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Tumoral immune resistance based on tryptophan degradation by indoleamine 2,3-dioxygenase

B.J. Van den Eynde *, I. Théate, C. Uyttenhove, D. Colau, L. Pilotte, V. Stroobant

Ludwig Institute for Cancer Research, de Duve Institute, Université catholique de Louvain, Brussels, Belgium

Abstract. Tumor cells constitutively express indoleamine 2,3-dioxygenase (IDO), which degrades tryptophan and lowers tryptophan concentration in the local microenvironment. Such altered microenvironment protects tumor cells from rejection by the immune system, as T lymphocytes are exquisitely sensitive to tryptophan shortage. This may explain the low clinical efficacy of cancer immunotherapy based on vaccination. Preclinical studies indicate that this immune resistance mechanism can be blocked by systemic delivery of a pharmacological IDO inhibitor, 1-methyl-L-tryptophan. These results suggest the clinical efficacy of cancer immunotherapy can be boosted by combined treatment of cancer patients with an IDO inhibitor.

Keywords: IDO; Cancer; Tryptophan; Cancer vaccine; Immunotherapy; Immune resistance

1. Introduction

Immunotherapy based on therapeutic vaccination of cancer patients is a promising new approach for cancer therapy. It is based on a thorough understanding of the antigens expressed by cancer cells and the nature of the immune response that can be raised against them. Clinical trials underway already indicate that this approach is not toxic and leads to significant clinical benefit in a minority of patients. However, it appears that an important factor limiting the efficacy of immunotherapy in non-responsive patients is the development of mechanisms

* Corresponding author. Tel.: +32 27647572; fax: +32 27647590.
E-mail address: benoit.vandeneynde@bru.licr.org (B.J. Van den Eynde).

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allowing tumors to resist or escape immune rejection. It is therefore critical to identify such mechanisms and design therapeutic approaches able to overcome it. Such approaches have the potential to boost the efficacy of cancer immunotherapy or other therapeutic strategies and achieve clinical benefit in a majority of patients.

2. Indoleamine 2,3-dioxygenase

Indoleamine 2,3-dioxygenase (IDO) is an intracellular enzyme that catalyses rapid tryptophan degradation, resulting in a local tryptophan depletion that severely affects T lymphocyte proliferation and is thereby profoundly immunosuppressive. This enzyme is not expressed in normal tissues with the exception of some dendritic cells. It is expressed at high levels in placenta, and it is inducible in most tissues by interferon-gamma. Pioneering studies by Munn and Mellor showed that the expression of IDO in placenta was required for immune tolerance of the foetus by the mother [1]. This tolerance results from an exquisite sensitivity of T lymphocytes to tryptophan depletion, which prevents their proliferation in response to an antigenic stimulus [2]. This appears to result from the induction of an integrated stress response involving the activation of GCN2 kinase [3]. Although IDO is an enzyme located in the cytosol, its activity reduces tryptophan concentration in the local extracellular microenvironment because tryptophan crosses the plasma membrane through passive transporters of the L-system of amino-acid transporters, according to concentration gradients [4].

3. Indoleamine 2,3-dioxygenase in tumors

We showed that many human tumors express IDO in a constitutive manner [5]. This was shown by RT-PCR in human tumor lines, and was then confirmed at the protein level by Western blot using a novel rabbit polyclonal antibody against human IDO. Enzymatic assays on tumor lysates also confirmed that tumoral IDO was enzymatically active. Since our antibody was able to stain tissue sections, we tested IDO expression in a large series of human tumor samples by immunohistochemistry. We found that a significant proportion of human tumors expressed IDO constitutively *in vivo* (Table 1). This expression did not appear to result from exposure to interferon-gamma, as most tumor samples studied did not show signs of inflammation. Moreover, the tumor stroma did not express IDO, which would have been the case if interferon-gamma had been responsible.

4. Tumoral immune resistance by expression of IDO

To test whether tumoral IDO provided protection of the tumor against immune rejection, we made use of a preclinical model system based on mouse tumor P815. We know that mice immunized against P1A, which is the major tumor antigen recognized by CD8 T lymphocytes on tumor P815, completely reject a challenge injection of a lethal dose of living P815 tumor cells. We then transfected P815 cells with an expression vector encoding IDO, and we used the IDO-expressing cells to challenge P1A-immmunized mice. We observed that immunized mice failed to reject IDO-expressing tumors (Fig. 1). This result confirmed that constitutive expression of IDO endows tumor cells with the ability to resist immune rejection by preventing T cell attack *in vivo*.