Antitumoral immune response: NKT cell-mediated immunotherapy

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Introduction

Cancer is a group of related diseases characterized by an uncontrolled growth of cells beyond their limits that can happen in any tissue of the body. Cancer awareness has been increasing because of its high incidence, morbidity and mortality, being a key subject in research for new, more effective therapies. The immune system is able to fight against tumors with a process known as cancer immunosurveillance. In this aspect, natural killer T (NKT) cells have been proved useful to control tumor growth and are therefore being studied for potential new strategies. Two main subsets of NKT cells have been described, type I or vNKT cells and type II or iNKT cells, with opposing roles in mediating tumor immunity. The therapeutic studies focus on iNKT cell activity because they generally enhance tumor immunity, taking advantage of both direct and adjuvant iNKT cell activity. So far the results are preliminary but promising.

Aims

• Describe NKT cells and their general role in the immune system, characterizing the two main subtypes of NKT cells as well as the immunoregulatory axis in which they are involved.
• Explain the role of NKT cells in tumor immunity, focusing on key mechanisms by which NKT cells seem to mediate cell response against tumors.
• Describe the current state of the NKT cell-based immunotherapy and the main experimental procedures used in former studies.

Methodology

Search in Pubmed database and in official websites of the World Health Organization and Clinical Trials using the following keywords: NKT cells, NKT cell, tumor, immunotherapy. Original and review papers were selected according to their date of publication, quality and specific topic.

RESULTS

NKT cells are a heterogeneous subset of lymphocytes that express receptors present both in NK cells (NK1.1 and T cells (αβ TCR and CD3D). The TCR recognizes glycolipid antigens presented by CD1d, a class I-like MHC molecule.

Two subsets of NKT cells are defined according to heterogeneity of TCR rearrangements:

<table>
<thead>
<tr>
<th>Type I NKT cells</th>
<th>Type II NKT cells</th>
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<tbody>
<tr>
<td>Invariant TCR</td>
<td>Diverse TCR</td>
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<tr>
<td>Reactive with α-GalCer</td>
<td>Reactive with sulfatides</td>
</tr>
<tr>
<td>Enhance tumor immunity</td>
<td>Suppress tumor immunity</td>
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Functions in general immunity

They play an important intermediary role between innate and adaptive immunity, being able to respond quickly to stimuli with abundant production of cytokines (mainly TNF-α and IL-12) that influence the polarization of the adaptive response. Depending on the specific subset and nature of activation, they have immune enhancing or immunosuppressive roles. Type I and type II NKT cells have contrasting roles in most of the cases and cross-regulate each other.

Tolerance Autoimmunity Allergies Infections Tumor immunosurveillance

TLR-4

NKT cells produce TNF-α cytokines, mainly INF-γ, that contribute to dendritic cell maturation and activate downstream effector cells with cytotoxic activity (NK cells and CD8+ T cells).

Functions and characterization of NKT cells

NKT cells produce Th1 cytokines, mainly INF-γ, that contribute to dendritic cell maturation and activate downstream effector cells with cytotoxic activity (NK cells and CD8+ T cells) and cross-regulate each other.

INKT cells in tumor immunosurveillance

Mechanisms of action

INDIRECT CYTOTOXICITY

DIRECT CYTOTOXICITY

MODULATION OF THE TME

INKT cells produce perforin and granzyme and present partial expression of CD78 (Fasl) or CD253 (TRAIL), showing direct direct cytotoxicity against tumor cells expressing CD1d

INKT cells produce TNF-α and granzyme B, inducing the death of TNF-α sensitive cells, tumor cells and MDSCs

INKT cells target tumor-supporting cells, like TAMs and MDSCs, and limit angiogenesis, setting an immune-permissive environment that allows them to control tumor growth.

Clinical approaches

Use of INKT cells in cancer immunotherapy

➢ Stimulation of INKT cells:
   - Direct administration of α-GalCer: it is the strongest activator of INKT cell activity, producing both direct and indirect anti-tumor activities. It inhibits tumor growth and increases survival in murine models. However, in clinical trials, no significant clinical responses were observed.
   - Administration of APCs pulsed with α-GalCer: it induces better anti-tumor responses from NKT cells than free α-GalCer administration while maintaining safety. Clinical trials reported partial responses.

➢ Transfer of activated INKT cells to the patient:
   - Ex vivo activation of autologous INKT cells: Isolated INKT cells or PBMCs (which include INKT cells, among other effector cells) from the patients were expanded and stimulated in vitro and infused back to patients. The best results were observed when iNKT and vNKT cells were infused together.
   - Adoptive transfer therapy of IPS-derived INKT cells: Functional INKT cells are generated from induced pluripotent stem cells and infused to patients. Better results are obtained if an activator of TNF-α polarization is also infused. This method is especially important in patients with low levels of NKT cells.

Conclusions and future prospects

INKT cells are intermediates between innate and adaptive immunity, mediating immune regulatory functions.

INKT cells are divided in INKT cells and iNKT cells according their TCR rearrangements, and in consequence respond to distinct lipid antigens presented by CD1d.

INKT cells potentiate the antitumor response whereas INKT cells suppress it.

INKT cells mediate antitumor response through 3 mechanisms: indirect and direct cytotoxicity and modulation of tumor microenvironment.

INKT cell-based cancer therapy has two main approaches: stimulation of the patient’s INKT cells through injection of exogenous ligands or infusion of INKT cells activated in vitro.

Differences of behavior of the different subsets, the simultaneous unspecific activation of several subfamilies of NK cells, the influence of the microenvironment and the severity of cancer in the patients undergoing the studies could partially explain the lack of conclusive results.

Together these results indicate that INKT cell-based cancer immunotherapy strategies are promising. However, more studies to understand the mechanisms of action and the interactions with other cell populations are required.

References