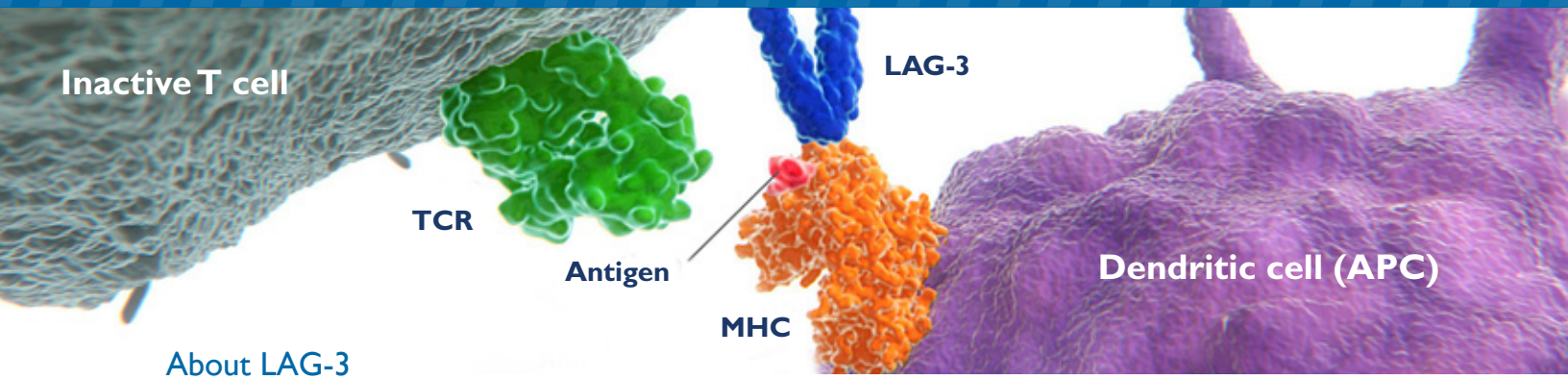
Lymphocyte-Activation Gene 3 (LAG-3) Immune Pathway



About LAG-3

Lymphocyte-activation gene 3 (LAG-3) is an immune checkpoint receptor protein found on the cell surface of effector T cells and regulatory T cells (Tregs) and functions to control T cell response, activation and growth.[1] T cells are a type of white blood cell that are part of the immune system. Activation of cytotoxic T cells by antigens enables them to kill unhealthy or foreign cells.[1]

LAG-3 and Immune Function

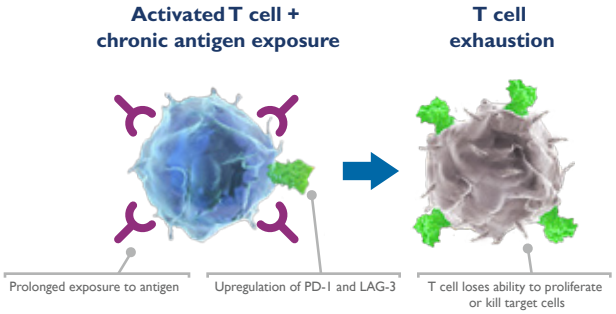
- After a T cell is activated to kill its target cell, LAG-3 expression is increased to turn off the immune response, so that the T cell does not go on to attack healthy cells.[2]
- Inhibition of the immune response is accomplished through the binding of LAG-3 to an antigen-presenting complex called MHC II, which together signal the T cell to stop activation and multiplication.[2,3]

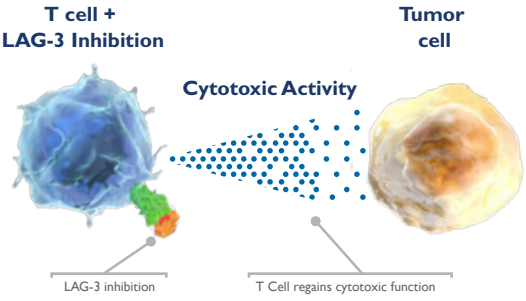
LAG-3 and T Cell Exhaustion

- However, in certain situations where T cells experience prolonged exposure to an antigen, such as cancer or chronic infection, the T cells become desensitized and lose their ability to activate and multiply in the presence of the antigen.[4]
- The desensitized T cell will also progressively fail to produce cytokines (proteins that assist in the immune response) and kill the target cells.[4]
- This process is called T cell exhaustion and is associated with an increased expression of inhibitory receptors such as LAG-3.[4]

LAG-3 and Cancer

- Because of its critical role in regulating exhaustion of cytotoxic T cells and Treg function, LAG-3 has become a target of study in the cancer field.
- In cancer, LAG-3 expressing exhausted cytotoxic T cells and Tregs expressing LAG-3 gather at tumor sites.[5,6]
- Preclinical studies suggest that inhibiting LAG-3 allows T cells to regain their cytotoxic function and potentially affect tumor growth.[7]





Interactions with Other Pathways

Preclinical studies suggest that targeting the LAG-3 pathway in combination with other potentially complementary immune pathways may be a key strategy to more effectively activate the antitumor immune response.

The LAG-3 pathway is just one of many immune pathways under investigation at Bristol-Myers Squibb. Learn more about our work in Immuno-Oncology by visiting:
https://iopathway.web.bms.com

[1]Nicholas Durham, Charles G. Drake et al. Lymphocyte Activation Gene 3 (LAG-3) modulates the Ability of CD4 T- cells to Be Suppressed in Vivo. PLoS ONE. November 2014. DOI: 10.1371/journal.pone.0109080. [2]Workman, C. J., Rice, D. S., Dugger, K. J., Kurschner, C. & Vignali, D.A. Phenotypic analysis of the murine CD4-related glycoprotein, CD223 (LAG3) Eur. J. Immunol. 32, 2255–2263 (2002). [3]Maçon-Lemaître L, Triebel F. The negative regulatory function of the lymphocyte-activation gene-3 co-receptor (CD223) on human T cells. Immunology 2005; 115:170–8. [4]Wherry, E. J. T cell exhaustion. Nature Immunol. 12, 492–499 (2011). [5]Huang CT, Workman CJ, Flies D, et al. Role of LAG-3 in Regulatory T Cells. Immunity. 2004; 21(4):503-513. [6]Camisaschi C, Casati C, Rini F, et al. LAG-3 Expression Defines a Subset of CD4+ CD25high Foxp3+ Regulatory T Cells That Are Expanded at Tumor Sites. J Immunol. 2010; 184(11):6545-6551. [7]Grosso JF, Kelleher CC, Harris TJ, et al. LAG-3 regulates CD8+ T cell accumulation and effector function in murine self and tumor-tolerance systems. J Clin Invest. 2007;117(11):3383-3392. [8]Seng-Ryong Woo, Dario A.A. Vignali, et al. Immune inhibitory molecules LAG-3 and PD-1 synergistically regulate T cell function to promote tumoral immune escape. Cancer Res. 2012 Feb 15; 72(4): 917–927

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