TRYPTOPHAN CATABOLISM AS A NEW MECHANISM OF ACTION OF GLUCOCORTICOIDS IN ALLERGIC AIRWAY INFLAMMATION

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Indoleamine 2,3-dioxygenase (IDO) is an intracellular heme-containing enzyme that catalyzes the first, rate-limiting step in the tryptophan catabolism along the kynurenine pathway. The functional expression of IDO by dendritic cells (DCs) has emerged in recent years as a major mechanism of peripheral tolerance [1]. IDO contributes to maternal tolerance in pregnancy, control of allograft rejection, and protection against autoimmunity, inflammatory pathology and allergy, including experimental asthma. Plasmacytoid DCs (pDCs) represent a specialized cell population that produces large amounts of type I interferons (IFNs) in response to viruses. Recently, murine and human pDCs have been credited with a unique ability to express IDO and mediate immunosuppression in specific settings. In particular, it has been demonstrated that endogenous pDCs protect against asthmatic reactions to harmless antigens. Therefore, therapies targeted at amplifying the intrinsic tolerogenic capacity of lung pDCs through an IDO-dependent pathway may limit the development of asthma.

Glucocorticoid-induced tumor-necrosis factor receptor (GITR) expressed on T cells and its natural ligand, GITRL, expressed on a variety of cells, including DCs, contribute to the control of immune homeostasis. Although the exact role played by GITR on T cells has not been clarified yet, the data obtained so far indicate an overall costimulatory function for its engagement by GITRL, an effect in line with the general outcome of the crosstalk between TNF ligand- and TNF receptor-like molecules. However, recent studies have also underscored an immunosuppressive, IDO-dependent role of pairs belonging to the TNF/TNFR family members. In the present study [2], by using a soluble form of GITR, GITR-Ig, we demonstrated that pDCs possess GITRL and that the engagement of GITRL by GITR activates a reverse signaling in these cells that results in the onset of IDO-dependent immune regulation. Dexamethasone administered *in vivo* activates IDO through the harmonious induction of GITR in $CD4^+$ T cells and GITRL in pDCs. IDO activation by the glucocorticoid contributes to protection against allergic bronchopulmonary aspergillosis. The ability of glucocorticoid to exert IDO-dependent protection in a model of allergic airway inflammation could provide new clues to an improved understanding of the complex action of these drugs in human respiratory allergies and asthma.

1. Grohmann U., Fallarino F., Puccetti P. (2003) Trends Immunol. 24:242-248.
2. Grohmann et al. (2007) Nature Med., in press.