medical sciences forum

MDPI

Abstract

LAG-3 Role in Infection †

Luisa Chocarro [1,*], Ester Blanco [1,2], Hugo Arasanz [1,3], Ana Bocanegra [1], Leticia Fernández-Rubio [1], Miriam Echaide [1], Maider Garnica [1], Pablo Ramos [1], Grazyna Kochan [1,*] and David Escors [1,*]

[1] Oncoimmunology Unit, Navarrabiomed-Fundación Miguel Servet, Universidad Pública de Navarra (UPNA), Hospital Universitario de Navarra (HUN), Instituto de Investigación Sanitaria de Navarra (IdiSNA), 31008 Pamplona, Spain; eblancop@navarra.es (E.B.); harasane@navarra.es (H.A.); bocaneg@navarra.es (A.B.); lfernanr@navarra.es (L.F.-R.); mechaidg@navarra.es (M.E.); mgarnics@navarra.es (M.G.); pramosca@navarra.es (P.R.)

[2] Division of Gene Therapy and Regulation of Gene Expression, Cima Universidad de Navarra, Instituto de Investigación Sanitaria de Navarra (IdISNA), 31008 Pamplona, Spain

[3] Medical Oncology Unit, Hospital Universitario de Navarra (HUN), Instituto de Investigación Sanitaria de Navarra (IdiSNA), 31008 Pamplona, Spain

* Correspondence: luisa.chocarro.deerauso@navarra.es (L.C.); grkochan@navarra.es (G.K.); descorsm@navarra.es (D.E.)

† Presented at the 1st International Electronic Conference on Molecular Sciences: Druggable Targets of Emerging Infectious Diseases, online, 1–14 September 2021.

Abstract: Lymphocyte activation gene 3 (LAG-3) is a cell surface inhibitory receptor with multiple biological activities over T cell activation and effector functions [1–3]. LAG-3 negatively regulates proliferation, activation, effector function and homeostasis of both CD4 and CD8 T cells. LAG-3 plays a regulatory role in immunity and emerged some time ago as an inhibitory immune checkpoint molecule, especially as a potential next-generation target for anti-cancer-targeted therapies. 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) [4–12]. Its upregulation in infection is usually associated with a high viral and bacterial load and a reduced survival rate, correlating with faster disease progression and a suppression of viral-specific, T cell-mediated immunity [6,8,12]. LAG-3 inhibits cell proliferation, cytotoxicity function, and cytokine production in response to infection [13]. For example, LAG-3 expression is significantly upregulated in hepatitis B virus (HBV)-specific CD8 T cells, acting as a suppressor of HBV-specific, cell-mediated immunity or even to the pathogenesis of hepatocellular carcinoma [7,12], and it enhances high bacterial burdens together with changes in Th1 responses during active Mycobacterium tuberculosis infections, with an increased expression in the lungs and particularly within the granulomatous lesions [10]. It also correlates with a high viral load within T cell exhausted cells in HIV infection [6]. Here, we will discuss the impaired control of cell-mediated immunity associated with the 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

Citation: Chocarro, L.; Blanco, E.; Arasanz, H.; Bocanegra, A.; Fernández-Rubio, L.; Echaide, M.; Garnica, M.; Ramos, P.; Kochan, G.; Escors, D. LAG-3 Role in Infection. *Med. Sci. Forum* **2021**, *7*, 14. https://doi.org/10.3390/ECMS2021-10835

Academic Editor: Claudiu T. Supuran

Published: 31 August 2021

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ECMS2021-10835/s1.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Chocarro, L.; Blanco, E.; Arasanz, H.; Bocanegra, A.; Fernández-Rubio, L.; Echaide, M.; Garnica, M.; Ramos, P.; Fernández-Hinojal, G.; Vera, R.; et al. 55P Clinical landscape of LAG-3-targeted therapy. *Ann. Oncol.* **2021**, *32*, S1362. [CrossRef]
2. Chocarro, L.; Blanco, E.; Arasanz, H.; Fernández-Rubio, L.; Bocanegra, A.; Echaide, M.; Garnica, M.; Ramos, P.; Fernández-Hinojal, G.; Vera, R.; et al. Clinical landscape of LAG-3-targeted therapy. *Immuno-Oncol. Technol.* **2022**, *14*, 100079. [CrossRef] [PubMed]
3. Chocarro, L.; Blanco, E.; Zuazo, M.; Arasanz, H.; Bocanegra, A.; Fernández-Rubio, L.; Morente, P.; Fernández-Hinojal, G.; Echaide, M.; Garnica, M.; et al. Understanding LAG-3 Signaling. *Int. J. Mol. Sci.* **2021**, *22*, 5282. [CrossRef]
4. Blackburn, S.D.; Shin, H.; Haining, W.N.; Zou, T.; Workman, C.J.; Polley, A.; Betts, M.R.; Freeman, G.J.; Vignali, D.A.A.; Wherry, E.J. Coregulation of CD8+ T cell exhaustion by multiple inhibitory receptors during chronic viral infection. *Nat. Immunol.* **2009**, *10*, 29–37. [CrossRef] [PubMed]
5. Doe, H.T.; Kimura, D.; Miyakoda, M.; Kimura, K.; Akbari, M.; Yui, K. Expression of PD-1/LAG-3 and cytokine production by CD4+ T cells during infection with Plasmodium parasites. *Microbiol. Immunol.* **2016**, *60*, 121–131. [CrossRef] [PubMed]
6. Graydon, C.G.; Balasko, A.L.; Fowke, K.R. Roles, function and relevance of LAG3 in HIV infection. *PLoS Pathog.* **2019**, *15*, e1007429. [CrossRef] [PubMed]
7. Li, F.J.; Zhang, Y.; Jin, G.X.; Yao, L.; Wu, D.Q. Expression of LAG-3 is coincident with the impaired effector function of HBV-specific CD8+ T cell in HCC patients. *Immunol. Lett.* **2013**, *150*, 116–122. [CrossRef] [PubMed]
8. Lino, A.C.; Dang, V.D.; Lampropoulou, V.; Welle, A.; Joedicke, J.; Pohar, J.; Simon, Q.; Thalmensi, J.; Baures, A.; Flühler, V.; et al. LAG-3 Inhibitory Receptor Expression Identifies Immunosuppressive Natural Regulatory Plasma Cells. *Immunity* **2018**, *49*, 120–133.e9. [CrossRef] [PubMed]
9. Liu, Y.; Sorce, S.; Nuvolone, M.; Domange, J.; Aguzzi, A. Lymphocyte activation gene 3 (Lag3) expression is increased in prion infections but does not modify disease progression. *Sci. Rep.* **2018**, *8*, 14600. [CrossRef] [PubMed]
10. Phillips, B.L.; Mehra, S.; Ahsan, M.H.; Selman, M.; Khader, S.A.; Kaushal, D. LAG3 expression in active mycobacterium tuberculosis infections. *Am. J. Pathol.* **2015**, *185*, 820–833. [CrossRef] [PubMed]
11. Roy, S.; Coulon, P.G.; Srivastava, R.; Vahed, H.; Kim, G.J.; Walia, S.S.; Yamada, T.; Fouladi, M.A.; Ly, V.T.; BenMohamed, L. Blockade of LAG-3 immune checkpoint combined with therapeutic vaccination restore the function of tissue-resident anti-viral CD8+ T cells and protect against recurrent ocular herpes simplex infection and disease. *Front. Immunol.* **2018**, *9*, 2922. [CrossRef] [PubMed]
12. Wuerdemann, N.; Pütz, K.; Eckel, H.; Jain, R.; Wittekindt, C.; Huebbers, C.U.; Sharma, S.J.; Langer, C.; Gattenlöhner, S.; Büttner, R.; et al. LAG-3, TIM-3 and vista expression on tumor-infiltrating lymphocytes in oropharyngeal squamous cell carcinoma-potential biomarkers for targeted therapy concepts. *Int. J. Mol. Sci.* **2021**, *22*, 379. [CrossRef] [PubMed]
13. Yang, Z.; Kim, H.; Villasboas, J.C.; Price-Troska, T.; Jalali, S.; Novak, A.J.; Ansell, S.M. Expression of Lag-3 Defines Exhaustion of Intratumoral Pd-1^{+} T Cells and Correlates with Poor Outcome in Follicular Lymphoma. *Hematol. Oncol.* **2017**, *35*, 260–261. [CrossRef]