慶 應 医 学 会 例 会

下記により例会を開催いたしますので、多数ご来聴ください。

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日　時　2019 年 9 月 30 日 （月） 18 ： 00

場　所　総合医科学研究棟１階ラウンジ

演　題 **Dissecting resistance to PD-1 blockade, one cell at a time**

Drew Mark Pardoll M.D., Ph. D.

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PD-1 pathway blockade has been approved for 16 different cancer types and is being tested in an additional 15. Despite its dramatic activity, the majority of patients do not respond to anti-PD-1 antibodies. We have shown that neoadjuvant anti-PD-1 given to lung cancer patients prior to resection of their primary tumor results in a nearly 50% major pathologic response rate (<10% of tumor bed consisting of viable tumor cells). This clinical format allowed us to obtain large numbers of TIL after anti-PD-1 therapy so that we could perform single cell transcriptomics and TCR repertoire analysis. As part of this analysis we could determine which genes and genetic programs were associated with successful anti-tumor response vs non-response. We found that T cells from non-responding tumors exhibited a broad stress response signature, while T cells from MPR tumors did not. While T cells from both responding and non-responding tumors expressed high levels of PD-1, PD-1+ T cells from non-responding tumors had higher levels of the canonical exhaustion factor TOX and other exhaustion-associated genes, including CD39, Tim3 and other checkpoints. T cells from non-responders demonstrated Treg from non-responding tumors were more numerous and expressed specific Treg inhibitory molecules. Taken together, T cells ronr-responding tumor encounter a high stress microenvironment and express high levels of transcriptional and membrane inhibitory molecules, some of which are therapeutically targetable.

PD-1 blockade a common denominator for cancer therapy

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The PD-1 pathway, including the immune cell receptor Programmed Cell Death 1 (PD-1) and its ligands, PD-L1 (B7-H1) and PD-L2 (B7-DC), mediates immunosuppression in the tumor microenvironment. Drugs that "release the brakes" on anti-tumor immunity by blocking PD-1 or PD-L1 have shown substantial and durable activity in multiple cancers, validating them as a "common denominator" for cancer therapy. Since September 2014, the US FDA has approved 6 different PD-1/PD-L1 antibodies to treat advanced cancers, including 15 tumor types and the broad genetically-defined MSI-high category. These drugs are now being applied in earlier stages of cancer, in the adjuvant and neoadjuvant settings. Tumor PD-L1 protein expression correlates with enhanced responsiveness of some cancers to anti-PD-1, while tumor mutational burden, reflecting neoantigen load, associates with likelihood of response in additional patients. The continued interrogation of potential biomarkers is expected to further refine the risk:benefit profile for PD-1/PD-L1 antagonists, increase our understanding of the mechanistic underpinnings of this pathway, and guide the development of more effective combination therapies.

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