LAG-3 role in infection

Luisa Chocarro[1]*, Ester Blanco[1], Hugo Arasanz[1,2], Ana Bocanegra[1], Leticia Fernández-Rubio[1], Miriam Echaide[1], Maider Garnica[1], Pablo Ramos[1], Grazyna Kochan[1]*, David Escors[1]*

1 Oncoimmunology Research Unit, Navarrabiomed-Fundación Miguel Servet, Universidad Pública de Navarra (UPNA), Complejo Hospitalario de Navarra (CHN), Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain.

2 Medical Oncology Unit, Complejo Hospitalario de Navarra (CHN), Instituto de Investigación Sanitaria de Navarra (IdiSNA), Pamplona, Spain.

* Corespondance: lchocard@navarra.es, grkochan@navarra.es, descorsm@navarra.es

Abstract

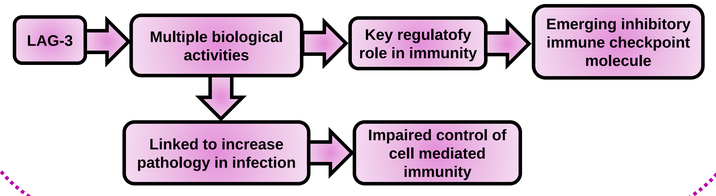
Lymphocyte activation gene 3 (LAG-3) is a cell surface inhibitory receptor with multiple biological activities over T cell activation and effector functions. LAG-3 plays a regulatory role in immunity and emerged some time ago as an inhibitory immune checkpoint molecule.

A systematic research was performed using the PubMed and ClinicalTrial.gov databases. Articles published up to 2021 meeting the inclusion criteria were investigated. LAG-3 expression has been linked to increased pathology in certain infections, such as the ones caused by Salmonella, Plasmodium parasites, Mycobacterium tuberculosis, human immunodeficiency virus (HIV), non-pathogenic simian immunodeficiency virus (SIV), in hepatitis B virus (HBV), human papillomavirus (HPV), chronic hepatitis C virus (HCV), lymphocytic choriomeningitis virus (LCMV) and herpes simplex virus 1 (HSV-1).

Here, we will discuss the impaired control of cell-mediated immunity associated with high accumulation of LAG-3 after infection, in most cases associated with a high bacterial/viral load, a reduced survival rate or persisting metabolic and inflammation disorders. Interestingly, the in vitro blockade of PD-1/LAG-3 interactions enhanced cytokine production in response to some of these infections.

Keywords: LAG-3; Immune Checkpoint.

Graphical abstract



Acknowledgments

We sincerely thank the Oncoimmunology Unit funders: 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..

LAG-3 molecular characterization

Cell surface inhibitory receptor

Extensive role in multiple diseases

Unknown mechanism of action

PD-1/LAG-3 co-signaling drive T cell dysfunctionality

Next-generation immune checkpoint in cancer immunetherapy

Key negative regulator of proliferation, activation, effector function, and immune homeostasis.

Promising clinical landscape

Comparable to PD-1 and CTLA-4

Its expression has been linked to increased pathology in certain infections

Chocarro, L.; et al. Int. J. Mol. Sci. 2021

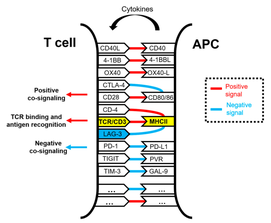


Figure 1. *Schematic representation of the molecular interactions occurring within the immunological synapse between a T cell and an antigen-presenting cell (APC) during antigen presentation and T cell activation. (Chocarro, L.; Int. J. Mol. Sci. 2021)*

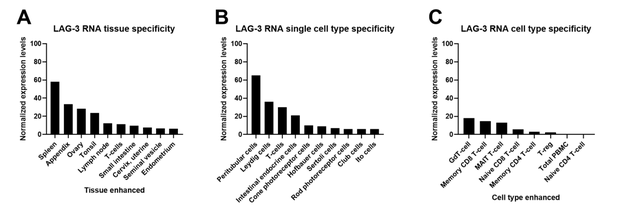


Figure 2. *LAG-3 protein and RNA expression profiles from Protein Atlas Analyses (http://www.proteinatlas.org). Images and data credit: Human Protein Atlas. Image and data available from: LAG3 protein expression profiles, The Human Protein Atlas. A) LAG-3 consensus normalized expression (NX) levels for 55 tissue types and 6 blood cell types, created by combining the data from the three transcriptomics datasets (HPA, GTEx, and FANTOMS), using the internal normalization pipeline. Color coding is based on tissue groups by common functional features. RNA tissue specificity is enhanced in lymphoid and ovary tissues. (B) Summary of LAG-3 single-cell RNA (NX) from the indicated single cell types. Color coding is based on cell type groups, each consisting of cell types with functional features in common. (C) The bar graph represents quantification of RNA-seq data (pTPM) from blood cell types and total peripheral blood mononuclear cells (PBMC) that have been separated into subpopulations by flow sorting. (Chocarro, L.; Int. J. Mol. Sci. 2021)*

LAG-3 role in bacterial infections

***Salmonella* infection** → LAG3+ CD138hi → Impaired control of immunity against infection → Higher bacterial load / Reduced survival rate

Lino, A.C.; et al. Immunity 2018

***Plasmodium* parasites infection** → Increased PD-1 and LAG-3 expression by activated CD4 cells → CD11ahi CD49dhi CD4 T cells express PD-1 and LAG-3 during infection

Doe, H.T.; et al. Microbiol. Immunol. 2016

P. yoelii 17XL, P yoelii 17XNL, P. chabaudi, P. vinckei, and *P. berghei*

In vitro blockade of PD-1/LAG-3 interactions enhanced cytokine production in response to infection

Active *Mycobacterium tuberculosis* infection → LAG-3 expression → CD4 T cells / NK cells

Phillips, B.L.; et al. Am. J. Pathol. 2015

Enhanced high bacterial burdens

Changes in Th1 responses

LAG-3 expression was shown to be increased in the lungs → Particularly within the granulomatous lesions

LAG-3 role in viral infections

Human immunodeficiency virus (HIV) infection → LAG3 upregulation → High viral load within a T cell exhausted subset → Faster disease progression

Graydon, C.G.; et al. PLoS Pathog. 2019

Nonpathogenic simian immunodeficiency virus (SIV) primary infection → Induced DNA methylation in the LAG-3 coding gene → A similar mechanism may be occurring in HIV-infected patients, which could contribute to persisting metabolic disorders

Jochems, S.P.; Clin. Epigenetics. 2020

Hepatitis B virus (HBV) infection → LAG-3 expression is significantly up-regulated in hepatitis B virus (HBV)-specific CD8 T cells → LAG-3 acts as a suppressor of HBV-specific, cell-mediated immunity / LAG-3 acts as a suppressor to the pathogenesis of hepatocellular carcinoma

Li, F.J.; Immunol. Lett. 2013

Chronic hepatitis C virus (HCV) infection → LAG-3 expression on CD8 T cells → Inhibition of cell proliferation, cytotoxicity function, and cytokine production / LAG-3 expression on CD4 T cells → Negatively associated with HCV-neutralizing antibody responses

Yang, Z.Z.; et al. Oncotarget 2017

Other chronic viral infections → Exhausted LAG-3+ CD8 T cells

McLane, L.M.; et al. Annu. Rev. Immunol. 2019. Anderson, A.C.; Immun. Cell Press 2016
Blackburn, S.D.; et al. Nat. Immunol. 2009. Richter, K.; et al. Int. Immunol. 2009.
Roy, S.; et al. J. Virol. 2009. Roy, S.; et al. Front. Immunol. 2018. Liu, Y.; et al. Sci. Rep. 2018.

Lymphocytic choriomeningitis viral (LCMV) infection / **Herpes simplex virus 1 (HSV-1) infection** → Increase in LAG-3 expression after infection

Human papillomavirus (HPV) status → LAG-3 expression

Wuerdemann, N.; et al. Int. J. Mol. Sci. 2021

Conclusions

- **A deeper understanding of the basic mechanisms underlying LAG-3 intracellular signaling will provide insight for further development of novel strategies for infection diseases.**
- **LAG-3 inhibitors may help the immune system, overcoming immune exhaustion to fight bacterial and viral infections.**

Chocarro, L.; et al. Int. J. Mol. Sci. 2021