CANCER AND PD-1 RECEPTORS

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Introduction

The last two decades have seen the end of the standing argument about whether the immune system has positive, negative or null effects on tumor development. Recent research have documented that intact immune system can prevent, control and promote tumor by a process we call 'Cancer Immunoediting'. In just the past few years, the rapidly advancing research of cancer immunology has produced new therapies that enhance the strength of immune responses against tumors. One of these therapies are focused in PD-1 receptor, that acts as a negative regulator of effector T cell activation and blocking its function has been an attractive target of immunotherapy of cancer.

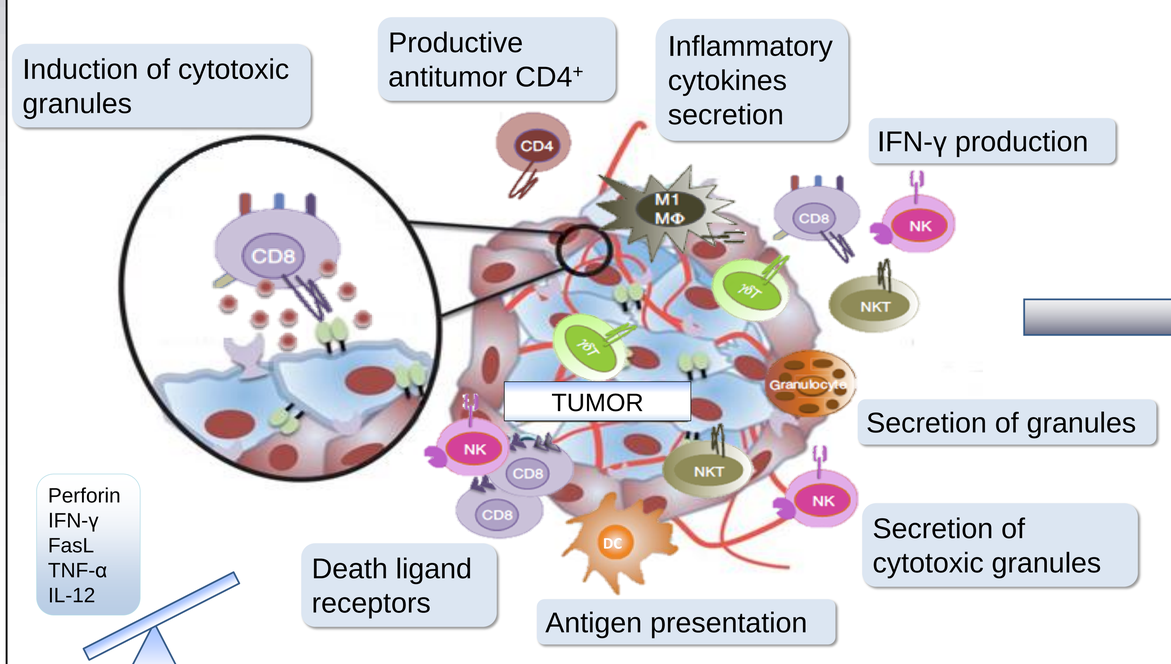
Objectives and methods

Current literature has been consulted and reviewed to achieve the following aims:
First part of this project introduces the central concept of cancer immunoediting and explains the different phases that conform it. We describe these phases with detail, focusing in the escape phase and in one important mechanism for tumor evasion: activation of PD-1 receptor. Finally, the project explains different strategies based in blockade this receptor or their ligands.

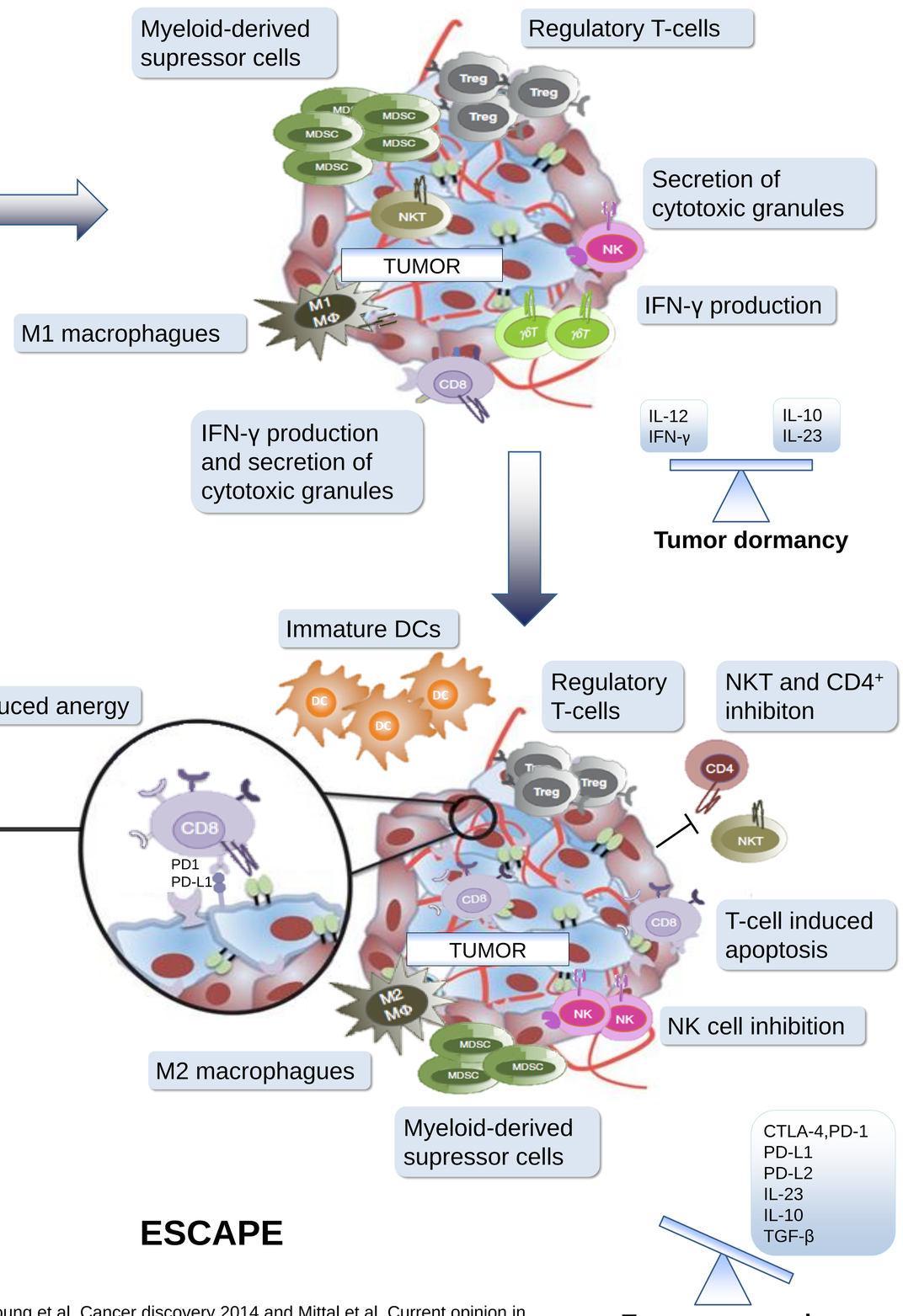
CANCER IMMUNOEDITING

The concept of cancer immunoediting tries to explain the evolution of the relationship that exists between cancer cells and the immune system during the development malignancy. This process has three distinct stages: elimination, equilibrium and escape. Elimination is equivalent to immune surveillance, in which immune system have a protective role against the development and growth of tumors. Despite evidence supporting this concept, tumor cells arise and grow progressively. This progression is driven by a selection of variant cells that can survive in normal conditions, and the elimination phase provides a selective pressure that generates immune-resisistant cells. This stage of equilibrium is reached when the immune system can control tumors but no longer eradicate them. With this continued selection, dormant tumors may develop to the phase of immune scape, in which cells can kill, evade, or tolerate the immune system.

ELIMINATION



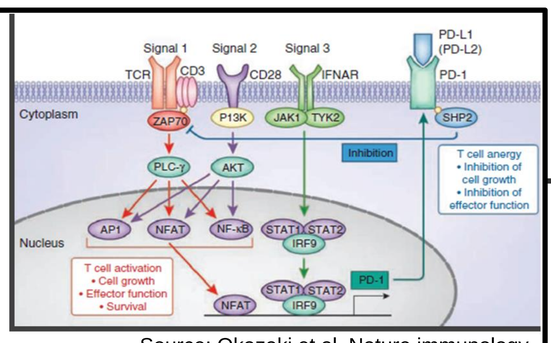
EQUILIBRIUM



Adaptation: Young et al. Cancer discovery 2014 and Mittal et al. Current opinion in immunology 2014

PD-1 Receptor

PD-1 expression is induced by TCR activation signals. When PD-1 binds with its ligands, PD-L1 or PD-L2, a signal which inhibits cell proliferation, cytokine production and cytolytic activity of T cells is transmitted and the immune response is attenuated.



Source: Okazaki et al. Nature immunology 2013

PD-1 interactions have different functions:

- Control the induction and maintenance of peripheral tolerance
- Regulate humoral immune response
- Control the induction of central tolerance

PD-1 and immune evasion of tumor cells

Tumor cells express more levels of PDL-1 or PD-L2 than normal tissues . In vitro experiments with tumor cells overexpressing PD-L1 demonstrated that expression of this ligand suppresses the cytotoxic activity of $CD8^+$ and increases T lymphocyte apoptosis.
In addition, IFN-y induces the expression of PD-1 ligands on the surface of several tumor cell lines, and the advantage of tumor effector functions is that IFN-y secreted by T lymphocytes for tumor destruction induces PD-L1 expression and avoids antitumor immune responses, which promotes tumor progression.

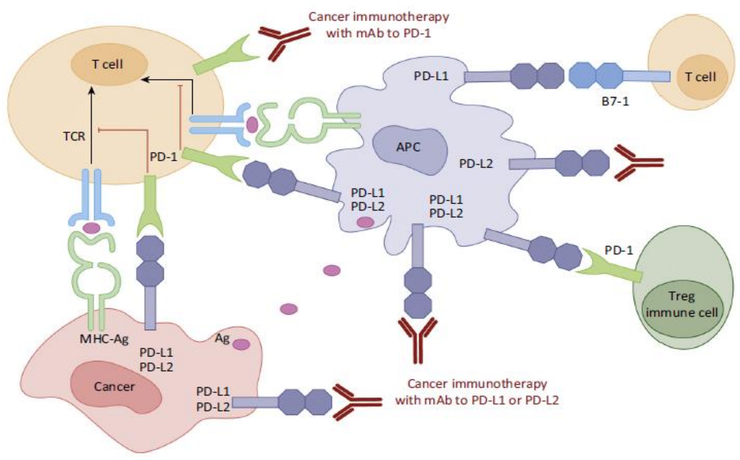
Mechanisms of anti-PD-1 and anti-PD-L1 immunotherapy

Blockade of PD-1 or its ligands increase T cells and IFN-γ at the tumor site and decrease the immunosuppressive myeloid-derived suppressor cells (MDSC).

The cytotoxic T lymphocytes promote:

- Effective immune response
- Prevent the induction of anergy
- Prevent the induction of apoptosis
- Decrease regulatory T cell levels
- Induce tumor regression
- Lead to tumor cell death by the NK cell mediated-antibody dependent cell cytotoxicity (ADCC) pathway

Blockade of this pathway is not expected to stimulate de novo immune response but it is useful to enhance immune responses against tumor antigens.



Adaptation: Ohaegbulam et al. Trends in molecular medicine 2015

Conclusions

- Further studies on cellular and molecular mechanisms are needed to understand the evasion of immune responses.
- Negative regulators of the immune system have been found to play important roles in restriction of effective antitumor immunologic responses.
- There are aspects of PD-L1/PD-1 interaction relevant for antitumor immunity that have been incompletely characterized.
- The blockade of the PD-1 pathway is considered a promising approach in anti-tumor immunotherapy. Additional studies are needed to define the spectrum of tumors in which blockade of this pathway will have antitumor effects.

References

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