The epigenetic mechanism by which vitamin D modulates the tolerance of the immune system

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Dr. Esteban Ballestar at the Josep Carreras Leukaemia Research Institute. Credit: Josep Carreras Leukaemia Research Institute

In autoimmunity, the mechanisms that guarantee that our defense system

does not attack our own body—tolerance to oneself—does not work properly. Multiple sclerosis, which affects one in every 1,000 people in Spain, is a serious autoimmune disease in which the immune system attacks the myelin sheath of some types of neurons, causing progressive neurological disability.

Dr. Esteban Ballestar, leader of the Epigenetics and immune diseases group at the Josep Carrreras Leukaemia Research Institute, and Dr. Eva Martínez-Cáceres, leader of the Immunopathology group at the IGTP-Hospital Germans Trias i Pujol, have recently published in the journal *Cell Reports* the mechanism by which vitamin D activates the tolerance program of dendritic cells.

Dendritic cells are a type of immune cells present in the blood and tissues, capable of detecting potential threats and displaying them to lymphocytes in the lymph nodes. Once there, they decide whether the system is going to tolerate that threat or attack it.

It is known that when dendritic cells are treated with vitamin D, they develop tolerogenic characteristics, so treatment with tolerant dendritic cells in multiple sclerosis patients could slow the progression of the disease. A growing number of experiments in animal models support this hypothesis and, as a matter of fact, the Neuroimmunology group of the Hospital Germans Trias i Pujol is carrying out an international clinical trial to check it in patients with multiple sclerosis. This trial is part of the European-funded project ReSToRe (www.h2020restore.eu/).

However, the fact that the mechanism underlying the appearance of this tolerance profile was unknown prevented further insight on this therapeutic approach. The article published in *Cell Reports*, by main authors Dr. Francesc Català-Moll, Anna Ferreté Bonastre and Gerard Godoy-Tena, concludes that the binding of the vitamin D receptor with the STAT3 protein results in the activation of TET2, a DNA

demethylating agent—a type of epigenetic mark—that, in dendritic cells, promotes the activation of tolerance genes.

Thus, the researchers manage to demonstrate, for the first time, that the relationship between vitamin D and the generation of the tolerance profile of dendritic cells is due to the modification of epigenetic marks by TET2, through the IL-6- JAK-STAT3, very well-known clinical target.

With this new information, a door opens to the use of existing drugs that interfere with the STAT3 pathway and optimize the production of tolerogenic dendritic cells, capable of stopping the progression of multiple sclerosis and other autoimmune diseases. This would be a new example of a promising cellular therapy, such as the CAR-T developed against cancer.

More information: Francesc Català-Moll et al, Vitamin D receptor, STAT3, and TET2 cooperate to establish tolerogenesis, *Cell Reports* (2022). DOI: 10.1016/j.celrep.2021.110244

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