

# Deciphering the complex interaction of the immune system with developing tumors

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## Abstract

We have shown that (a) mice lacking an intact immune system form more spontaneous and chemically induced tumors than wild type mice and (b) tumors from immunodeficient mice are more immunogenic than those from immunocompetent mice. Based on these observations we proposed the term "cancer immunoediting" to describe the dual host-protective and tumor-promoting actions of immunity on developing tumors. We now think of cancer immunoediting as a process comprised of three phases: Elimination—the host-protective phase comparable to cancer immunosurveillance; Equilibrium—a phase where residual tumor cells circumventing elimination may persist in the host and undergo immunologic sculpting; and Escape—the phase in which immunity can no longer restrain tumor growth permitting emergence of clinically-apparent, progressively-growing tumors. A large body of data now exists that demonstrates the existence of the elimination phase and identifies several immune components (such as the interferons, perforin and lymphocytes) that play obligate roles in the process. Similarly, a significant amount is known about mechanisms underlying progression of the immunoediting process into the escape phase involving alterations of either the tumor (via loss of immune recognition structures) or the host immune system (through the induction of cells with potent immunosuppressive activity). However, no experimental data currently exists that documents the existence of the equilibrium phase. We therefore treated large numbers of wild type mice and RAG2<sup>-/-</sup> mice (that lack T cells, B cells and NKT cells) with low doses of 3'-methylcholanthrene (MCA) carcinogen and followed the clinical course of the two cohorts for more than 200 days. As expected, RAG2<sup>-/-</sup> mice formed sarcomas at the site of MCA injection more rapidly and more frequently than the wild type cohort. However, when tumor-free, low-dose MCA-treated wild type mice were depleted at day 200 of CD4<sup>+</sup> and CD8<sup>+</sup> cells and IFN- $\gamma$ , a high percentage rapidly developed sarcomas that displayed an unusual growth phenotype when transplanted into naïve recipients. These tumors did not form in wild type mice exposed to low-dose MCA and then treated at day 200 with control mAb or in MCA-treated RAG2<sup>-/-</sup> mice injected with either control or anti-CD4/CD8/IFN- $\gamma$ . These results demonstrate that the immune system is capable of maintaining cancer in a persistent sub-clinical state and thereby provide the first experimental support for the existence of the equilibrium phase of cancer immunoediting.