

Dendritic cells in cancer immunotherapy — a short review

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Dendritic cells (DCs) are rare leukocytes that are uniquely potent in their recent application to therapeutic cancer vaccines. Isolated DCs loaded with tumour antigen ex vivo and administered as a cellular vaccine have been found to induce protective and therapeutic anti-tumour immunity. In the present report we describe the most common methods of culturing DCs and delivering tumour antigens and we summarise clinical trials of cancer immunotherapy using DCs-based vaccines.

key words: dendritic cells, tumour antigen, immunotherapy

INTRODUCTION

Dendritic cells are regarded as the most potent antigen-presenting cells [7]. They possess an extraordinary capacity to capture and process antigen and contain all that is needed to stimulate T cell immunity, including high levels of major histocompatibility complex, co-stimulatory and adhesion molecules [1]. These properties, coupled with the fact that it is now possible to generate large number of functional DCs *ex vivo*, have led to interest in the use of DCs-vaccines to induce anti-tumor immunity [1, 7]. The preparation of DC-vaccines consists of a 3-stage process: the generation of immature DCs from different cell populations using various stimulators, delivering the tumour antigens and, finally, the administration of vaccines to patients [4, 7].

PREPARATION OF DENDRITIC CELL-BASED VACCINES

Dendritic cells provide a variety of important features to generate an immune response, making them very attractive cells for the immunotherapy of cancer [2, 8]. A prerequisite for the use of DCs in therapy is the development of techniques to generate large numbers of DCs in culture. We can isolate DCs precursors from the blood by using density-based purification [4, 7]. Circulating immature

DC precursors represent less than 1% of the peripheral blood mononuclear cells (PBMC). There is the possibility of amplifying the circulating DCs by treatment donors with Flt3 ligand or GM-CSF [2, 7, 8]. A more effective approach is to culture DCs from either non-proliferating CD14⁺ monocytes or proliferating CD34⁺ precursor cells [2, 4, 7]. CD14⁺ monocytes can be differentiated into immature dendritic cells by culture with IL-4 and GM-CSF, whereas the protocols to produce DCs from CD34⁺ cells include additional cytokines, such as SCF, Flt3 and TNF- α [7, 8]. Another method of generating DCs is the use of calcium ionophore (CI), which induces a very rapid differentiation from CD34⁺ cells, CD14⁺ monocytes as well as CML-progenitor cells to mature DCs [7].

The next step in the preparation of DC-vaccines is to stimulate dendritic cells by tumour antigen. The loading of antigen to dendritic cells can be achieved by several approaches. Many studies have used synthetic peptides as antigens such as Mage-1, Mage-3, gp-100 and MUC-1 [2, 7]. The advantage of this approach is a well-defined antigen, which reduces the possibility of autoimmunity and cross-reactivity and facilitates *in vitro* and *in vivo* monitoring [7]. Due to the fact that only a few tumour-specific antigens have been identified, strategies using the whole antigen

array of the tumour cells have been explored: DCs can be fed tumour lysates or acid-eluted peptide mixtures [2, 7, 8]. Several studies have used apoptotic tumour cells as an antigen source [7]. The immunogenicity of DCs pulsed with apoptotic tumour cells can be improved by cytokines to improving the function of DCs (TNF- α , IL-1, IL-6 or CD40L) [7]. The role of necrotic cells as a source of antigen for DCs remains controversial. Some investigations have shown that necrotic cells are needed for complete maturation of DCs and therefore provide an obligatory signal to DCs internalising apoptotic tumour cells [7]. A different strategy for using the whole tumour cell is the use of DC-tumour hybrids, generated by electrofusion or polyethylene glycol (PEG) treatment [2, 4]. So far allogeneic and autologous DC-tumour hybrids have been used in clinical trials. A new method of delivering tumour antigens is to insert the genes encoding the tumour-associated antigen (TAA) into DCs [7]. As vectors the most commonly used are retroviral and adenoviral vectors, rarely pox viruses and herpes viruses [7]. In some instances cationic lipids and plasmid-coated gold particles serve as non-viral vectors [7]. Another possibility is to pulse dendritic cells with tumour-derived mRNA. In the human *in vitro* system, RNA-pulsed DCs were as effective in eliciting antigen-specific responses as peptide-pulsed DCs [7, 8].

Especially in haematological diseases such as CML and AML, several groups have used DCs arising from the malignant cells [2, 7, 8]. Since the pathological event occurs in the DC precursor, DCs generated *in vitro* or *in vivo* present the antigens of the tumour cells. It has been demonstrated that monocyte-derived DCs from CML-patients carry the characteristic Bcr-Abl antigens and generate CML-specific cytotoxic responses [7].

CLINICAL TRIALS OF DENDRITIC CELL VACCINATION

Many clinical DCs vaccination studies have been initiated or completed. These have focused mostly

on solid tumours, such as melanoma, breast, ovarian, renal and prostate cancers, because these tumour-associated antigens are far better defined than in other tumour types [3, 5, 6]. A series of clinical trials is beginning in haematological malignancies such as lymphoma, multiple myeloma and chronic and acute myelogenous leukemia, where DCs are cultured from the malignant cells [3, 5]. The recent therapy described includes glioma patients and gastrointestinal patients [3, 6]. These trials have nonetheless established the general safety and feasibility of this approach, in addition to demonstrating clinical anti-tumour activity [3, 5, 6]. These results have suggested a broad series of questions about manufacturing DCs on a large scale or using tumour antigens regardless of patient haplotype. These issues should be addressed in future trials.

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