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INDOLEAMINE 2,3-DIOXYGENASE (IDO) AND IMMUNE TOLERANCE

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SUMMARY:

Indoleamine 2,3-dioxygenase (IDO) is an intracellular and extrahepatic enzyme predominantly found in many cells, especially macrophages. Tryptophan degradation generates kynurenine, and this pathway of tryptophan metabolism is an effective mechanism for modulating the immune response.

The IDO facilitates immune tolerance and is one of the main actors involved in the inhibition of cell proliferation, including activated T cells. IDO induces production of reactive oxygen species (ROS) and nitric oxide (NO) radicals. Several pathways involved in the regulation of immune response are regulated by redox mechanisms. Reactive oxygen and nitrogen species (ROS-RNS) and other redox active molecules play key roles in immunity.

KEYWORDS: Indoleamine 2,3-dioxygenase. Tryptophan metabolism. Kynurenine

RESUMEN:

La indolamina 2,3-dioxigenasa (IDO) es un enzima predominante extrahepática intracelular y se encuentra en numerosas células, principalmente macrófagos. La degradación del triptófano genera quinurenina, y esta vía del metabolismo del triptófano, constituye un mecanismo eficaz de modulación de la respuesta inmune.

La IDO facilita la tolerancia inmunológica, y es uno de los principales actores implicados en la inhibición de la proliferación celular, incluyendo las células T activadas. La IDO induce la producción de especies reactivas de oxígeno (ROS) y radicales de óxido nítrico (NO). Varias vías implicadas en la regulación de respuesta inmunológica se regulan por mecanismos redox. Las especies reactivas del oxígeno y nitrógeno (ROS-RNS) y otras moléculas activas redox cumplen funciones clave en la inmunidad.

PALABRAS CLAVES: Indolamina 2,3-dioxigenasa. Metabolismo del Triptófano. Quinurenina

Tryptophan and kynurenine

There are nine amino acids that are called "essential" because the body is unable to synthesize them and must acquire them from external sources, mainly through the diet. One of these is tryptophan. Once it has been absorbed in the body, it can be found in the circulation in the free form or, most commonly, bound to albumin. Tryptophan plays a role in protein synthesis, as well as in several metabolic pathways, producing different metabolites, of which kynurenine is one¹.

Tryptophan can be metabolized via different pathways. It is oxidized by opening the indole ring, which is started either by the enzyme tryptophan 2,3-dioxygenase (TDO), which is mainly found in the liver, and is induced by corticosteroids², or by another enzyme called indoleamine 2,3-dioxygenase (IDO)³.

Indoleamine 2,3-dioxygenase (IDO) is predominantly an extrahepatic enzyme, and can be found in numerous cells, including macrophages, microglia, neurons and astrocytes⁴⁻⁶. Kynurenine is produced during the metabolism of tryptophan. This pathway is the most important route of tryptophan metabolism, since it is an efficient modulation mechanism of the immune response. Furthermore, other metabolites from this pathway can synergize or antagonize these effects³. This pathway is regulated by certain cytokines and inflammatory molecules, among which is interferon gamma (IFN- γ)⁷ which induces IDO in cells of the immune system⁸⁻⁹. IDO is effectively the first enzyme of that pathway, and is activated when an immune response is produced via IFN- γ . In turn, the depletion of tryptophan and the production of kynurenine modulate the immune response.

The kynurenine pathway is implicated in many diseases and disorders, and there are many pathological conditions in which an imbalance between tryptophan and kynurenine has been found. The list, up until now, includes neoplastic diseases, protozoal infections such as malaria, as well as bacterial and viral infections, such as Human Immunodeficiency Virus (HIV), autoimmune diseases such as rheumatoid arthritis and multiple sclerosis, and a wide spectrum of neurological conditions such as Alzheimer's disease, lateral amyotrophic sclerosis, and Huntington's chorea, as well as psychiatric diseases such as depression and schizophrenia. We can see a panorama:

IDO possesses an effective bactericide mechanism and has been associated with cell immunosuppression. IDO activity in infected cells provokes a powerful bactericide effect to fight against the propagation of infection by means of the degradation of tryptophan by autotrophic bacteria, causing their death. The metabolites, among which is kynurenine, also have a bactericide effect that is toxic for bacteria. In the last few years, increasing evidence has been shown that IDO also plays an important role in viral infections, including HIV¹⁰, hepatitis B and C¹¹, and influenza¹².

In patients on hemodialysis, there is an increase in tryptophan degradation associated with an increase in the concentration of neopterin, which indicates the active involvement of IDO¹³.

Some neuropsychiatric symptoms that appear in people of advanced age seem to be associated with a low grade chronic inflammation, possibly due to changes in the enzyme pathways of tryptophan metabolism mediated by IDO. It has been associated with disorders such as schizophrenia and depression¹⁴. Capuron et al¹⁵ experimentally demonstrated that the level of infection, measured by the serum interleukin-6 and C-reactive protein levels, was related to a decrease in the concentration of tryptophan and an increase in the level of kynurenine in the blood, which suggested an increase in IDO-induced tryptophan catabolism. The increase in tryptophan metabolism is also associated with depression symptoms such as asthenia, lack of motivation, anorexia, and pessimism. Age correlates significantly with the concentrations of immunological markers and neuropsychiatric symptoms.

There are many studies on the importance of IDO in neoplastic disease, and we have contributed some experiences in our Research Unit¹⁶⁻¹⁸. It has been demonstrated that IDO plays a fundamental role in immune tolerance to neoplastic cells. Song et al¹⁹ demonstrated the inducing effect of kynurenine apoptosis on the human neoplastic cell line NK92 MI. In cultures, treatment with L-kynurenine induces growth inhibition due to the apoptosis, depending on the dose employed. And this opens the doors to new therapeutic targets, which are being explored²⁰.

The role of IDO in inducing immune tolerance

IDO continues to be shown as an important molecule involved in immune tolerance, since it is one of the main actors involved in the inhibition of cell proliferation, including activated T cells, and thus playing a decisive role, that enables pregnancy, mediates in autoimmunity, and intervenes in neoplasms ²⁰.

IDO was initially described as an essential enzyme for maternal-fetal tolerance. In 1998, Munn et al²¹ observed that gestation in mice was immediately rejected when an IDO inhibitor was administered to pregnant mice, and formulated the hypothesis that the expression of IDO was necessary to prevent immunological rejection of the fetus. They regarded IDO as a catabolizing enzyme of tryptophan, expressed in trophoblasts and macrophages. By means of tryptophan degradation, IDO could suppress the activity of T cells, preventing rejection of the fetus.

The control of the supply of micronutrients is a strategy to regulate the cell-mediated immune response. The cells that induce IDO, promote tryptophan metabolism, necessary for cell proliferation, and thus intervene in the immune response. In this sense, it has been shown that IDO activity promotes cell metabolism changes that affect the cellular and systemic response due to inflammatory or immunological stimuli in different clinical conditions such as neoplastic processes, chronic infections, autoimmune conditions, allergy syndromes, and transplants ²².

The anti-proliferative character of IDO in bacteria, protozoa, and tumor cells was described for the first time by Pfefferkorn in 1984²³, and by Taylor and Feng in 1991²⁴.

IDO promotes the degradation of tryptophan into kynurenine within the cells. This has wide implications in the immune response of the body.

It is currently known that IDO forms part of a local, rapid immune regulation mechanism, called "metabolic immune regulation", by inducing a systemic immune tolerance, a protector of violent immune reactions ²².

The role of kynurenines in the immune system is evident, due to the immunosuppressive effect of IDO. There is evidence of an interaction between the kynurenine pathway, the cytokines, and the nervous system. IDO plays a key role in connecting the immune system with the kynurenine pathway. Pro-inflammatory stimuli activate the tryptophan metabolic pathway, while IDO, on promoting the degradation of tryptophan, exercises an immunosuppressive effect that includes inhibition of T cell functions, the activation of T cell regulators, and the inhibition of NK lymphocytes. There is a close relationship between the cytokines (IFN- α , IFN- γ , TNF- α , TGF- β , IL-4 e IL-23) and the kynurenine system. IDO exercises a regulatory effect against the activation of antigen presenting cells mediated by interferon, with a feedback mechanism that modulates the immune response, maintaining homeostasis ²⁵.

Oxidative stress and immunomodulation

IDO induces the production of reactive oxygen species (ROS) and nitric oxide (NO) radicals. Gostner et al²⁶ noted that reactive oxygen and nitrogen species (ROS-RNS) and other active redox molecules fulfil key functions in immunity. Along with other pathogenic agent defense strategies, the redox reactions activate and modulate the immune response, and play an active role in the start and termination of cell repair processes.

Several pathways involved in the regulation of the immune response are regulated by redox mechanisms. The enzyme, nitric oxide synthase (NOS) induces the generation of nitric oxide (NO) in several cell types. This compound, despite its low reactivity, is a powerful antioxidant and inhibits the expression and function of IDO ²⁷. The induction of IDO and NOS in the inflammatory response mediated by IFN- α appears to be mutually regulated [28]. The absence of NO enables IDO to be more active in the inflammation site.

The regulation mechanisms due to redox activation ensure the correct development of the immune processes, and the imbalance in redox homeostasis, as may occur in chronic states of anoxia, leads to failures in the control mechanisms that favor the development of different pathological conditions, as we have observed in recent clinical studies²⁹.

Interferon-gamma is the most powerful inducer of the ROS-RNS formation in target cells, such as macrophages. The immunomodulation that prompts tryptophan degradation through IDO, is initiated during the cellular immune response, concomitant to the production of ROS-RNS by immunocompetent cells. Treatment with the antioxidant N-acetyl-cysteine (NAC) completely protects the NK lymphocytes against the apoptosis induced by L-kynurenine. Furthermore, Song et al. ¹⁹ found that treatment with the inhibitor, z-VAD-fmk (pan-caspase z-Val-Ala-Asp (OMe) fluoromethylketone) and ZB4 (a Fas-antibody antagonist), slightly inhibits the apoptosis induced by L-kynurenine, which suggests that this induced apoptosis is mainly produced by a pathway mediated by ROS. Thus, the kynurenine resulting from the IDO activity may cause cell death through a ROS route in NK lymphocytes, by interaction processes between lymphocytes and cancer cells in the modulation of the immune response.

The complex interaction between tryptophan, IDO and the kynurenines themselves needs to be investigated further and in different pathological conditions. The capacity of the kynurenine pathway in the design of new treatment strategies is already being explored.

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It would be very interesting to study the mechanisms induced by kynurenine in patients with cutaneous and systemic lymphoma given its role in cell apoptosis in T and NK cells, since these cell lines are related with the pathogenesis of these diseases.

Comentario del revisor Dr Carlos G. Musso. Carlos G. Musso, MD. (UBA), PhD. (U. Salamanca). IAGG Research Network. Sub-Chief Nephrology and Internal Milieu Division

This is a very clear review and update on the role of the enzyme indoleamine 2,3 dioxygenase (IDO) in the degradation of tryptophan into kynurenine and its broad impact on the phenomenon of immune tolerance of the organism.



It is extremely important to advance in the understanding of the mechanisms regulating immune tolerance, since it would be the ideal treatment in clinical settings currently handled by immunosuppression, as is the case of inhibiting rejection in organ transplantation.
