Relationship of Metabolic Alterations and PD-L1 Expression in Cisplatin Resistant Lung Cancer

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Abstract

Despite numerous reports on immune checkpoint inhibitor for the treatment of non-small cell lung cancer (NSCLC), the response rate remains low but durable. Thus cisplatin still plays a major role in the treatment of NSCLC. While there are many mechanisms involved in cisplatin resistance, alteration in metabolic phenotypes with elevated levels of reactive oxygen species (ROS) are found in several cisplatin resistant tumors. These resistant cells become more reliant on mitochondria oxidative metabolism instead of glucose. Consequently, high ROS and metabolic alteration contributed to epithelial-mesenchymal transition (EMT). Importantly, recent findings indicated that EMT has a crucial role in upregulating PD-L1 expression in cancer cells. Thus, it is very likely that cisplatin resistance will lead to high expression of PD-L1/PD-1 which makes them vulnerable to anti PD-1 or anti PD-L1 antibody treatment. An understanding of the interactions between cancer cells metabolic reprogramming and immune checkpoints is critical for combining metabolism targeted therapies with immunotherapies.

Keywords: Lung cancer; PD-L1; EMT; Resistance; Cisplatin

Introduction

Treatment for early stage lung cancer is surgery but most patients already have locally advanced or metastatic disease at the time of diagnosis. Chemotherapy combined with radiation therapy or chemotherapy alone remains the primary modality of treatment for stage 3 and 4 disease. Targeted agents such as erlotinib or gefitinib (EGFR inhibitor) or crizotinib or ceritinib (ALK inhibitors) have shown activity in NSCLC (non-small cell lung cancer) which possess these putative types of mutation. However, both EGFR mutation and ALK mutation are rare (only 5-20%) and usually occur in women and non-smokers. Immunotherapies with checkpoint inhibitors has received much attention lately. They offer a longer duration of response; however, the response rate is still very low in lung cancer. In fact, a recent report on PD1 inhibitor (programmed death-1) did not show improved efficacy over standard chemotherapy as first line treatment in lung cancer and did not receive FDA approval as first line therapy for NSCLC. Another checkpoint inhibitor pembrolizumab has received FDA approval for first line treatment but only in tumors which express PD-L1 (program death receptor ligand-1). Therefore, platinum containing regimen remains the first line treatment in patient with NSCLC. Despite a 50% initial response rate to platinum-based chemotherapy, the majority of lung cancer patients develop resistance to treatment. Thus, cisplatin resistance remains the major impediment for the treatment of lung cancer.

Accumulating evidence suggests that tumor metabolism is in fact intercoordinated to drug resistance and it has proven to be one of the most important challenges in cancer treatment [1-3]. The observations of metabolic differences in cancer cells were first reported by Otto Warburg [4,5]. He showed that cancer cells prefer to utilize glucose even in the presence of oxygen; hence this led to the term "aerobic glycolysis". This difference in energy metabolism between tumor and normal tissue has been utilized successfully in the development of a diagnostic imaging technique, fluoro-deoxy-glucose positron emission tomography (FDG-PET) for cancer detection. However, what is not known is why certain tumors are PET-negative (not taking up FDG), and why PET negativity does not always correlate with tumor response. Thus, it is conceivable that PET negative's tumors have undergone metabolic reprogramming after chemotherapy and are no longer addicted to glucose. To further support this notion, it has been shown that therapy-resistant tumors have altered metabolic phenotypes relative to treatment-naive tumors, with increased reliance on mitochondrial metabolism in the resistant cancers [6-9]. Increased mitochondrial metabolic activity can lead to high levels of reactive oxygen species (ROS) [10]. In fact, many have discovered that elevated reactive oxygen species (ROS) are found in cisplatin resistant (CR) cells only those derived from patients who failed cisplatin [11-14].

ROS, a harmful by-product of metabolism played an important role in signaling pathways. ROS is known to facilitate the activation of receptor tyrosine kinase signaling as well as PI3K/AKT which play a vital role in cell growth/proliferation, survival, and motility [15,16]. Moreover, during the past decade, elevate ROS level in tumor cells have been implicated in epithelial-mesenchymal transition (EMT) [17-19]. Importantly, recent reports have shown that EMT played an essential role in upregulating PD-L1 (programmed death ligand-1) expression [20].

In this review, we provide a possible link between metabolic alteration and PD-L1 expression in cisplatin resistant lung cancer (Figure 1). Understanding these complex interrelationships will provide a new approach in overcoming the cisplatin resistance in lung cancer.

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studies have shown that reduction in lactate dehydrogenase A (LDHA) glutamine becomes the conditionally essential amino acid. Moreover, energy demand and biosynthesis. In this regard, reports have shown sources to replenish TCA cycle intermediates (anaplerosis) for their others [27] have shown that cisplatin resistant (CR) cells are no longer recognized as the main carbon skeleton source of energy, we and through oxidation of Cys caused inhibition of the glycolytic enzyme pyruvate kinase M2 (PKM2) [358]. On the other hand, reduced PKM2 activity allows accumulation of HIF1α target gene expression. Cells expressing high levels of PKM2 is a key protein in directing tumor cells toward glycolysis [25]. PKM2 which converts phosphoenolpyruvate (PEP) to pyruvate, could be an answer for the aerobic glycolysis observed in Warburg’s theory. 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immunosuppressive CD8+ tumor infiltrating lymphocytes in preclinical models of lung, melanoma, pancreatic cancer, and breast cancer [61-63]. Importantly, microRNA200 and ZEB1 axis, which is known to control cancer cell migration/invasion and EMT, can also regulate PD-L1 expression. Decrease in PD-L1 expressions was reported as a consequence of ectopic microRNA 200 expression or ZEB1 knockdown models [20]. In fact, low microRNA200 with high ZEB1 and PD-L1 expressions in mesenchymal tumors created a microenvironment of decreased CD8+ T-cells populations [20].

PD-L1, a ligand of PD1 is an immune regulatory protein deriving from B7 family of T-cell co-regulatory molecules [64]. Their interaction prevents T-cell activation and proliferation including cell apoptosis and creates cancer resistance. So far, PD-L1 was found in many solid neoplasms such as cancer of the breast, colon, esophagus, stomach, ovaries, pancreas and lung [64]. As a prognostic marker, PD-L1 expression is a poor prognostic factor for gastric cancer, liver cancer, esophageal cancer, ovarian cancer, bladder cancer, but served as a prognostic marker for adenocarcinoma of esophagus, breast, ovaries, pancreas and lung [64]. As a prognostic marker, PD-L1 expression defines a subset of human melanoma tumors with increased microRNA200 and ZEB1 axis, which is known to control cancer cell migration/invasion and EMT, can also regulate PD-L1 expression. Blocking PD1 and PD-L1 interaction with checkpoint inhibitor(s) in combination with ROS inducing agent may lead to new approaches to overcome cisplatin resistant lung cancer.

Concluding Remarks

Immunotherapy with checkpoint inhibitors has received much attention lately. This type of therapy offers a longer duration of response; however, the response rate is still low in lung cancer. In fact, a recent report on immunotherapy did not show improved efficacy over standard chemotherapy and failed as first line treatment in lung cancer. Therefore, the majority of lung cancer patients still require the traditional chemotherapeutic agents such as cisplatin or carboplatin to control their disease. We have found that the major biochemical alterations in cisplatin resistance are increasing ROS and metabolic reprogramming which can be used to kill cisplatin resistant cells. Furthermore, the tumor microenvironment may also be modified in these resistant tumors by multiple factors including immune cells such as tumor-infiltrating lymphocyte. These resistant cells undergo epithelial-mesenchymal transition to enable invasion/metastasis as well as escape immune surveillance by expressing PD-L1/PD1 axis. ZEB1 and microRNA200 can regulate this axis. KRAS or EGFR mutation may also influence PD-L1 expression. Blocking PD1 and PD-L1 interaction with checkpoint inhibitor(s) in combination with ROS inducing agent may lead to new approaches to overcome cisplatin resistant lung cancer.

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