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Abstract C036: Restoration of T effector cells function by targeting senescent cancer-associated fibroblast in tumor microenvironment of stroma-rich cancers

Yao Wang; Hara Apostolopoulou; Arjun Sanyal; Hong Sun; Cynthia Sieland; Kavya Gupta; Jiayu Ye; David Gibbs; Paul Wong; Ntranos Vasilis; Sui Huang; James Gardner; Ajay Maker; Thea Tlsty; Anil Bhushan; Tamara Alliston

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Abstract

The stroma that surrounds the tumor in many solid cancers exhibits potent immunosuppressive activity to promote tumor progression and confer resistance to immune-based therapies. Cancer associated fibroblasts (CAFs) encompassing functionally distinct populations are key components of the stroma that are emerging as a key cell type in regulating an immune response. However, the mechanisms by which CAFs can directly suppress the immune activity to promote tumor growth is not clear. Here, we identify that a subset of CAF in both rodent and human stromagenic cancers that displays characteristics of senescent fibroblasts and referred to as sCAFs. We show that sCAFs secrete a decoy protein that interferes with cytotoxic activity of activated T effector (Teff) cells. In mouse models for stroma-rich pancreatic cancer, administration of an antibody that blocked the decoy protein resulted in recalibration of the stromal fibroblast by promoted the formation of interferon-licensed-fibroblast cells at the expense of sCAFs. This switch not only enhanced infiltration of tumor-infiltrating T cells but also alleviated their direct suppression resulting in enhanced effector function and tumor regression. Collectively, these results point to the potent immunosuppressive activity of sCAFs mediated by decoy protein as a mechanism by which stroma can promote tumor progression. As stromagenic-cancers are resistance to current therapies, the development of treatments involving blocking of decoy protein may inhibit tumor growth and improve patient survival.

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