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INTRINSIC PROGRAMMED DEATH LIGAND 1 (PD-L1) ROLE IN PROMOTING TRIPLE NEGATIVE BREAST CANCER (TNBC) PROGRESSION

By

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Abstract

The Triple Negative Breast Cancer (TNBC) malignancy is characterized by lack of estrogen, progesterone, and HER2 receptors expression, making targeted drugs ineffective. TNBC has a high proliferative rate, which results in a poor prognosis. Chemotherapy, the primary treatment for metastatic breast cancer, is not an ideal choice due to its toxicity towards normal cells. Therefore, Cancer-targeted therapy has been developed to improve the specificity and strength of the immune system against cancer cells. PD-L1 is an immunosuppressive protein that inactivates T cells by binding to the inhibitory receptor PD-1. The clinical use of PD-L1 blockade agents has progressed beyond basic mechanistic studies. However, the lack of knowledge on how PD-L1 regulates cancer hallmarks can lead to missed therapeutic opportunities. The main objective of this research is to identify the phenotypic changes in TNBC cells after PD-L1 gene knockout and pinpoint the PD-L1 related intrinsic cellular signaling pathways responsible for promoting cancer growth and metastasis. The study investigates PD-L1 role in the progression of TNBC MDA-MB-231 cancer by using three designs of CRISPR-Cas9 lentiviral particles to knock out the PD-L1. Our results revealed that PD-L1 knockout significantly inhibited MDA-MB-231 cell proliferation and colony formation in vitro and tumor growth in the chick embryo chorioallantoic membrane (CAM) model in vivo. PD-L1 knockout also decreased the migration and invasion of MDA-MB-231 cells in vitro. We demonstrate a potential mechanism by which PD-L1 promotes MDA-MB-231 cells' malignancy through the regulation of PI3K/AKT and MAPK/ERK pathways. We have also reported that PD-L1 regulate the expression of p21, RhoA, c-Fos, c-Myc, Survivin, COX-2, in TNBC cells. Our findings provide insights into new potential cancer therapeutic strategies and suggest the development of anti-PD-L1 combination therapies for effective TNBC treatment.

Keywords: PD-L1; TNBC; proliferation; migration; invasion; CAM; Akt; ERK.