Cancer immunosurveillance, immunoediting and inflammation: independent or interdependent processes?

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When immune cells and developing tumor cells localize to a common microenvironment, an assemblage of interactions takes place; this results in either tumor destruction by way of immunosurveillance or tumor outgrowth. These events put a functional imprint onto the emerging tumor repertoire because tumor cells arising in the presence of a fully functional immune system are less immunogenic than those that develop in the absence of immunity (i.e. in RAG2$^{-/-}$ and perforin$^{-/-}$ mice). However, other studies suggest that the immune system can also actively promote formation of certain tumors. These apparent disparate effects of immunity on tumorigenesis provide a unique model for study of the decision-making process that dictates immune function within a tumor.

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Introduction

Recent findings in the field of tumor immunology have forged a broader understanding of immune system–tumor cell interactions. Notably, the formulation of the cancer immunoediting hypothesis not only delineates a role for the immune system in the active elimination of immunogenic tumor cells (i.e. immunosurveillance) but also stresses the importance of immunity in promoting the outgrowth of less immunogenic tumor cell variants. This model provides the framework to appreciate the protracted effects of the immune system as it attempts to control tumors. The three phases of cancer immunoediting — elimination, equilibrium and escape — have been reviewed in depth elsewhere [1–3]. We focus this review on recent advances in our understanding of the molecular and cellular machinery that drive immunosurveillance, and summarize recent findings that continue to illustrate the distinction between immunosurveillance and immunoediting. We also consider how cancer immunosurveillance and cancer immunoediting [1–4,5••,6–9] are related to the concept of inflammation-induced tumor promotion [10–12,13•]. Our goal in this review is to advance the concept that the panoply of immune system–tumor cell interactions that have been reported are non-mutually exclusive combinations of various positive and negative forces in action, with the protective actions of immunity being the best possible result and the tumor-promoting immune actions being the worst.

The distinction between cancer immunosurveillance and cancer immunoediting

The complete destruction of a developing tumor by the immune system, a process originally envisioned by Ehrlich [14] and later coined 'cancer immunosurveillance' by Burnet and Thomas [15,16], is rarely appreciated in clinical settings. Nevertheless, recent experiments in mice demonstrate scenarios in which developing tumors are indeed recognized and destroyed by the intact immune system [1,5••,17••]. Specifically, over the past 12 years, several laboratories have documented increased incidences of carcinogen-induced and spontaneous cancer in immunodeficient mice compared with wild-type (WT) mice, thus providing strong evidence for the existence of immunosurveillance.

By contrast, evidence of immunoediting relies not only on measurement of tumor incidences but also on assays that detect differences in the tumor cells themselves. Although certain tumor cells can indeed be destroyed by the immune system, it is clear that a tumor can be composed of a heterogeneous mixture of distinct cell clones [18,19]. Thus, interactions between the immune system and tumor cells could lead to a variety of outcomes. The cancer immunoediting hypothesis predicts that, whereas one outcome is complete elimination of a developing tumor, another is the generation of a sculpted tumor cell repertoire that displays either reduced immunogenicity [17••] or an increased capacity to inhibit protective anti-tumor immune responses [2,5••,20–23].

Experimental evidence for immunoediting in mouse cancer models

To reveal the process of immunoediting, the immunogenicities of tumor cell lines obtained from immunodeficient and immunocompetent mice were compared by monitoring their growth following transplantation into either immunodeficient recombinase activating gene 2-null (RAG2$^{-/-}$, which lack T, B and NK-T cells) mice or WT hosts. Cell lines that form tumors in both WT and

$RAG2^{-/-}$ hosts were denoted 'progressors' whereas cell lines that were rejected in WT hosts but grew in $RAG2^{-/-}$ mice were designated 'regressors'. In a cohort of methylcholanthrene (MCA)-induced sarcomas produced in immunodeficient $RAG2^{-/-}$ mice, 8 out of 20 (8/20) behaved as regressors and 12/20 behaved as progressors when transplanted into naïve syngeneic WT recipients. By contrast, 17/17 MCA-induced sarcomas from WT mice displayed a progressor growth phenotype [17••]. In addition, the increased immunogenicity of regressor tumors compared with progressor tumors was supported by the finding of a higher ratio of $CD8^+$ T cells:$CD25^+$ T-regs that infiltrated the former [24•]. These data demonstrate that the quality of the tumor cells that emerge after chemical carcinogenesis reflects the immune environment in which the tumor originally developed.

Although abundant evidence for immunoediting has been obtained from chemical carcinogenesis studies, the role of the immune system in sculpting oncogene-driven cancers remains unclear. Using an oncogene-driven cancer model, Willimsky and Blankenstein [25•] studied tumor cell lines from mice that had been engineered to sporadically activate the SV40 T-antigen (Tag), thereby giving rise to Tag-expressing tumors in various tissues. Remarkably, whereas 11/11 tumor cell lines from these mice formed tumors when transplanted into $RAG1^{-/-}$ mice, all were rejected when transplanted into WT mice. Because they were able to obtain regressor tumors from WT mice, the authors concluded that immunoediting does not occur in this system. However, no comparison was conducted between the relative immunogenicities of Tag-induced tumor cells derived from WT and immunodeficient mice, and thus no conclusions can be drawn about the presence or absence of immunoediting in this system. Furthermore, because Tag is necessary for tumor formation but also serves as a strong rejection antigen, it is unlikely that a repertoire of tumor cells displaying heterogeneous (i.e. 'editable') levels of Tag could have been generated. Thus, the experimental design of this study was not suitable to address whether oncogene-driven cancers can be edited, and additional studies are needed that employ oncogenes that are not also dominant rejection antigens.

Evidence of immunoediting in humans

We previously reviewed several lines of evidence supporting the conclusion that cancer immunoediting also occurs in humans [2]. These findings include: increased incidences of cancers of non-viral origins in immunosuppressed transplant patients compared with non-immunosuppressed individuals; the discovery that cancer patients often develop immune responses to the tumors that they bear; and a correlation between the presence and location of intratumoral tumoricidal ($CD8^+$) and tumor-protective ($CD25^+Foxp3^+$) lymphocytes. Recently, additional data have been reported showing that the quantity and quality of immune responses within colorectal tumors is a remarkably reliable prognostic indicator [26••]. Specifically, Galon *et al.* [26••] performed genomic and *in situ* immunostaining analyses on tumors from a large number of colorectal cancer (CRC) patients, and found that a strong *in situ* immune reaction in the tumor correlated with a favorable prognosis (hazard ratio 2.379; $p < 0.0001$), regardless of the tumor invasion T stage, differentiation stage and lymph node invasion. These results suggest that, once human CRCs become detectable, the adaptive immune response can still take a role in preventing recurrence, thus highlighting how dynamic immune system–tumor cell interactions can influence patient mortality.

New players in the cancer immunoediting process: NKG2D, IFNα/β and IL-23

A comprehensive list of immune cells and molecules involved in cancer immunoediting is reviewed elsewhere [2,5••,9]; this includes a cast of performers such as αβ T cells, γδ T cells, natural killer T cells, natural killer (NK) cells, signal transducer and activator of transcription 1, interferon γ (IFNγ), perforin, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) and interleukin 12 (IL-12). However, as predicted by the cancer immunoediting model, the complexity of host–tumor interactions has recently led to the identification of additional participants in this process, three of which are discussed in this review: NKG2D, type I interferon and IL-23. The recent addition of IFN-producing killer dendritic cells (IKDCs) [27] to the troupe is discussed in more depth in a review in this issue of *Current Opinion in Immunology* by Zitvogel and co-workers. Interestingly, all players have intimate connections with the innate immune system.

NKG2D and its ligands

NKG2D is an activating receptor expressed on all NK cells, some γδ T cells, some natural killer T cells, and some αβ T cells. NKG2D has taken centre stage as a major component that facilitates immunologic recognition of cells undergoing stress, because NKG2D ligands are induced on virally infected cells and primary cells undergoing DNA damage and are constitutively expressed on tumor cell lines [28–34]. A role for NKG2D in cancer immunosurveillance was recently demonstrated by two groups [35••,36•] who used separate strategies to induce NKG2D dysfunction. Using an MCA chemical carcinogenesis mouse model, Smyth *et al.* [35••] showed that mice treated with a function-blocking NKG2D-specific monoclonal antibody (mAb) developed more MCA-induced sarcomas than mice treated with irrelevant control mAb. NKG2D is also known to play an important role in preventing cutaneous carcinogenesis, as mice engineered for transgenic expression of the NKG2D ligand Rae-1 displayed reduced NKG2D-mediated effector function that was correlated with an increased susceptibility to chemically induced primary and transplantable skin carcinomas [36•]. The effector cell that

utilizes NKG2D for tumor surveillance in these studies is most likely to be the NK cell, although a role for other cell types has not been ruled out to date.

Smyth *et al.* have also provided evidence that NKG2D and its RAE-1 family ligands play important roles in specifying tumor immunogenicity [35••]. In this study, 5/5 MCA-induced sarcomas from C57BL/6 strain perforin-deficient mice were characterized as expressing high levels of the NKG2D ligand RAE-1, whereas 5/5 MCA-induced sarcomas from WT mice displayed low to no expression of RAE-1. When the immunogenicity of one tumor from each group was analyzed by *in vivo* growth in WT mice, the tumor derived from the perforin-deficient mouse regressed whereas the tumor from the WT mouse grew progressively. Furthermore, spontaneously arising lymphomas from perforin$^{-/-}$ (seven cell lines tested) and perforin$^{-/-}$ x β2m$^{-/-}$ (three cell lines tested) mice also consisted largely of regressor tumor cells compared with spontaneous lymphomas from IFNγ$^{-/-}$ mice, which consisted largely of progressor tumor cells (three cell lines tested) [37,38]. Nevertheless, the IFNγ$^{-/-}$ mice developed lymphomas at an incidence comparable to that of perforin$^{-/-}$ mice, providing additional evidence that cancer immunosurveillance (detected by cancer incidences) is not exactly the same process as cancer immunoediting (detected by generation of regressor versus progressor cell lines). One interpretation of this finding is that lymphomas that emerge from IFNγ$^{-/-}$ mice are edited in a perforin-dependent manner that is insufficient to allow immunosurveillance to occur. It will be interesting to examine whether lymphomas that arise in IFNγ$^{-/-}$ mice display low levels of RAE-1, as NKG2D ligand expression might indeed be a quantifiable indicator of perforin-mediated immunoediting. To this end, it is notable that RAE-1 expression is decreased when the PDV1 skin cancer cell line is passaged through WT mice, but is not diminished when the cells are passaged through TCRβ$^{-/-}$ mice. This result suggests that, in this model of skin cancer, RAE-1 is a target of an immunoediting process and that αβ T cells function as the 'editors' [39].

Type I interferon

A crucial function for type I interferons (IFNα/β) in immunosurveillance and immunoediting was shown by Dunn *et al.* in a recent study that compared the incidence and immunogenicity of MCA-induced sarcomas produced in interferon-alpha/beta receptor subunit 1 (IFNAR$^{-/-}$) mice versus WT mice [9,40•]. At two different MCA doses, sarcoma incidences were higher in IFNAR$^{-/-}$ mice than in syngeneic WT mice. Moreover, 40% of the MCA-induced sarcomas derived from IFNAR$^{-/-}$ mice were regressors, whereas 100% of MCA-induced sarcomas from syngeneic WT mice were progressors. Finally, when transplanted into IFNAR$^{-/-}$ mice, immunogenic regressor tumors grew progressively. However, these tumors were rejected when IFNα/β responsiveness was selectively restored to the hematopoietic compartment of IFNAR1$^{-/-}$ mice. By contrast, IFNα/β responsiveness at the level of the tumor cell did not contribute to the *in vivo* growth behaviour of tumors. Current studies are underway to identify the host hematopoietic cells that require IFNAR1 to mediate anti-tumor effector functions.

Immunosurveillance and/or/despite inflammation

To date, we have focused on the role of the immune system in protecting the host from cancer. However, some other mouse models of cancer have shown that the inflammatory actions of the immune system can promote tumor development and/or growth. The connection between chronic inflammation and tumor development has been reviewed extensively elsewhere and is also the topic of a review in this issue of *Current Opinion in Immunology* by Coussens and co-workers [10–12,13•]. The last section of our review attempts to resolve the apparent conflict between the opposing host-protective and tumor-promoting roles of the immune system. Notably, we maintain that the current segregation of cancer immunosurveillance and immunoediting from tumor-promoting inflammation has led to a tendency to consider the two processes as mutually exclusive. This dichotomous view facilitates the interpretation that either one or the other outcome occurs. However, it is unclear whether the mutual exclusivity of these processes has experimental support.

Instead, we propose that cancer immunoediting and inflammation can be functions of separate, potentially overlapping, immune algorithms. In other words, the statement that the immune system promotes or prevents cancer cannot be interpreted without specifically defining which immune components participate in each process and, equally importantly, which cancer model is being studied. For example, CD4$^+$ T cells are protective in a murine model of human papilloma virus (HPV)-induced cervical carcinoma, whereas both CD4$^+$ T cells and B cells promote inflammation and enhance tumor incidence in a mouse model of HPV-induced skin carcinogenesis [41,42•,43]. In a two-stage chemical carcinogenesis protocol to induce skin cancer, αβ T cells promoted cancer at high doses of carcinogen, whereas γδ T cells inhibited tumor formation at low doses of carcinogen [44]. Finally, whereas CD8$^+$ T cells have been shown to perform a host-protective role in many models of murine and human cancer, this tumoricidal T cell population either plays no role at all or has a small tumor-promoting role in the HPV-induced skin cancer models [2,26••,43,45–47]. Thus, experimental support for the potential co-existence of immunoediting and tumor-promoting inflammation within the same cancer model and even in the same cell population can be found in the recent literature. Although these processes can co-exist spatially, they might nevertheless be temporally distinct. For example, it is possible

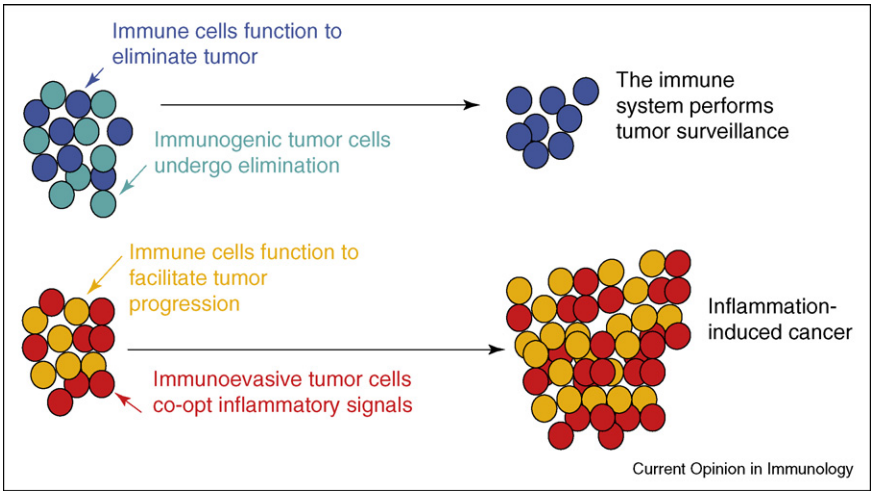
that inflammation occurs before immunoediting to promote the transition between pre-neoplasia and neoplasia [48•] or that it occurs after immunosurveillance, perhaps by promoting the transition from equilibrium to the escape phase of immunoediting [2].

Is it possible for effectors that mediate immunosurveillance to intermix with those that promote cancer within the same tumor? Clearly, an orchestrated immune response against a developing tumor will contain different types of effector cells and molecules, thereby increasing the probability that tumor-promoting and tumor-eradicating activities can co-exist. Evidence for this possibility was reported in a recent study that showed that blockade of NF-κB function converted tumor necrosis factor α (TNFα)-induced tumor growth into TRAIL-mediated tumor regression [49,50]. In this study, the CT-26 colon cancer cell line proliferated in response to lipopolysaccharide (LPS) administration *in vivo* but regressed when the NF-κB pathway was blocked specifically in the tumor. Importantly, the regression was mediated by induction of TRAIL, which (most likely) was expressed on NK cells responding to LPS-induced IFNα/β production. Thus, in an inflammatory environment induced by LPS, both TNFα (tumor-promoting) and TRAIL (tumor-eliminating) functions were present in the tumor mass. However, when NF-κB was present, the tumor responded to TNFα by growing progressively. In the absence of NF-κB function, the tumor regressed in response to TRAIL. These results show that the pro-inflammatory cytokine TNFα is capable of inducing tumor-promoting inflammation, despite the presence of the pro-surveillance cytokine TRAIL.

IL-23, IL-12 and epistasis

The previous work suggested that inflammation can be dominant over immunosurveillance in certain tumor model systems. However, by extending this genetic metaphor, one must also consider that, depending on the tumor model, either inflammation or immunosurveillance can be epistatic to the other. In a broad panel of human tumors, Langowski *et al.* [51••] found significant messenger RNA upregulation of both subunits of IL-23. Because clinically evident human tumors typically have escaped immunosurveillance, the authors hypothesized that the preponderance of IL-23 in human tumors suggested that it played a causative role in promoting tumor development. Towards this end, the authors induced papillomas in mice that lacked a subunit of IL-23, as well as in mice that lacked a subunit of the pro-surveillance cytokine IL-12. As predicted, the mice that lacked functional IL-23 were resistant to tumor development, whereas the IL-12-deficient mice developed increased numbers of papillomas. Given the incongruent effects of these genes, the authors then tested which phenotype would be suppressed in mice deficient in both cytokines. Mice deficient in both IL-23 and IL-12 were resistant to primary tumor development, indicating that IL-23 is epistatic to IL-12. However, when tumors were transplanted into mice treated with antibodies that blocked IL-23 or both IL-12 and IL-23, the combined blockade indicated that IL-12 function was epistatic to IL-23. Thus, the nature of the tumor model has a profound effect on which immune function is epistatic. Moreover, because the model employed in these studies is known to be dependent upon a strong inflammatory response, more work is needed to explore the relative

Figure 1



The anti-tumor response represents a unique model for studying cell fate decisions. Top: Pro-surveillance immune cells (dark blue) function to eliminate immunogenic tumor cells (aqua). Bottom: Tumor-promoting immune cells (orange) facilitate tumor cell (red) outgrowth. Unresolved questions include: Which immune cells/effector molecules participate in cancer immunosurveillance/immunoediting and/or tumor-promoting inflammation? What characteristics of the tumor influence the function of infiltrating immune cells? How can immune function be harnessed for clinical benefit?.

importance of inflammation versus immunoediting in other primary tumor models.

Conclusions

Although numerous studies using several different tumor models have revealed a definitive role for certain immune components in protecting the host from cancer, a seeming 'controversy' persists about whether the immune system protects against or promotes cancer. Perhaps this conflict arises from the inaccurate generalization of immune function. To state simply that ''the immune system protects against cancer'' is just as accurate (or as inaccurate) as to state ''the immune system promotes cancer''. Clearly, not all immune components play fixed roles in all models of cancer. In this review, we have argued that the relationship between cancer immunoediting and cancer-promoting inflammation cannot be simply defined based on single tumor models, and in fact might change even within related systems. Thus, we suggest that, rather than developing models to segregate immunosurveillance from inflammation-induced cancer, tumor immunologists should attempt to understand the factors that help orchestrate which immune cells are cast in a protagonist versus antagonist role. The tumor microenvironment represents a complex system in which individual immune cells make potentially interconnected decisions (Figure 1) to attack tumor cells, ignore their presence, or enhance their development and/or survival. These decision-making processes, and the potential to beneficially influence them in the clinical setting, represent significant areas of research that beckon future studies.

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This landmark article illustrates the importance of IL-23 in promoting tumor formation in the context of IL-12 function.