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Overcome resistance to cancer immunotherapy

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Abstract

Cancer is one of the main public health problems in the world. Systemic therapies such as chemotherapy and more recently target therapies as well as immunotherapy have improved the prognosis of this large group of complex malignant diseases. However, the insurgence of mechanisms of resistance is one of the major impediments towards curative treatment of cancer. While several mechanisms of drug chemo resistance are well defined, resistance to immunotherapy is still insufficiently unclear due to the complexity of the immune response and its dependence on the host. In this regard, multiple factors can be related to immunotherapy resistance: characteristics of the tumor microenvironment (TME); presence of tumor infiltrating lymphocytes (TILs), such as CD8 + T cells associated with treatment-response; presence of tumor associated macrophages (TAMs); activation of certain regulators (like PIK3γ or PAX4) found present in non-responders; a low percentage of PD-L1 expressing cells; tumor mutational burden (TMB); gain or loss of antigen-presenting molecules; genetic and epigenetic alterations correlated with resistance. In a recent study conducted in lung cancer patients, we showed that mutations that functionally inactivate the tumor suppressor STK11 (also known as LKB1) in non-small cell lung cancer (NSCLC) confer resistance to anti-PD-1 immunotherapy and standard of care chemotherapy. In particular, we found an association between STK11 mutations and resistance to anti-PD-L1 or dual anti-PD-L1 plus anti-CTLA4 immunotherapy in early-stage NSCLC clinical trials. Translational endpoints indicated a potential role for STAT3 signaling within the tumor microenvironment in establishing an immunosuppressive microenvironment. Using an anti-sense oligonucleotide approach in pre-clinical models to attenuate STAT3 activity in immune and stromal cells, we showed that checkpoint immunotherapy resistance was reversed when STAT3 knockdown re-programmed the tumor microenvironment to a more immunostimulatory phenotype.

Short summary: Loss of function STK11 (LKB1) mutations confer resistance to anti-PD-L1 or dual anti-PD-L1 plus anti-CTLA4 immunotherapy in non-squamous NSCLC, but pre-clinical data indicate this may be overcome by inhibiting STAT3-mediated immunosuppression in the tumor microenvironment.

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