IMMUNOSUPPRESSION INDUCED BY CANCER CELLS: PD-1 AND CTLA-4 PATHWAYS

Biochemistry Degree
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INTRODUCTION

- Cancer cells induce immunologic tolerance → absence of an immune response against certain antigens, causing the escape of these cells from the immune system.
- 2 groups of tumor antigens: True tumor-specific antigens (encoded by normal cellular genes), and tumor-associated antigens (encoded by normal cellular genes).

Strategies to enhance tumor dissemination and/or survival.

Key points:

- CTLA-1 and PD-1
- Downregulation of Ag presentation machinery
- Secretion of immunoregulatory cytokines
- Defects in proximal TCR-mediated signaling
- Immunosuppressive mechanisms
- CTLA-4 pathway
- CTLA-4 (Cytotoxic T-lymphocyte associated antigen protein 4), a 223 aa glycoprotein that belongs to lg superfamily and has an extracellular lg-like domain. → regulator of T-cell activation (figure 4).
- Ligands: B7-1 (CD80) and B7-2 (CD86), expressed in APCs and in tumor cells.

DIFFERENCES BETWEEN PD-1 AND CTLA-4

<table>
<thead>
<tr>
<th>CTLA-4</th>
<th>PD-1</th>
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<tbody>
<tr>
<td>Expression T-cells</td>
<td>T-cells, B-cells and myeloid cells</td>
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<tr>
<td>Interaction with AP2 (endocytosis) Yes</td>
<td>No</td>
</tr>
<tr>
<td>SHP-2 association Indirectly</td>
<td>Directly</td>
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Implications

PD-1 more broadly in the regulation of immune responses
CTLA-4 undetectable on the cell surface; PD-1 greater expression
CTLA-4 preserves a little PI3K activity, whereas PD-1 affects a global inhibition of T-lymphocytes

IMPLICATIONS FOR CANCER IMMUNOTHERAPY

A variety of checkpoint blocking agents have been developed to block PD-1 and CTLA-4 signaling (including monoclonal Ab). Examples: Nivolumab and Pembrolizumab (anti-PD-1), Ipilimumab (anti-CTLA-4).

PROS
- More effective than classical therapies in metastatic cancers.
- Synergistic activity → combinatorial therapies.

CONS
- Side effects.
- Very new, don’t know the long-term side effects.
- Currently very expensive therapies → not accessible to everyone.

CONCLUDING REMARKS

- PD-1 and CTLA-4: powerful negative regulators of the immune response (KD experiments, development of autoimmunity) → very important role in the regulation of the immune system.
- CTLA-4 KO mice developed autoimmune diseases and died at 3-4 weeks old → significant role in the development of peripheral tolerance to self-proteins.
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- Cancer uses this mechanism to evade and escape from IS cells → tolerance toward cancer cells leading to the development of malignant tumors.
- Therapy: It’s difficult to find a monotherapy that works at 100% because there are many different molecules and mechanisms involved, → combinatorial therapies should be tested.

REFERENCES