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Meeting abstract

Protumor immunity and breast cancer development

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For decades, it was generally accepted that leukocytic infiltrations in tumors represented a failed attempt of the immune system to eradicate *damaged* cells. While indeed some aspects of failed anti-tumor immunity exist, what we now appreciate is the fact that multiple protumor immune programs are instead co-opted by nascent tumors, and in so doing significantly enhance tumor development, including breast cancer. Based upon our evaluation of human clinical specimens revealing significant infiltration of breast tumor tissue by both T lymphocytes and macrophages, we asked the question as to whether adaptive immunity was perhaps enhancing protumor properties of macrophages and thereby potentiating breast carcinogenesis. Utilizing the MMTV-PyMT mouse model of mammary carcinogenesis, $CD4^+$ T cell-deficient mice, and an *ex vivo* three-dimensional organoid co-culture model, we revealed a tumor-promoting role for T_H2-$CD4^+$ T effector cells that elicit pro-tumor, as opposed to cytotoxic, bioactivities of tumor-associated macrophages (TAMs) and enhancement of pro-metastatic epidermal growth factor (EGF) receptor signaling programs in malignant mammary epithelial cells. These novel findings provide a mechanism explaining how T_H2-activated TAMs achieve HIGH level expression of EGF necessary for inducing survival, invasive growth and metastatic programs in malignant cells, and together indicate that anti-tumor acquired immunity, mediated by $CD4^+$ T lymphocytes are usurped in pro-tumor microenvironments and instead promote cancer by engaging cellular components of the innate immune system, and identifies new cellular targets, namely T_H2-polarized $CD4^+$ T lymphocytes, for anti-cancer therapy.

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