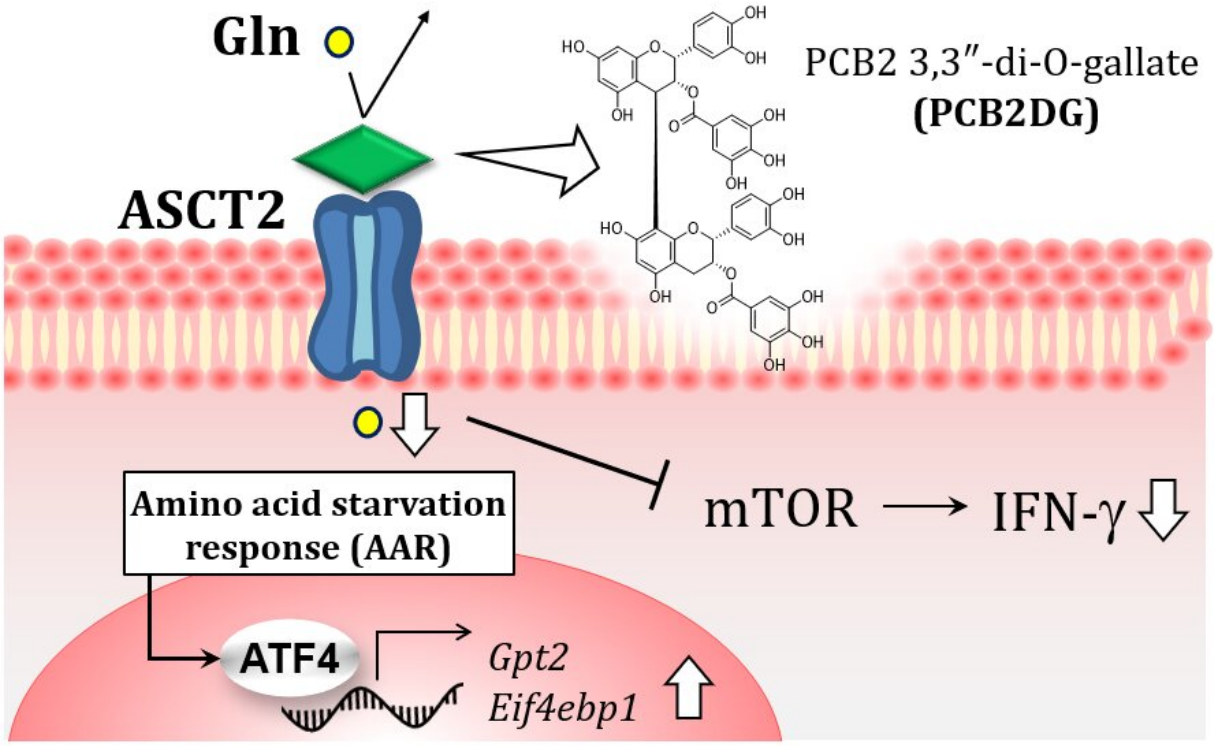
Polyphenols may be missing component in regulating inflammatory immune responses

February 21 2023



The inhibition of IFN-γ production in CD4+ T cells caused by the dietary polyphenol PCB2DG was mediated by the activation of the AAR pathway through inhibition of glutamine influx via the direct interaction of PCB2DG with ASCT2. Credit: Katsunori Endo and Sachi Tanaka, Shinshu University

PCB2DG, a polyphenol with anti-inflammatory properties, works by

targeting and directly interacting with the major glutamine transporter protein, alanine serine cysteine transporter 2 (ASCT2), to inhibit the uptake of glutamine, an important amino acid found in the blood.

This reduction of intracellular glutamine accumulation in CD4+ T cells also reduces the production of interferon-gamma, or IFN-γ showing promise in the future of dietary polyphenol treatment for those suffering from autoimmune diseases. Additionally, the identification of ASCT2 as the target protein of PCB2DG is one of the main achievements of the study, giving way to new opportunities to study the effects dietary polyphenols have on immune responses.

Researchers published their results on December 23, 2022 in *International Immunopharmacology*. In it, the target molecule of polyphenols in immune cells was identified, as well as providing clarification on how PCB2DG works to suppress glutamine influxes within CD4+ T cells. The study used previous research by the same team to build upon their original hypothesis of cytokine inhibition in the presence of PCB2DG and other common food-derived polyphenols.

"Since activated T cells have been suggested to cause autoimmune diseases, it is expected that administration of PCB2DG will improve the pathologies of these diseases," said Katsunori Endo, first author of the paper and researcher at Shinshu University.

Procyanidins are dietary polyphenol compounds found in many commonly consumed plant materials, such as tea leaves, grapes (and therefore wine), and cacao. These procyanidins are combined with the functional group "gallate," allowing for greater interactions with various protein surfaces. Combine the two and we have our subject: PCB2DG. This subject has been shown to inhibit glutamine uptake in CD4+ T cells thanks to its ability to bind to the glutamine transporter protein discovered in this study, ASCT2.

By "starving" cells of glutamine, an amino acid response (AAR) is generated, then inducing the activity of activating transcription factor 4 (ATF4) which promotes gene expression to synthesize amino acids. Since T cell activation depends on the presence of extracellular amino acids like glutamine for use as a base to build upon, glutamine and other amino-acid deficient cells are unable to supply the requirements for such T cell activation, leading to a reduced inflammatory response.

"We showed previously that the immunomodulatory effects of PCB2, PCB2 3-O-gallate, and PCB2 3″-O- gallate were obviously lower than those of PCB2DG. Therefore, the specific structure of PCB2DG, i.e. a dimeric polyphenol including two gallate groups, is likely important for its binding to ASCT2 and remarkable immunomodulatory effects," Endo said.

Configuration and structure of molecules are crucial when it comes to physiological responses, as most interactions are not possible unless a "lock and key" mechanism is present to set off a chain of reactions. Understanding exactly what structure is needed to unlock the immunomodulating capabilities of polyphenols on immune cells was a large part of the question this research has helped to answer.

Successful studies performed on mice will give more information on whether this is a viable treatment plan that can be developed for later use in humans. The future of this work looks toward confirming PCB2DG's role in improving disease. Ultimately, the aim will be to improve the cases of those suffering from autoimmune diseases, particularly those which may be improved by decreasing the excessive activation of T-cells in diseases mediated by IFN-γ.

More information: Katsunori Endo et al, Procyanidin B2 3,3″-di-O-gallate suppresses IFN-γ production in murine CD4+ T cells through the regulation of glutamine influx via direct interaction with ASCT2,

International Immunopharmacology (2022). DOI: 10.1016/j.intimp.2022.109617