Semaphorin 4A improves the efficacy of anti-PD-1 antibody

Keywords: lung cancer, immune checkpoint inhibitors, semaphorins, T lymphocytes, cancer immunity

Although immune checkpoint inhibitors have brought major advances in cancer treatment, their effectiveness is still far from satisfactory. We need to develop novel biomarkers and therapies that strengthen their effectiveness.

Yujiro Naito, Shohei Koyama, Atsushi Kumanogoh (Graduate School of Medicine, Osaka University/IFReC), and the research group shows that histologically Semaphorin 4A (Sema4A)-positive non–small cell lung cancer (NSCLC) responded significantly better to anti–programmed cell death 1 (PD-1) antibody than Sema4A-negative NSCLC. Intriguingly, SEMA4A expression in human NSCLC was mainly derived from tumor cells and was associated with T cell activation. Sema4A promoted cytotoxicity and proliferation of tumor-specific CD8+ T cells without terminal exhaustion by enhancing mammalian target of rapamycin complex 1 and polyamine synthesis, which led to improved efficacy of PD-1 inhibitors in murine models. Improved T cell activation by recombinant Sema4A was also confirmed using isolated tumor-infiltrating T cells from patients with cancer. Thus, Sema4A might be a promising therapeutic target and biomarker for predicting and promoting ICI efficacy.

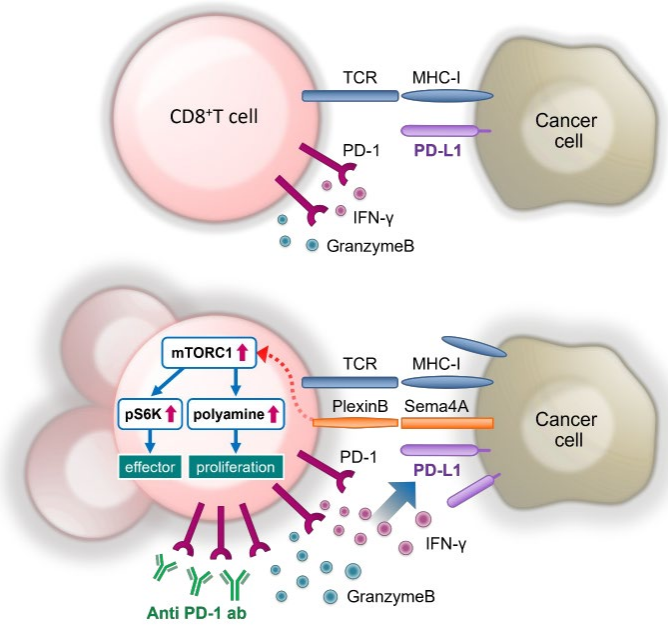

Figure Schematic of the role of Sema4A in the tumor microenvironment.
Sema4A expressed by tumor cells ameliorated anti-tumor function and proliferation of CD8+ T cells by promoting mTORC1-S6K signaling and polyamine synthesis.

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