commercially available. For example, c-MET is a well known tumor antigen, is deregulated in many types of human malignancies, including cancers of kidney, liver, stomach, breast, and brain.

MATERIALS AND METHODS:

Generation of DCs: First, the isolation of monocytes from patient's blood sample by negative selection takes place. Then these monocytes are cultured for the generation of DCs by using commercially available kits, such as the DC Generation Medium DXF (C-28052, PromoCell). The dendritic cell immunophenotype is characterized by flow cytometry analysis for CD80 and CD86.

Antigen loading of DCs: There is no standard protocol for antigen loading. For the ideal vaccine, DCs must stably present tumor-associated antigens (TAAs). This can be achieved with peptide-transfected DCs. Transfection of DCs can be managed by using commercial available kits, such as the PromoFectin-Polypeptide (PK-CT-2000-POL-96, PromoKine). The successful presentation of the peptide from the DCs is tested by flow cytometry analysis for the desired peptide.

Peptide selection: Peptides representing immunodominant epitopes of tumor antigens are the most common sources of antigen. Transfection of DCs with an 8-9 mer peptide is thought to be more effective because it helps skip the processing of the entire antigen from the DCs. In addition, the presentation of the TAAs from DCs is specialized, as they present only the desired epitope. The selection of the peptide can be made by using web based epitope databases, such as the Immune Epitope Database (IEDB). This peptide can be designed to selectively trigger T-, B- or both cell types immune responses.

Dosing and administration of DCs: The route of administration may be critical to the success of DC vaccination, although there is no consensus as to which route is most effective. Clinical trials have evaluated intranodal, intradermal, subcutaneous, intravenous and intratumoral administration; some of these studies used multiple routes of administration in sequential or comparative formats.

CONCLUSIONS:

Comparative studies with immature or mature DCs have shown that only mature DCs stimulate T-cell responses and enhance homing to draining lymph nodes, the sites where therapeutic T-cell responses must be initiated. Additional studies must be carried out to evaluate the most effective DC subtypes, the optimal conditioning and activation stimuli, the optimal route of administration and the optimal dose and frequency of DC vaccinations.

SELECTED REFERENCES:

- Turnis, M. E. and C. M. Rooney (2010). "Enhancement of dendritic cells as vaccines for cancer." *Immunotherapy* 2(6): 847-862.
- Figdor, C. G., I. J. de Vries, et al. (2004). "Dendritic cell immunotherapy: mapping the way." *Nat Med* 10(5): 475-480.
- Gilboa, E. (2007). "DC-based cancer vaccines." *J Clin Invest* 117(5): 1195-1203.

