Abstract

LAG-3 Role in Infection †

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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 [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

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References