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Control of Th17 cell development in the tumor microenvironment by tumor cells

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Abstract

Infiltration of immune cells, such as macrophages and T cells, in primary tumors and metastatic sites plays an important role in influence tumor progression and metastasis. Cytokines and lipid mediators secreted by tumor cells also play a critical role in inducing chronic inflammation in the tumor microenvironment. We found that Th17 cells were increased in the peripheral blood, spleen and tumor tissues of mammary gland tumor-bearing mice. IL-23, the Th17 cell survival factor, was also overexpressed in tumor tissues from mice and humans with breast cancer. Soluble molecules secreted only from breast tumor cells but normal breast epithelial cells induced IL-23 protein secretion in DCs via induction of p19 mRNA expression. We further found that tumor-secreted PGE_2 through EP2 and EP4 receptors enhanced IL-23 p19 gene transcription through binding to the cAMP-response element in the p19 promoter. Blocking PGE_2 synthesis by NS398, a COX2 inhibitor, abrogated the enhancement of p19 expression both *in vitro* and *in vivo*. Furthermore, blocking PKA by H89 completely abrogated the inductive effects of tumor conditioned medium and PGE_2 on p19 transcription, whereas the cAMP active analog, Forskolin mimics the PGE_2 effect. Taken together, our results indicate that tumor-secreted PGE_2 induces IL-23 but not IL-12 production in the tumor microenvironment leading to Th17 cell expansion. This inductive effect of PGE_2 on IL-23 p19 transcription is mediated through cAMP/PKA signaling transduction pathway. These results elucidate an important interaction between tumor and host cells that reduce host anti-tumor immunity. Strategies controlling IL-23 overexpression could serve as new targets for development of antitumor immunotherapy.

Biography

Liu completed his postdoctoral training at the Weill Medical College of Cornell University. He is currently a tenure-track assistant professor at Saint Louis University School of Medicine. He has published more than 40 peer-reviewed papers in reputed journals. His primary research interest focuses on cytokine regulation in macrophages and its effects on T cell development in breast cancer and autoimmune diseases.