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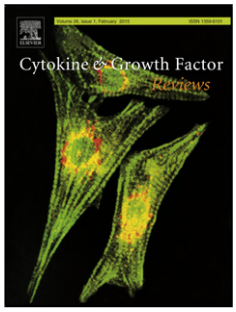

Title: Constitutive and acquired <!–<query id="Q1">Please check the ÏOC headf̈or correctness.</query>–>mechanisms of resistance to immune checkpoint blockade in human cancer

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<AT>Constitutive and Acquired Mechanisms of Resistance to Immune checkpoint blockade in Human Cancer

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<ABS-HEAD>Highlights► Monoclonal antibodies directed against regulatory pathways in T lymphocytes are revolutionizing medical oncology. ► Patients affected by melanoma, Hodgkin's lymphoma, Merkel cell carcinoma, and head and neck, bladder, renal cell or non-small cell lung cancers are sensitive to immune checkpoint blockade (ICB). ► Patients affected by breast, colon and prostate cancers are less sensitive to this therapeutic approach. ► Several mechanisms of constitutive or acquired resistance to ICB have been identified. ► Therapeutic strategies stemming from pre-clinical models can improve clinical outcomes for patients resistant to ICB.

<H1>4 <ABS-HEAD>Abstract

Cancer immunotherapy with monoclonal antibodies directed against regulatory pathways in T lymphocytes has been revolutionizing medical oncology, and the clinical success of monoclonal antibodies targeting either cytotoxic T lymphocyte antigen-4 (CTLA-4) or program death-1 (PD-1) in patients affected by melanoma, Hodgkin's lymphoma, Merkel cell carcinoma, and head and neck, bladder, renal cell or non-small cell lung cancer is way beyond the most optimistic expectation. However, immune checkpoint blockade (ICB) has failed to arrest progression in a consistent amount of patients affected by those tumors, and various histological types, including breast, colon and prostate cancer, are less sensitive to this therapeutic approach. Such clinical findings have fueled massive research efforts in the attempt to identify pre-existing and acquired mechanisms of resistance to ICB. Here we focus on evidences emerging from studies in humans on how tumor cells and the tumor microenvironment contribute to the heterogeneous clinical responses, and we propose strategies stemming from pre-clinical models that might improve clinical outcomes for patients.

5 KeyWords: Cancer immunotherapy; immune checkpoint; monoclonal antibodies; resistance; interferon; T lymphocytes

<H1>1. Introduction

A great advantage in harnessing the immune system against cancer is endowed in the peculiar characteristics of tumor-specific T lymphocytes, the ultimate effector mechanism: once activated, T cells patrol any tissue in our body in search of specific target cells. Thus, if well equipped and tightly controlled, tumor-specific T cells find and terminate only cancer cells [1].

Activating T cells for therapeutic benefit in cancer requires several steps that can be summarized in the ``cancer-immunity cycle'' [2]. As a first step, tumor antigens are released and captured by professional antigen presenting cells [e.g., dendritic cells (DCs)], which get activated by inflammatory signals (e.g., cytokines and damage associated molecular patterns), and migrate to secondary lymphoid organs and tumor-associated tertiary lymphoid structures [3]. Here, captured antigens are processed and presented to T cells by DCs by means of the major histocompatibility complex (MHC)-I and MHC-II molecules. Recognition of antigen-MHC complexes is not sufficient for naive T cell activation, and the costimulatory molecule CD28