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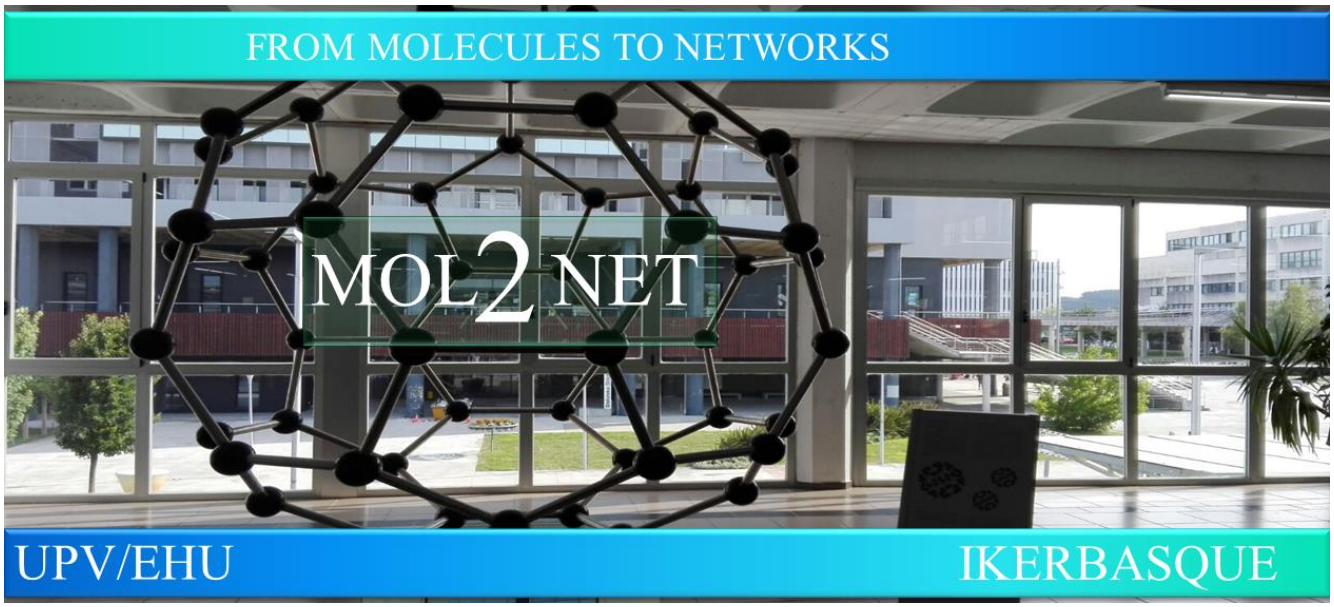
MOL2NET'22, Conference on Molecular, Biomedical & Computational Sciences and Engineering, 8th ed.



LAG-3 Role in Inflammatory Diseases

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Abstract.

Lymphocyte activation gene 3 (LAG-3) is a cell surface inhibitory receptor with multiple biological activities over T cell activation and effector functions. LAG-3 plays a regulatory role in immunity and emerged some time ago as an inhibitory immune checkpoint molecule. A systematic research was performed using PubMed and ClinicalTrial.gov databases. Up-to-date published articles meeting the inclusion criteria were investigated. LAG-3 expression has been linked to increased pathology in certain inflammatory disorders, such as HDL Hypercholesterolemia and Inflammatory Bowel Disease. LAG-3 protein expression levels have been significantly associated via transcriptomic studies with high HDL cholesterol (HDL-C) and HALP (HDL-C ≥ 60 mg/dL). Indeed, LAG-3 deficiency altered lipid raft formations and cell phosphosignaling, processes leading to an enhanced proinflammatory state, and increased production of inflammatory cytokines such as TNFα (Golden et al, Insight 2016; Rodriguez et al, Curr. Atheroscler. Rep. 2021; Chocarro et al, Int J Mol Sci 2021). LAG-3 has been reported to be a modulator of T cell regulation in inflammatory responses in the intestine (Do et al, Mucosal. Immunol. 2016; Chocarro et al, Int J Mol Sci 2021). In addition, LAG-3+-regulatory T cells are required to suppress the inflammatory activities of CX3CR1+ macrophages to maintain tissue homeostasis during lymphoid cell-driven colitis (Bauché et al, Immunity 2018; Chocarro et al, Int J Mol Sci 2021). Moreover, LAG-3+ cells have been shown to be increased in the inflamed mucosa and correlate with endoscopic severity and disease phenotype in ulcerative colitis. Here, we will discuss the impaired control of cell-mediated immunity associated with high accumulation of LAG-3 in inflammatory disorders (Chocarro et al, Int J Mol Sci 2021). Interestingly, in vitro blockade of PD-1/LAG-3 interactions enhances cytokine production in response to cancer and infections, and it is demonstrating promising results in several clinical trials for the treatment of various cancers, suggesting it could have a similar effect in inflammatory disorders (Chocarro et al, IOTECH 2022). A deeper understanding on the basic mechanisms underlying LAG-3 intracellular signaling will provide insight for further development of novel strategies for autoimmune and inflammatory disorders (Chocarro et al, Int J Mol Sci 2021).

Keywords: *LAG-3, Inflammatory Diseases, HDL Hypercholesterolemia, Inflammatory Bowel Disease*

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Funding

The OncoImmunology group is funded by the Spanish Association against Cancer (AECC, PROYE16001ESCO); Instituto de Salud Carlos III (ISCIII)-FEDER project grants (FIS PI17/02119, FIS PI20/00010, COV20/00000, and TRANSPOCART ICI19/00069); a Biomedicine Project grant from the Department of Health of the Government of Navarre (BMED 050-2019); Strategic projects from the Department of Industry, Government of Navarre (AGATA, Ref 0011-1411-2020-000013; LINTERNA, Ref. 0011-1411-2020-000033; DESCARTHES, 0011-1411-2019-000058); European Project Horizon 2020 Improved Vaccination for Older Adults (ISOLDA; ID: 848166); Crescendo Biologics Ltd. supported the OncoImmunology group for the development and testing of PD-1 and LAG-3 bispecifics.