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IMMUNOLOGY

Stalemate

It has been hypothesized that the immune system can maintain tumours in a state of equilibrium, such that the tumour does not regress or expand. Clear evidence for this has now been produced by Mark Smyth, Robert Schreiber and colleagues.

The immune system has crucial roles in shaping cancer development: it can detect early lesions through immunosurveillance and eliminate them, it is thought to maintain tumours in a state of equilibrium, and tumour cells with either reduced immunogenicity or with increased capacity to attenuate the immune response can escape equilibrium and progress. This process as a whole is termed cancer immunoediting.

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The authors used C57Bl/6 and 129/SvEv mouse colonies established in two different laboratories and injected age- and sex-matched groups with 3′-methylcholanthrene (MCA), a chemical carcinogen known to induce sarcoma formation in mice. As the authors were interested in the mice that did not develop progressively growing tumours, all mice with expanding tumours by 200 days were eliminated from the study. The mice that developed only small, stable masses at the injection site were treated with either control immunoglobulins or a mixture of monoclonal antibodies to deplete $CD4^+$ and $CD8^+$ cells and to neutralize interferon-γ (IFNγ). Of these mice, 60% developed progressively growing tumours; no tumours were seen in the control mice. These experiments were repeated several times with similar results. Importantly, suppression of natural killer cell function (part of the innate immune response) did not induce tumour outgrowth, indicating that suppression of T- and B-cell function (the adaptive immune response) is influential.

To examine this process in more detail the authors used recombination-activating gene-deficient mice (*Rag1*- or *Rag2*-knockout mice), which have an innate, but not an adaptive, immune response. When subjected to the same MCA and monoclonal antibody protocol, few of these mice developed late-onset tumours; most developed progressively expanding tumours by 200 days. In the mice that did develop late-onset tumours, the time to tumour outgrowth was longer than that of the tumours that grew out in wild-type mice treated with anti-CD4, anti-CD8 and anti-IFNγ antibodies at 200 days. The more rapid outgrowth of tumours in the wild-type immunosuppressed mice indicate that these tumours probably have fully transformed cells that can proliferate in the absence of the adaptive immune response. This was further supported by the fact that atypical fibroblast-like cells that grew out of the stable MCA-generated masses from the wild-type mice formed tumours when injected into *Rag2*-null mice.

Interestingly, some of the control wild-type mice developed late-onset sarcomas, indicating that these might arise from cells that had escaped equilibrium. In agreement with the cancer immunoediting theory, cells explanted from these tumours should be able to evade the immune response in syngeneic mice, unlike those that exist in the small masses, which should be immunogenic. The authors confirmed this with most mice developing tumours when injected with cells from the late-onset sarcomas, whereas up to 51% of the cells from the small masses were rejected.

These results clearly indicate that the immune system can maintain tumours in a state of equilibrium and that cells that escape this process are more able to evade the immune response.

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ORIGINAL RESEARCH PAPER Koebel, C. M. *et al.* Adaptive immunity maintains occult cancer in an equilibrium state. *Nature* 18 November 2007 (doi 10.1038/nature06309)