**NANOG drives immune-refractory states by blocking anti-tumor immunity cycle**

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Tumor cells undergo molecular evolution under various therapeutic pressures such as immune-editing caused by intrinsic or extrinsic anti-tumor immunity. Due to the exquisite specificity and potency of the immune system, cancer immunotherapy is in theory the most precise and powerful approach for controlling cancer metastasis and minimal residual disease, as well as for preventing relapse. However, current data from clinical trials indicate that immunotherapy rarely yields significant benefits for cancer patients in terms of tumor progression and long-term survival. The existing paradigm is that the poor clinical outcomes of immunotherapy are primarily caused by mechanisms of peripheral immune tolerance, especially within tumor microenvironment. Here, in this presentation, we report that anti-immunity drives the evolution of tumor cells towards a stem-like phenotype that promotes both tumor growth and EMT-like metastatic phenotypes and nullifies the cytotoxic T lymphocyte (CTL) response as well as other types of cancer therapeutic agents such as cisplatin and gamma-irradiation. The emergence of these phenotypes requires the transcription factor Nanog, which is increased during therapeutic selection. Strategies that blunt Nanog expression or target Nanog signaling pathway in the tumor could improve the clinical management of therapy-refractory cancer.