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Review Article

PROGRAMMED DEATH LIGAND -1: A REVIEW

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ABSTRACT

Aim: To review the details of programmed death ligand 1 genes and its biological role.
Objective: This review aims at analyzing the clinical significances of programmed death ligand gene 1 in cancers and autoimmunity.
Background: Programmed death-ligand 1 (PD-L1) also known as cluster of differentiation 274 (CD274) or B7 homolog 1 (B7-H1) is a protein that in humans is encoded by the CD274 gene. Programmed death-ligand 1 (PD-L1) is a 40kDa type 1 transmembrane protein that has been speculated to play a major role in suppressing the immune system during particular events such as pregnancy, tissue allografts, autoimmune disease and other disease states such as hepatitis. Normally the immune system reacts to foreign antigens where there is some accumulation in the lymph nodes or spleen which triggers a proliferation of antigen-specific CD8+ T cells.
Reason: To create awareness about the advantages of PD-L1 gene.

INTRODUCTION

Programmed death-ligand 1 (PD-L1) also known as cluster of differentiation is a protein encoded in humans by gene CD274[1]. Programmed death-ligand 1 (PD-L1) is a type 1 transmembrane protein of 40kDa criteria. It has been enquirer to play a major role in suppressing the immune system duringdiseased and normal states. Their role is seen pregnancy, tissue allografts, autoimmune disease and other disease states such as hepatitis. Normal body function in which the immune system reacts to foreign antigens. This leads to accumulation of the precursor cells in the lymph nodes or spleen which triggers a proliferation of antigen-specific CD8+ T cells. An inhibitory signal is produced due to the binding of PDL-1 to PD-1 or B7.1. This inhibitory signal reduces the proliferation of these CD8+ T cells at the lymph nodes and they are able to control the accumulation of foreign antigen specific T cells in the lymph nodes. This again lower regulates Bcl -2 gene through programmed cell death or apoptosis in the lymph nodes. Thus, their activity is evident during immune reactions [2].

Structure of the Pdl-1

According to a study done by Zak KM *et al*, [3] it showed that crystals of the PD-L1 complex that were obtained diffracted to 2.45 Å resolution and contained an asymmetric unit . PDL-1 assumes a β-sandwich immunoglobulin-variable topology forming a characteristic disulfide bridge; however PD-1 lacks the second disulfide common to other family members. The molecule is well defined by electron density, safe for a region between C′D strands. However, previous reports done by Lázár-Molnár *et al*., 2008; Zhang *et al*., 2004; Cheng *et al*., 2013 shows that there is not much dimerization of crystal lattice in solution[4,5,6].

Signalingof the Pd-L1 Protein

Signaling includes engagement of PD-L1 with its receptor PD-1 on T cells delivers a signal that inhibits T cell receptor mediated activation of IL-2 production and T cell proliferation. The mechanism involves inhibition of ZAP70 (a protein expressed near the surface membrane of T cells) phosphorylation and its association with CD3ζ(amino acid ectodomain)[7]. It is necessary for the activation of transcription factors NF-κB and AP-1 which leads to the production of interleukin 2 which in turn is due to PD-1 signaling attenuation PKC-θ (an enzyme) activation loop phosphorylation. Contribution to ligand induced T- cell receptor down modulation during antigen presentation to native cells is due to signaling of PDL-1 and PDL. This down modulation is due to inducement of ubiquitin ligament CBL-b[8]

Role of pdl-1 sjogren's syndrome affected mice

Expression of PDL-1 and PD-1 in the submandibular glands of NOD (non obese diabetic) mice increases during the development of SS-like disease. Increased PDL-1 and PD-1 expressions are shown in patients with Sjorgen syndrome [9].

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The mRNA levels in the submandibular glands were determined in the mice to examine whether PD-L1 and PD-1 expression is elevated during the development of Sjorgen syndrome. Firstly, it determined the time course of disease development in the female NOD/ShiLtJ mice by examining mice aged 4-, 7-, 10- and 12 weeks. The results showed that the disease onset started around 10 weeks of age in the great majority of these mice, based on the presence of leukocyte foci in the submandibular gland. Thus they assessed PDL-1 and PD-1 gene expression at 4-, 7- and 10 weeks of age by real-time PCR analysis. The study showed that the amounts of both PD-L1 and PD-1 mRNA in the submandibular glands were significantly increased between age 4 and 7 weeks. And between age 7 and 10 weeks it was seen that PD-1 mRNA levels were further increased. Thus, the study concluded that elevation in the levels of PDL-1 and PD-1 in the submandibular glands is a negative feedback phenomenon in the mice to suppress autoimmune responses and hinder the further development of this disease.[10]

Increased Pd-L1: A Prognosis in Hepatic Cellular Carcinoma

Despite all other facts, a great clinical significance of PDL-1 gene expression is seen in patients with hepatocellular carcinoma. However, the results were conflicting and inconclusive. Xiaobin Gu *et al*,[11]conducted a meta-analysis to combine controversial data to precisely evaluate this issue. This meta-analysis indicated that over expression of PD-L1 was predictive. It had shortened Overall survival and Disease free survival OR recurrence free survival in patients with hepatic cellular carcinoma. Differentiation, vascular invasion, and AFP (alpha fetoprotein) elevation are also seen as a prognosis for hepatic cellular carcinoma. Thus they concluded that it was a great bio marker for prognosis.

Diffuse large b- cell lymphoma and pdl-1: Diffuse large B-cell lymphoma (DLBCL) is defined as diffuse proliferation of large neoplastic B lymphoid cells that efface the preexisting architecture. Although recent studies have subdivided DLBCL into some morphologically, biologically, or clinically distinct disease entities, a large number of cases remain heterogeneous.[12] Anthracycline- based chemotherapies combined with rituximab, have long been the standard and best therapy for DLBCL. Although more than half of patients achieve long-term revocation, these therapies are sometimes ineffective, particularly in patients with high- risk disease. New treatment strategies based on underlying molecular oncogenic mechanisms are necessary in regard to address this concern. In reference to this a study was done to show that PD-L1 is also expressed on DLBCL tumor cells and tumor- infiltrating nonmalignant cells, primarily macrophages. In contrast, PD-1 is expressed on tumor-infiltrating lymphocytes (TILs), and the presence of a large number of PDL-1tumour infiltrating lymphocytes is associated with favorable overall survival (OS) in patients with DLBCL. Furthermore, the presence of high levels of plasma-soluble PDL-1 is associated with poor overall survival and acts as a potent novel biomarker in Diffuse large B cell lymphoma. These results suggest that the PD-1/PD-L1 pathway contributes to tumor cell survival. [13]

CONCLUSION

Since this programmed death ligand 1 is involved in prognosis of deadly diseases like cancers, melanoma, lymphoma etc., the awareness of this gene expression in humans is very necessary.

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