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REVIEW

New insight into cancer immunotherapy

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Abstract A key point for maintenance of the immune system homeostasis is the balance between the capacity to recognize and fight exogenous molecules and the capacity to avoid auto reactivity. The disruption of this balance induces the progression of several immune diseases such as autoimmune diseases, allergies, infections or cancer.

A promising therapeutic approach to treat these diseases is immunotherapy. In cancer, both active and passive immunotherapies have been tested with promising results, such as the blocking of immunological checkpoints like CTLA-4 and PD-1. These treatments, in the market since a few years ago, aim to redirect the patient's immunological response by inhibiting the induction of regulatory T cells, both in the priming and effector phases.

This strategy sheds light on the immunological mechanisms that control the regulatory response mediated by T cells and opens new lines of research into other immunological diseases such as allergy, in which the induction of a regulatory response is necessary to avoid allergic progression and which is the main objective of allergen-specific immunotherapies available today.

The main feature of the immune system is its capacity to discriminate ''self'' and ''non-self''. The key point for this feature is the interaction between the TCR molecules located on the surface of T cells and the complex formed by MHC:Antigen (Ag) located on the surface of antigen-presenting cells (APC). It is during this process of antigen presentation that the T cells need to discriminate between self and non-self antigens.[1]

This capacity is due to the wide TCR repertoire displayed by T cells. This repertoire is obtained during T cell development in the thymus. Here, T cell progenitors are subjected to sequential selection processes. First, they undergo a positive selection, where cells expressing functional TCR receptors with a high avidity for self-antigens are selected. Next, the selected cells experience a negative selection in which those with a high avidity for self-antigens are depleted and those with low- or intermediate-avidity are released

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into the peripheral blood. This process is known as central tolerance.[2]

Thus, once in circulation and in order to avoid an autoimmune response, when these cells that can recognize self-antigens with low or intermediate avidity meet cells expressing self antigens they display mechanisms like induction of anergy, apoptosis or immunosuppression, which constitutes the peripheral tolerance.[2,3]

Importantly, these processes are controlled by what is known as ''immunological checkpoints'' that we discuss later in this review.

Immune response against tumors

Under homeostatic conditions, the immune system must be able to recognize exogenous stimuli and fight against them without affecting self-tissue. Dysregulation in this balance results in several pathologies either by excessive immune reactivity, which leads to autoimmune diseases or allergy, or by excessive tolerance, favoring tumor progression and infections.

In the case of cancer, tumor cells that were originally self-cells are identified by the immune system as non-self due to the expression of tumor-associated or tumor-related antigens.[4] Recognition of these molecules by the immune system triggers the activation of effector CD8 T cells, NK cells, M1-macrophages that will together eliminate the tumor cells.[5] However, this does not always occur. In some cases, the continuous interaction of the immune cells with the tumor cells induces a so-called ''immunoedition'', which favors evasion of the immune system by the tumor.[6,7] Usually, these results from the tumor cells' capacity to reduce the expression of tumoral antigens, reduce the expression of MHC on the cell surface, or induce the secretion of immunosuppressive mediators such as TGFb or IL10. Together, all these ''immunoeditions'' facilitate a loss of immunogenicity by the tumor cells, the induction of immunosuppression and support tumor progression.[8]

Owing to the important role of the immune system in the progression and outcome of the tumor, since several years ago different strategies aiming to redirect or activate/inhibit the immune response in cancer have been tested as potential therapeutic tools. A systematic review of all the immunotherapeutic approaches in cancer will be presented, placing special emphasis on the most promising and novel strategies with a proven significant efficacy in several cancers. We, also, discuss how these strategies in cancer can contribute to improving several immunotherapeutic strategies developed for the treatment of other immune diseases such as allergy.

Immunotherapy in cancer

Immunotherapy is considered as the treatment that aims to restore or intensify patients' immune response (definition from the National Cancer Institute (NCI), NIH). In cancer, immunotherapy is divided into two groups depending on the therapeutic agent used and the condition of the patients' immune system. In general, passive immunotherapy is used when patient immune response is weak or unable to respond, and involves using molecules or cells that, once in the patient's body, are able to compensate for the patient's immunological deficiency. On the other hand, active immunotherapy aims to stimulate the effector functions of the recipient immune system. In order to do this, the patient's immune system must be functional and responsive to the stimuli received[9] (Fig. 1).

Passive immunotherapy

Among passive immunotherapy approaches, the use of tumor-specific monoclonal antibodies has been the most popular treatment in cancer for years. Tumor-targeting mAbs are the best-characterized form of anticancer immunotherapy and, perhaps, the most widely employed in the clinic. This treatment aims to specifically alter the signaling functions of receptors expressed on the

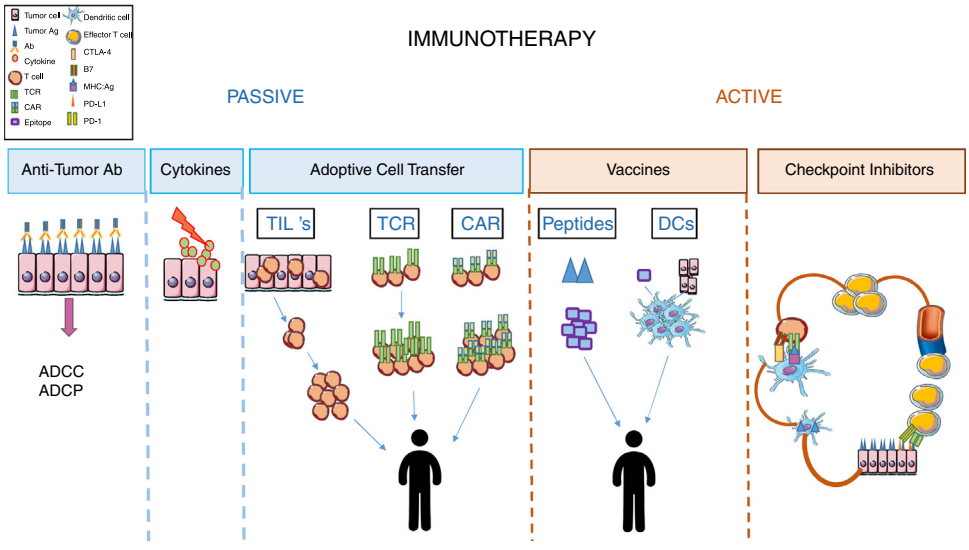

Figure 1 Diagram showing the methodological approaches in cancer immunotherapy.