Sensitizing Non-Small Cell Lung Cancer (NSCLC) to Immunotherapy

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Overview

non-small cell lung cancer (NSCLC) has a poor prognosis and low survival rates. Recently developed immunotherapy has revolutionized the therapy for NSCLC, significantly prolonging the overall survival of advancedâ€‘stage patients. However, only 15-20% of the patients respond to immunotherapy and benefit from it. The group of Dr. Yifat Merbl identified a new protein whose expression controls NSCLC tumor responsiveness immunotherapy. By down-regulation of this protein, non-responding patients could potentially overcome the resistance to immunotherapy and significantly improve their survival.

Background and Unmet Need

NSCLC comprises approximately 85-90% of all known lung cancer cases, is often diagnosed only after the patients become symptomatic, once the disease has already advanced. In these stages, most conventional treatments are not effective and the 5-year survival rate is low. Recently developed immunotherapies considerably improved the overall survival (OS) rates of patients (from 5.5% to 20% 5-year OS of advanced stages). However, the majority of patients eventually fail to respond to immunotherapy, and only 15 to 20% achieve a partial or complete response[1â€“3]. Therefore, many efforts are currently invested to avoid or overcome immunotherapy resistance to improve patient outcome.

The Solution

The group of Dr. Yifat Merbl identified a new target whose expression affects the responsiveness of NSCLC tumors to immunotherapy. Therefore, down regulation of this protein in cold tumors can possibly sensitize them to immunotherapy.

Technology Essence

The group of Dr. Yifat Merbl developed MAPP (Mass Spectrometry Analysis of Proteolytic Peptides), a unique method to isolate and identify the peptides captured inside or near the proteasome. Using this technique on NSCLC patient samples, the group identified PSME4, a regulatory protein that directly binds to and attenuates the activity of the immunoproteasome in NSCLC cells. Consequently, tumors enriched with PSME4 are characterized by low inflammation and reduced responsiveness to immunotherapy, demonstrating a cold tumor signature (Figure 1). Using a mouse orthotopic model, the group further demonstrated that splenic lymphocytes exposed to tumor cells with PSME4 knockdown (KD) exhibited a better killing ability of the tumor cells. Therefore, downregulation of PSME4 levels in NSCLC tumors can sensitizes these tumors to immunotherapy treatment.

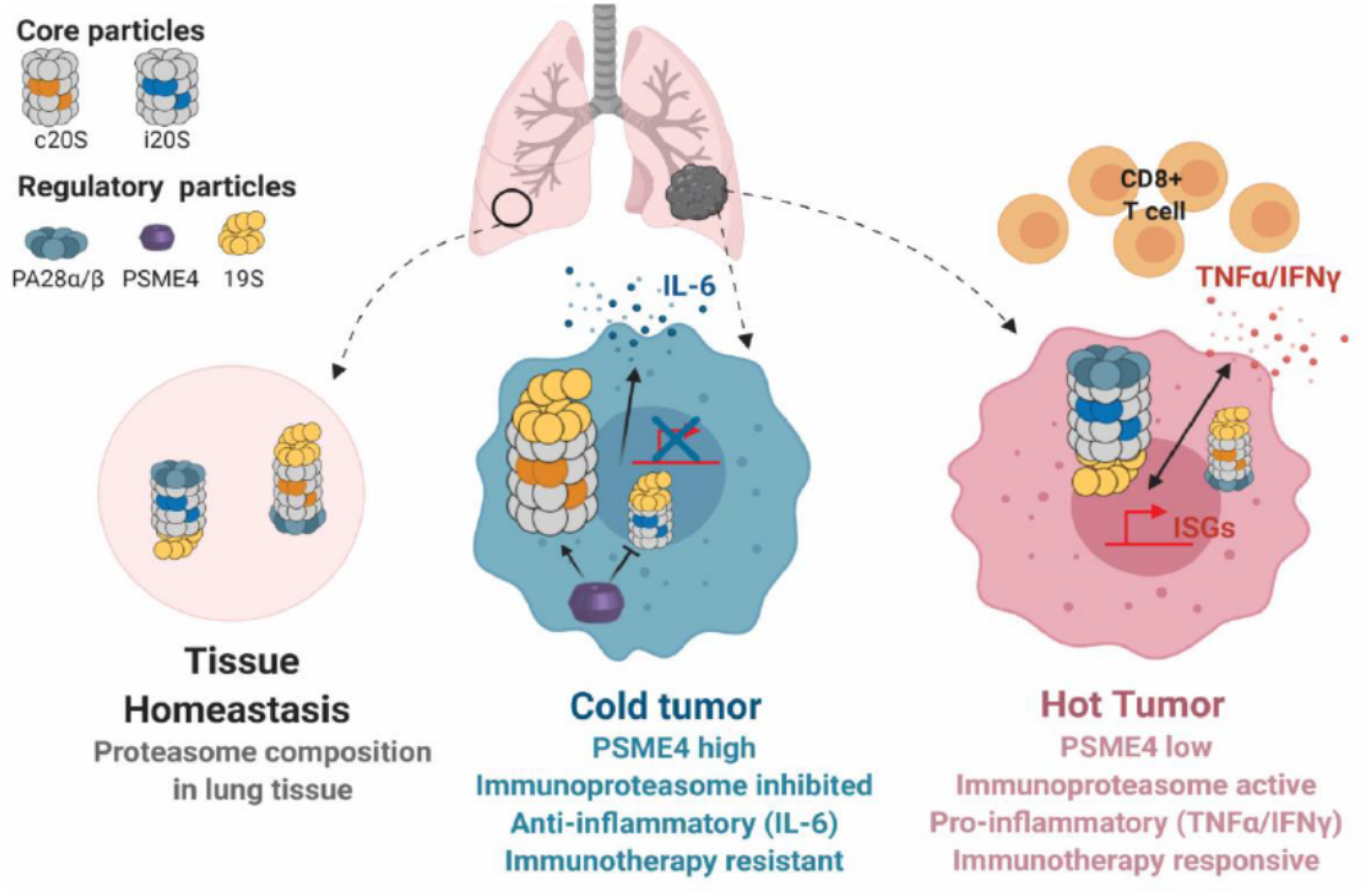

Figure 1 â€“ Responsiveness to immunotherapy is dependent on PSME4 expression.

Applications and Advantages

Increasing responsiveness rates of NSCLC patients to immunotherapy

Development Status

The group proved that PSME4 levels are correlated with responsiveness to immunotherapy in NSCLC patients. Using mouse model, PSME4 KD of tumor cells increased the cytotoxicity response of lymphocytes to tumor cells.

References

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