

Cancer immunoediting: Recent progress in elimination and equilibrium

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Abstract

Cancer immunoediting is the process by which immune system components protect the host against primary tumor development and/or enhance tumor escape either by sculpting tumor immunogenicity or attenuating anti-tumor immune responses. We have previously shown that lymphocyte perforin protects the host from developing spontaneous B cell lymphoma. We now show in a variety of oncogene- and irradiation-driven mouse models of cancer that perforin is an important suppressor of B cell malignancies. The immune system:tumor interactions are postulated to occur in three continuous phases: elimination, equilibrium, and escape. We have used injection of the carcinogen methylcholanthrene (MCA), a tumor induction model, to examine the role of a series of cell types and signalling molecules that suppress or promote tumor development in both the elimination and equilibrium phases. Regulatory T cells (Tregs) have been shown to be present in MCA-induced tumors and postulated to promote *de novo* tumor development, however previous studies employed anti-CD25 antibody that is known to additionally affect various effector lymphocyte populations. Here we have used various regimes to deplete CD4⁺, CD25⁺, FR4⁺, or FoxP3⁺ cells and shown that depletion of FR4⁺ or FoxP3⁺ cells alone at the time of tumor initiation provided the greatest protection from tumor development. Furthermore, protection appears intact in the absence of NK, CD8 or NKT cells, or perforin, DR5 or IFN- γ , and is only lost with the concurrent depletion of NK cells and CD8⁺ T cells or absence of both perforin and IFN- γ . These data illustrate the remarkable diversity of effector response suppressed by Tregs. Recently we demonstrated that MyD88-deficient mice were resistant to MCA-induced sarcoma. Candidate MyD88-dependent pathways of interest include IL-1 and many of the TLR. Now we show that early, but not late, neutralization of IL-1 β also protected mice from sarcoma induction. For the first time using the MCA model our work has identified small inert lesions containing tumor cells in an equilibrium state. An attenuated dose of the carcinogen MCA causes an initial wave of tumors affecting a small proportion of mice, however the apparently healthy surviving mice harbor dormant tumors kept in check by adaptive IL-12/IFN- γ -dependent immunity. We have further explored temporal nature and other factors regulating this state of tumor:immune equilibrium as well as attempting to establish other mouse models of this state.

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