東京医学会

東京医学会　第 2749 回集会

日時：平成 30 年 6 月 7 日(木)　17：00～18：00

場所：教育研究棟　13F　第 5 セミナー室

演者：**Rosemary J. Akhurst PhD**

(所属) Helen Diller Family Comprehensive Cancer Center, University of California at San Francisco

演題：**Targeting the TGFβ signaling pathway for oncology.**

紹介：Resistance to checkpoint blockade therapy for human melanoma, and urothelial and colon cancers, has recently been associated with signatures of epithelial mesenchymal transformation (EMT) and/or elevation of TGFβ signaling. Our lab and those of others have shown that TGFβ signaling is a key regulator of reversible epithelial to mesenchymal transition (EMT) in vitro and in vivo, and that TGFβ is a major driver of tumor progression and metastasis through multiple effects on the tumor and tumor microenvironment. In a chemically induced squamous carcinoma cell (SCC) allograft model, we find that anti-PD-1 therapy significantly elevates immunosuppressive Treg numbers in tumors, and increases the number of tumor cells expressing nuclear p-Smad3, an immediate downstream target of the TGFβ receptor complex, and a marker of TGFβ signaling. Moreover, we have shown that systemic administration of TGFβ blocking antibodies in vivo, can elicit potent anti-tumor activity in mice carrying tumors of high neoantigen load, and that this effect is potentiated by checkpoint blockade. Monotherapy with anti-TGFβ blocking antibodies or combination therapy with anti-PD-1 can lead to complete tumor regression with ensuing anti-tumor immunity in the mouse SCC model, and these studies have directly resulted in a Novartis clinical trial using this drug combination.

In this SCC model, we have shown that the anti-tumor effect of TGFβ blockade is completely dependent on both CD8+ cytotoxic T cells and CD4+ T effector cells. Moreover, TGFβ blockade enhances the anti-tumor effects of PD-1 blockade in part by depleting intratumoral Treg that are increased in number in response to anti-PD-1 therapy. Thus, the immune system is absolutely required for anti-TGFβ elicited tumor rejection. Nevertheless, our preliminary data also suggest a role for anti-TGFβ therapy in enhancing immune rejection through direct activity on the tumor cell.

Various drugs that target different components of the TGFβ signaling pathway have been developed pre-clinically, and several of these have been tested in Phase I and II clinical trials. Studies suggest that TGFβ blockade drugs tested in the clinic, so far, show little toxicity.

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共催：分子病理学教室