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T cell tolerance to tumor antigens: Lessons learned from a TRAMP (mouse)

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Immune suppression is a critical obstacle to achieving successful cancer immunotherapy. Loss of T cell responsiveness can be mediated by a variety of mechanisms, many of which occur in the tumor microenvironment. We previously reported that tumor-associated dendritic cells (TADC) contribute to induction of tolerance and suppressive activity in tumor antigen-specific T cells in both human and murine (TRAMP) prostate cancer. Expression of the transcription factor FOXO3 was critical for TADC tolerogenic behavior (JCI, 2011). More recently, we have studied how TADC acquire this suppressive function. We now demonstrate that mast cells which infiltrate tumors (TA-MC) contribute to immune suppression in the prostate tumor microenvironment. Mast cells were identified as approximately 25-30% of the total $CD45^+$ TRAMP prostate tumor-infiltrating leukocytes and were capable of degranulation and suppressing T cell responses in vitro. Similar activities were noted for human prostate TA-MC. Purified TA-MC spontaneously secreted IL-13 and TGF-β, whose levels were further increased by FcβR cross-linking or LPS stimulation. Co-culture of TRAMP TA-MC with DC induced FOXO3 expression and tolerogenicity comparable to that of TADC. The suppression of Ag-specific T cells and the induction of tolerogenic DC by TA-MC were found to be dependent on secretion of TGF-β and IL-13 by TA-MC during in vitro co-culture, with IL-13 playing a more prominent role. Similarly, in vivo blockade of IL-13 and TGF-β improved TADC function and promoted anti-tumor immunity. Our findings reveal novel mechanisms that favor immune tolerance over anti-tumor immunity and therefore identify promising targets for the enhancement of cancer immunotherapy.

Biography

Hurwitz received his Ph.D. from the Albert Einstein College of Medicine in 1994, where he studied the role of the blood-brain barrier in HIV infection of the central nervous system (CNS). He continued his training at UC Berkeley as a Postdoctoral Fellow. His studies were on the role of T cell co-stimulatory signals in modulating anti-tumor and autoimmune responses. In 1999, Hurwitz was appointed Assistant Professor of Microbiology and Immunology and Urology at SUNY Upstate Medical University in Syracuse, NY. His research program moved to the Frederick National Laboratory for Cancer Research in 2003, where he is a Principal Investigator and his laboratory continues to study T cell tolerance to antigens relevant in anti-tumor immunity and autoimmune disease in animal models.

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