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Short Communication

Systematic review on PDL-1 exression in human cancer

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ABSTRACT

Cancer is a leading cause of death worldwide with devastating mortality and morbidity. They present with myriad and exhaustively variable prodromes and symptoms or syndromic forms. Therapeutic modalities like chemotherapy and radiotherapy target replicative potential and excessive proliferative nature of neoplasms. Of the hallmarks of cancer, evasion of immune response to tumor proliferation is the target for another treatment option – immunotherapy, which has come into prominence over the last decade. Immunotherapy was developed when Dr. James Allison discovered a protein receptor on T cell surface, the cytotoxic T-lymphocyte antigen 4, which was later found to be involved in immunosuppression in cancer. The idea behind immunotherapy was conceived by Dr. Allison when experiments were conducted over decades and proteins were sought that could antagonize CTLA-4 and in theory could overturn the immunosuppressive nature of T cell behavior in a neoplastic background.

Immunotherapeutic strategies have evolved to include vaccines, oncolytic viruses, adoptive transfer of ex vivo activated T and natural killer cells, and administration of antibodies or recombinant proteins that stimulate T cells or block the immune checkpoint pathways, the so-called immune checkpoint inhibitors. Examples of immune check point targets include cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programmed cell death protein 1 (PD1;CD279) and programmed cell death protein 1 ligand (PDL-1;CD274). [1]

1. Introduction

From a biochemical perspective, PD-L1/2 are responsible for activating T cell activation, proliferation, migration and cytotoxic activity and is involved in anti-tumor immune response mechanisms in cancer. PDL1 upregulation causes an anti tumor inflammatory response, mediated by macrophages, activated T cells and B cells, Dendritic cells and epithelial cells. PD-L1 is associated with an immune environment with abundance of CD8 T cells, Th1 cytokines, and interferons. [2,3]

Immune evasion of cancer cells is mediated by directly inhibiting effector cytotoxic cells listed above using PD-L1/PD-1 interactions. This is mediated by inhibiting mTOR/AKT signaling pathway, which deregulates expression of interferon. PD-L1 can also directly deliver anti-apoptotic signals to tumor cells, helping them survive IFN mediated effector cell cytotoxicity. PD-L1, in addition, can be expressed in tumor cells, stromal cells and other immune cells, including tumor-infiltrating myeloid lineage cells and T cells. [4,5]

Mechanism of activation of PDL1 activity can involve multiple signaling pathways. interferon gamma (IFNγ) produced by T cells can activate the Janus kinase (JAK) signal transducer and activator of transcription (STAT) pathway, leading to transcriptional activation of interferon regulatory factor 1 (IRF1), which activates by binding to the PD-L1 promoter region. Alternatively, Tumor necrosis

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factor alpha (TNFα) and IFNγ also activate the NF-κB pathway leading to activating PD-L1 transcription. [1,6,7]

PD-L1-expressing cancer cells have been found to be significantly more resistant to T cell mediated cytotoxicity by providing a protective 'molecular shield' that inhibits their function. [1,2,8,9]

PD-L1 expression also interferes with a multiple pro-apoptotic signals, the likes of first apoptosis signal receptor (Fas)-Fas ligand (FasL) interactions or pro-apoptotic drugs, alternatively also by enhancing core survival pathways. These mechanisms form a framework for the clinical breaking ground in immunotherapy. As with all paradigm shifting modalities, immunotherapy has been developed in clinical settings far more intensively and extensively than in the bench based lab workups. In truth, molecular data and biochemical knowledge regarding PDL1 or PD1 have been found to be less extensively studied than their use in therapeutic endeavors. Other mechanisms by which these entities act on the neoplastic cell can include effect on glucose metabolism. As studied, antiCTLA-4, anti-PD-1 or anti-PD-L1 antibody treatment in the form of immunotherapy restores glucose levels within the tumor environment, suggesting that they regulate glucose metabolism in cancer cells. PD-L1 inhibits T cell effector activities by binding PD1. It favors cancer cell survival and tumor progression via the modulation of metabolic pathways. [1,3,10,11]

On a molecular overview, two mechanisms have been identified — reactivation of dormant inactivated tumor-infiltrating T cells and other inflammatory cells that would then produce cytotoxic mediators, such as IFNs and sensitization of tumor cells to IFN-induced apoptosis—directly activating cytotoxicity over cancer cells.

PD-L1 is a emerging target for cancer therapy, because it plays a role in anti-tumor immunity by inhibiting the T cell immunity as well as by activating the protumoral amplification of the PD-L1 genes. Activation at p24.1 on chromosome 9 leads to PD-L1 upregulation in various cancers like breast cancer, lymphoma, lung cancer, and expression of fusion transcript CIITA-PD-L1 on 9p24.1, leads to overexpression of PD-L1 in primary mediastinal large B-cell lymphoma (PMBCL). [2,12] Single nucleotide polymorphisms (SNPs) from 3'-UTR of the PD-L1 are correlated with PD-L1 expression in gastric cancers (GC).

Other solid and hematologic malignancis involved with PD1/PDL1 mutations and epigenetic changes include melanoma, RCC, NSCLC, bladder, head and neck, cervical cancer, glioblastoma multiforme, breast cancer, gastric carcinoma, esophageal cancer, hepatocellular carcinoma, pancreatic cancer, colorectal cancer, thymic cancer, ovarian cancer, sarcoma, unknown primaries, acute myeloid leukemia, other leukemias, B-cell lymphomas, multiple myeloma and a myriad of other tumors. [2,13,14]

PD-L1 expression can also be epigenetically regulated. For example, the enhancer of EZH2, an epigenetic modifier, negatively regulates PD-L1 by upregulating interferon-responsible factor 1 (IRF-1) and thus subsequently interferon in hepatocellular carcinoma.

Other factors like overexpressed MYC, HIF-1 alpha and HIF-2 alpha are involved in PD-L1 upregulation in cancers like melanoma, NSCLC, lymphoma, head and neck squamous cell carcinoma (HNSCC), breast cancers. Activating mutation of NF-kappa B and STAT3 can target PD-L1 promoter in the absence of cytokine to upregulate the PD-L1 expression in melanoma and NK/T cell lymphoma. Other molecular signaling mechanisms disrupted include oncogenic MEK-ERK signaling pathway, KRAS, BRAF, and EGFR pathways. [1–3,13,14]

2. Source of Funding

None.

3. Conflict of Interest

None.

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