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CONVENTIONAL DCS AND ENDOGENOUS TRYPTOPHAN DERIVATIVES PREVENT THE DEVELOPMENT OF ANTI-FVIII ANTIBODIES IN HEMOPHILIA A MODEL

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Hemophilia A is a genetic disorder that manifests itself through an inability to form blood clots within the body. Since this is due to the absence of a clotting protein (factor VIII), the gold-standard treatment is to inject the protein that is missing into the patient's circulation to make up for the deficiency (1). Unfortunately, about 30% of hemophilia A patients develop inhibitors against this infused protein and render the treatment ineffective. The interaction between factor VIII and the body's white blood cells are important for inhibitor generation as well as the tolerance to factor VIII, which is the absence of inhibitor generation to the protein (2). We reported that the inhibitor-positive status was associated with reduced activity of the immune-regulatory enzyme indoleamine 2,3-dioxygenase 1 (IDO1) in dendritic cells (DCs), that promotes regulatory effects via the production of tryptophan catabolites, known as kynurenines. Some of those tryptophan derivatives are endogenous ligands for the Aryl hydrocarbon receptor (AhR) (3).

In this study, we tested the potential of tryptophan-related AhR ligands for inhibiting the development of anti-FVIII antibodies in hemophilic (F8 KO) mice. To this aim, F8 KO mice hemophilic mice were treated with recombinant human FVIII (rhFVIII) alone or in combination with selected AhR ligands once weekly for four weeks. All mice treated with rhFVIII developed high-titer anti-FVIII antibodies after 4 weeks of treatment.

Administration of specific tryptophan metabolites prevented the generation of anti-FVIII antibodies in almost 80% of F8 KO mice. The protective effect of these AhR ligands was negated by co-administration of the AhR antagonist CH-223191 or in AhR KO mice. Moreover the protective effect was abrogated in mice lacking selected dendritic cell subsets.

Similar results were obtained by administration of engineered gold nanoparticles loaded with the same tryptophan metabolite and rhFVIII. In addition, in the same model we found that treatment with AhR ligands not only suppressed FVIII-specific antibody titers but, resulted in increased protection against specific bacteria and fungi infection.

Thus, these results suggest that the engagement of AhR, by specific tryptophan derivatives in selected DC subsets, may be a possible new strategy to control the immune response to rhFVIII, while protecting against specific infections

Le cellule dendritiche convenzionali e derivati del triptofano inibiscono la formazione di anticorpi anti-FVIII in un modello di emofilia A.

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