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Genetically engineered mouse models of cancer reveal new insights about the anti-tumor immune response

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Abstract

Cancer is a complex disease that can originate in virtually all tissues of the body, and tumors progress through many different stages during their development. While genetic mutations in the emerging cancer cells drive this disease, it has become increasingly clear that cancer development is strongly influenced by the surrounding microenvironment. Cells of the immune system are critical components of this extrinsic network of cancer regulators, contributing significantly to the microenvironment of most cancers and either promoting or inhibiting the initiation and progression of this disease. Genetically engineered mouse (GEM) mouse models of spontaneous cancer are starting to shape our understanding of how anti-tumor T cells may act to prevent or inhibit cancer progression in some settings and not others. Lessons learned from investigating spontaneous mouse cancer models have important implications for directing clinical efforts that attempt to direct a cancer patient's immune system to eradicate their disease.

Introduction

Understanding the role of the immune system in human cancer requires the use of animal models that faithfully recapitulate the diversity of interactions between immune cells and the heterogeneous forms of cancer that affect humans. At the same time, these models must allow for hypothesis-driven experimentation, providing reproducible tumor initiation and growth, as well as the capacity to monitor T cells and other cells of the immune system reacting to the tumors. Interest in GEM models of cancer to study anti-tumor immune responses has increased significantly recently, with these models serving as a valuable alternative to the more widely used transplantable and carcinogen induced cancer models. GEM cancer models have led to new biological insights about the importance of tumor antigens, the impact of the tumor type, origin, and underlying genetics in determining immune responses, and the role of immune tolerance versus immunoediting in the process of tumor escape. They have also provided an advanced platform for understanding and improving immunotherapy by revealing aspects of the immune response that can control tumor responsiveness to chemotherapies, targeted therapies, and immunotherapies. The opportunities and limitations of these models compared to alternative cancer models are highlighted in Table 1 and have been recently reviewed [1–3].

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Why use spontaneous mouse models of cancer?

GEM models of cancer represent a diverse collection of genetically modified mice that are predisposed to develop specific types of cancer spontaneously [4]. Such models can be divided into two forms: germline GEM models, which develop cancers in an unregulated (spontaneous) fashion, and conditional GEM models, which provide spatiotemporal control of tumor onset utilizing tissue-specific, ligand-regulated, and/or viral-based technologies [2]. By transforming normal cells *in situ* with defined genetic events, GEM models can recapitulate the genetic and histopathological characteristics of nearly all forms of human cancer as well as the progression of tumors from the stage of initiation to advanced forms of the disease. In stark contrast, transplant models of cancer involve the introduction of large numbers of fully progressed, relatively homogeneous tumor cell clones into the animal. Furthermore, these often involve ectopic sites (typically subcutaneous) where no equivalent human cancer develops [5]. This form of delivery inevitably leads to massive tumor cell death that can elicit an immune response. In addition, the rapid growth of most transplanted tumors leads to the death of the recipient within a few weeks if untreated. As such, the analysis of the immune response to the tumor, as well as any immune-modulatory therapy, occurs in an acute setting rather than in the context of a more natural course of tumor progression or within an established tumor microenvironment [6,7]. Importantly, critical differences in immunosurveillance and therapeutic responses have been described between equivalent autochthonous and transplanted tumors [8,9], and it is plausible that the number of cells, progressed state, and cellular milieu of transplanted tumors may influence these differences [10–13]. Consequently, interactions between the immune system and cancers in this setting are likely dominated by the transplantation itself, making it difficult to recapitulate the contextual diversity of immune responses that clearly vary in different human cancers (Figure 1). While carcinogen induced cancers can be as good or better than GEM in their capacity to model human cancer, their genetic complexity, considerable variation in progression, and the limited number of cancers that can be modeled are drawbacks. To improve the utility of these models, high doses of carcinogens are often used to increase the penetrance and reduce the latency of tumor formation, potentially generating exceptionally large numbers of carcinogen-induced neoantigens [14,15].

Tumor antigens and tracking tumor-reactive T cells

Understanding T cell responses against cancer hinges on our ability to monitor the persistence and function of tumor-reactive T cells. As tumor-reactive T cells may make up only a small fraction of tumor-infiltrating lymphocytes ([8] and unpublished data), it is important that tumor models do not rely on phenotyping bulk CD8 T cell populations. In this regard, transplantable models have advantages, as they are easily modified to express antigens that lead to monitorable anti-tumor immune responses and offer one of the few systems to obtain truly tumor-specific expression of model antigens. Carcinogen-induced cancers are highly immunogenic, harboring tumor-specific antigens (TSAs) that drive anti-tumor T cell responses. However, due to the spontaneous development of these TSAs, it is not possible to track the T cell responses in the setting of primary tumor formation [14]. While GEM models of cancer accurately recapitulate many aspects of human cancer, their stimulation of a tumor-specific immune response is likely to be less pronounced, in part due to the genetic programming of driver mutations in oncogenes and tumor suppressor genes [10,14]. Therefore, GEM cancer models may need to be modified to express antigens to model the anti-tumor T cell responses observed in human cancers [16]. In fact, because GEM cancers remove much of the antigenic complexity that is uncontrolled in transplantable or carcinogen-induced tumors, they may provide the cleanest system to introduce specific antigens and allow for a focused investigation of tumor-specific T cells. One strategy to express model tumor antigens in GEM tumors utilizes tissue-specific

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promoters to restrict antigens to the same organ, likely modeling tumor-associated antigens (TAAs). However, this approach may fundamentally alter the phenotype of responding T cells because the antigens are also expressed in normal cells of the target tissue and well before tumor formation [17–20]. The recent use of conditional GEMs to study T cell responses to tumors largely circumvent this issue by linking the expression of oncogenes to model antigens, allowing for tumor-specific expression of model antigens [21,22]. Nevertheless, it has proved to be challenging to completely prevent antigen expression in the thymus or other cells prior to tumor formation [21].

Attempts to control antigen expression have ultimately allowed for some functional comparisons of the T cell responses against TSAs versus TAAs [23]. Although T cells responding to germline GEM models of cancer typically become tolerant (often systemically), this may be the result of T cells responding to the more commonly modeled TAAs. In an effort to investigate T cell responses against TSAs expressed from endogenously arising tumors, we developed model systems to either introduce TSAs or overexpress TAAs antigens in autochthonous mouse lung cancers utilizing conditional GEM models [8,21]. These studies, along with others [22,24], indicated that TSAs may be uniquely capable of evoking potent endogenous T cell responses against tumors that delay or prevent cancer development. In another approach, we utilized a conditional GEM model of sarcomagenesis to show that TSA expression was required for the process of immunoediting against endogenous sarcomas [10]. More broadly, it seems tumor immunogenicity results from mutations that generate TSAs (a common characteristic of most cancers) [14], but this may not be an obligatory step in the tumorigenic process. This has important implications for T cell responses against human cancers, as not all cancers may harbor potent TSAs. Nevertheless, targeting TSAs has the benefit of specificity for tumors, reducing the risk of inducing autoimmune reactions, and targeting mutations in tumors that are necessary for driving the disease, precluding tumor escape by antigen loss [24,25]. In the post-genomic era, there is great potential to utilize DNA sequencing to rapidly identify mutations in individual tumors, computationally predict peptides that can best stimulate T cell responses, and vaccinate patients against the unique TSAs in their tumors [26,27].

Tumor type, origin, and genetics affect the T cell response

Over four decades ago, R.T. Prehn speculated that the tissue in which a cancer arises influences how the immune system responds to cancer [28]. However, this issue still has not been adequately addressed experimentally. Instead, discoveries made in a particular model or form of cancer are often interpreted to be broadly applicable to all immune-tumor interactions. While this may have some truth in transplantable cancer models (Figure 1), it does not appear to be the case in human cancers. A tremendous diversity of T cell responses can be observed in different cancers and responses can vary depending on contextual elements of each cancer, such as the originating tissue, the state of immunosurveillance or immunoregulation at that site, the genetics of the developing tumor, or as already described, the nature of the antigens driving the immune response.

Perhaps the best examples of how the contextual elements of cancers can affect the immune response comes from considering the evidence that adaptive immune responses to some tumors can promote tumor progression [29,30]. Mammary and skin cancers are aided by $CD4^+$ T or B cells that promote the activity of innate immune cells that can support tumor development and spread. Interestingly, however, in the context of immunotherapy or chemotherapy, the activity of these adaptive immune cells can be shifted to promote anti-tumor behavior [31,32]. Cytokines are known to have pleitropic activities, and may have opposing roles in different forms of cancer. Cancers of the skin were recently shown to be inhibited by T cell responses that were supported by the presence of thymic stromal

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lymphopoietin (TSLP), whereas TSLP is known to drive several epithelial cancers by promoting pro-tumorigenic inflammation [33,34]. Tumor necrosis factor (TNF) is a classic example of a cytokine known to promote inflammation and cancer in some settings, while also serving as a critical effector arm for adaptive immune responses against cancer in others [35–37]. Additional cytokines like GM-CSF or IL-10, typically thought to have positive or negative effects on anti-tumor T cell responses against cancers, respectively, were recently shown to have the opposite function in specific cancers [38–40], often via their modulation of immunosuppressive cells that block anti-tumor responses [41,42]. In several cases, the underlying oncogenic drivers of the cancer have been shown to directly regulate cancer cell production of these immune modulators, such as ras-induced GM-CSF or KIT-induced Ido production [38–40,43]. These are intriguing observations given that oncogenes have also been found to activate pathways in tumors that can promote anti-tumor immune responses, including by upregulating stress ligands recognized by NKG2D receptors on NK or T cells [44]. Indeed, the contribution of cytokines to tumor progression can be quite complex and have countervailing roles depending on the type and stage of the disease [45].

Adding to the complexity, recent studies from our lab have shown that T cell responses can diverge dramatically against different cancers even if they have the same TSAs and underlying genetic events. T cell responses against sarcomas of the hind limb induced by expression of oncogenic K-ras and loss of p53 function were fully functional and blocked tumor formation or forced TSA loss. In contrast, in a model of adenocarcinoma of the lung driven by the same mutations and expressing the same TSAs, responding T cells were not fully functional, could not drive TSA loss, and only delayed the malignant progression of the cancers [8,10]. It is tempting to speculate that the different immune environments of the tissues that give rise to these two forms of cancer dictate the divergent anti-tumor immune responses in each context. Because the lung is constantly exposed to irritants, allergens and the antigens of inhaled pathogens, it is likely to harbor sensitive immune-regulatory networks to prevent detrimental immune responses to innocuous encounters, imposing a more stringent threshold for adaptive immune activation against cancer. However, the muscle tissue that gives rise to sarcomas would normally be exposed to antigens solely in the context of a pathogenic infection and, thus, may have fewer regulatory requirements for activating cells of the adaptive immune system to any antigen, including those that arise in developing tumors. These results emphasize the contextual diversity of cancer that can be investigated with different genetic drivers and in different tissues. Importantly, too, therapies targeting particular immune pathways as treatment for cancer must exercise caution and consider the opposing effects such therapies may have on promoting other forms of cancer.

Immune tolerance or immunoediting driven tumor escape? It depends!

Whether cancers progress because of immune tolerance or the evolution of tumor-escape mechanisms has been a topic of great debate. Most likely both mechanisms are relevant in different contexts or at different points in tumor progression, as autoregulatory tolerance mechanisms may provide an alternative route for tumors to progress unedited by dampening functional immune responses. Indeed, an examination of recent studies using spontaneous mouse models of cancer provides evidence that both mechanisms of tumor evasion occur, again likely depending on the contextual elements of each cancer. T cell tolerance may stem from the fact that anti-tumor responses are fundamentally different than responses to acute pathogenic infections, which the immune system has evolved to resist. There are many parallels in the phenotypes of T cells responding to cancer and chronic infections [46]. Immune tolerance to cancer may result from the induction of immune regulatory pathways (potentially co-opted by tumors) that evolved to prevent autoimmune disease in the setting of persistent infectious disease. T cells may be driven to exhaustion or anergy in response to tumors due to chronic antigen presentation at tumor sites [19,47,48]. Vaccination regimens

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often improve the function of T cells, indicating that natural priming against tumor antigens may be insufficient in many contexts [8,49]. Alternatively, models of pancreatic and breast cancer have shown that tumors actively recruit myeloid-derived suppressor cells (or T regulatory cells) that suppress adaptive immune responses at tumor sites [38,39,42].

Theories of immunoediting postulate that tumors evolve mechanisms to bypass anti-tumor immune responses and, thus, tumors are shaped by these encounters [16]. The remnants of these interactions can be identified by changes in tumor cells that make them less susceptible to immune recognition and destruction (i.e. less immunogenic). Immunoediting by the adaptive immune system has been appreciated for nearly a decade and evidence continues to accumulate for the role of T cells in the elimination of nascent tumors, tumor maintenance in a dormant state (equilibrium phase), and ultimately, tumor escape [10,14,35,45,50]. Broadening the scope of immune cells capable of regulating tumor development, recent studies demonstrated that innate cells of the immune system, particularly NK cells, participate in immunoediting tumors [11,44].

Improving therapy by combining immunotherapy with conventional cancer therapies

The primary goal of cancer therapy is to induce tumor cell death while sparing normal cells and limiting general toxicity. Immunotherapies utilizing anti-tumor T cells promise tremendous tumor specificity. However, chemotherapies and targeted therapies may also support even better anti-tumor immune responses (Figure 2) [51]. DNA damage responses induced by various chemotherapeutic drugs have been demonstrated to up-regulate stress or danger signals on tumor cells that alert the immune system, stimulating the recruitment and anti-tumor activity of T cells and NK cells or enhancing tumor antigen presentation by dendritic cells [52]. In addition, these therapies can promote anti-tumor immune responses by modulating or depleting immunosuppressive cell populations [51,53,54]. However, it is becoming apparent that the effect of these therapies is connected to the particular immune microenvironments of tumors, once again highlighting the need for experimental models that recapitulate the diversity of tumor immune environments of different human cancers [55,56].

Several elegant proof-of-principle experiments using spontaneous mouse models of cancer have demonstrated that the efficacy of targeted therapies depends on the activity of concomitant anti-tumor T cell responses [43,56,57]. Interestingly, it was shown that complete eradication of tumors targeted with oncogene-specific blockade was only achieved when combined with T cell responses, which more broadly target the tumor tissue, not only destroying tumor cells directly but also the tumor vasculature [56,57]. In the context of chemotherapy, the efficacy of doxorubicin to treat carcinogen-induced sarcomas required $CD8^+$ T cells [58]. However, diverse chemotherapeutics (paclitaxel, doxorubicin) in the treatment of breast cancer were antagonized by the recruitment of innate immune cells to the tumor microenvironment [32,59]. In these settings, blocking the migration of these cells to tumors improved chemotherapeutic responses.

Conclusion

An important next step for cancer immunology should be to embrace the diversity of immune environments that likely shape immune responses to cancers that arise in different tissues. GEM models of cancer provide the means to recapitulate the great diversity of human cancers, preserving the specific contextual elements of different forms of cancer that affect anti-tumor T cell responses. The goal moving forward should be to utilize more models, employing different underlying genetics and tissue origins, as well as developing

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new strategies to better mimic the T cell response by modulating the nature of the tumor antigens (TSAs versus TAAs) that direct it. In addition to the impressive utilization of these GEM models for testing novel therapies and combinations of therapies, the inclusion of strategies for *in vivo* imaging and monitoring the dynamic interactions of the cells within the tumor microenvironment are providing an additional layer of mechanistic information about how to improve immunotherapies [47,59,60]. Finally, these studies have revealed that effective immune therapies against cancer not only boost T cell responses to tumors, but also counteract the many regulatory networks that likely restrict the duration of active immune responses. Taking lessons from the study of autoimmune diseases, which represent rare breakdowns in these regulatory networks, may provide important clues to improve immune-based treatments for cancer.

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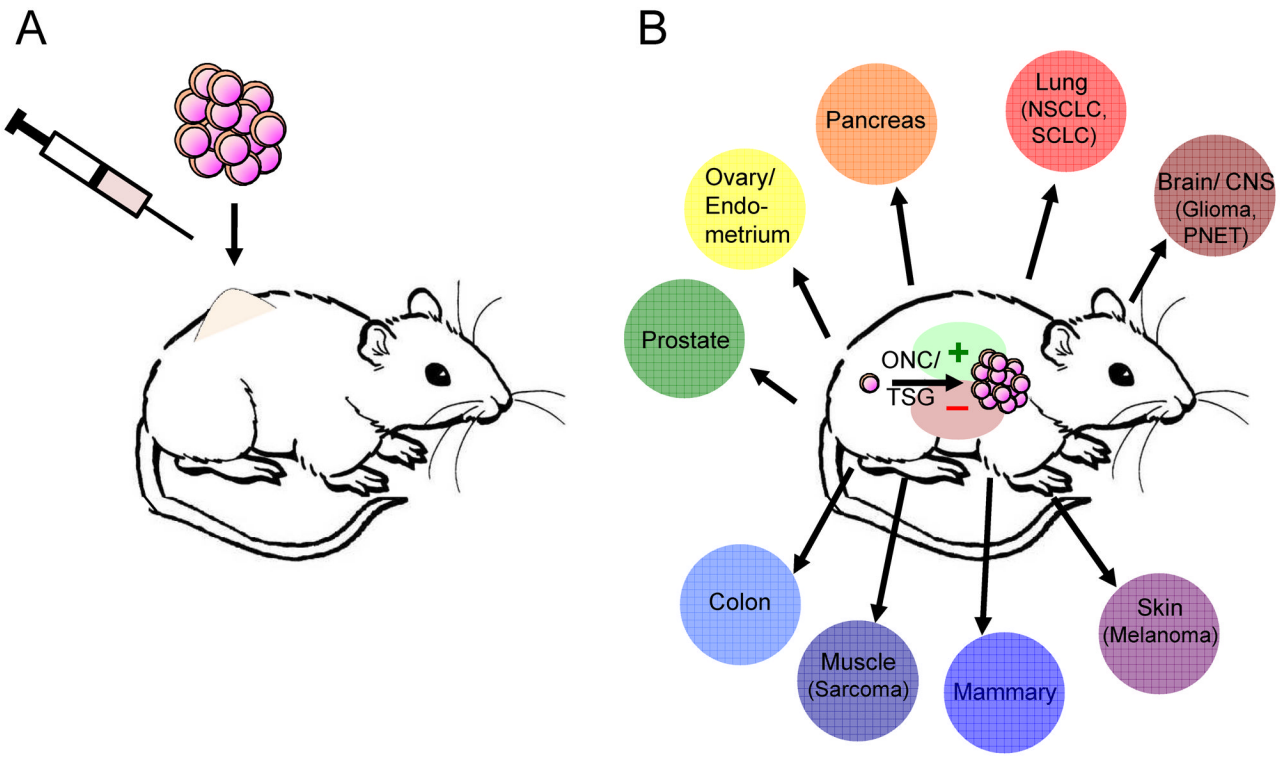

Figure 1. Key differences between transplanted models of cancer and spontaneous or genetically engineered mouse models of cancer affect the immune response to tumors

A, transplanted tumors introduce large numbers of fully progressed tumor cells into a limited diversity of immune environments (typically subcutaneous inoculation). B, cancers in GEM models originate from single cells that are transformed *in* situ through the activation of oncogenes (ONC) and inactivation of tumor suppressor genes (TSG) and progress in the unique immune environments of their native tissues. Furthermore, studies using GEM cancers can interrogate the role of defined genetic events that drive each cancer in activating (+) or suppressing (–) immune responses.

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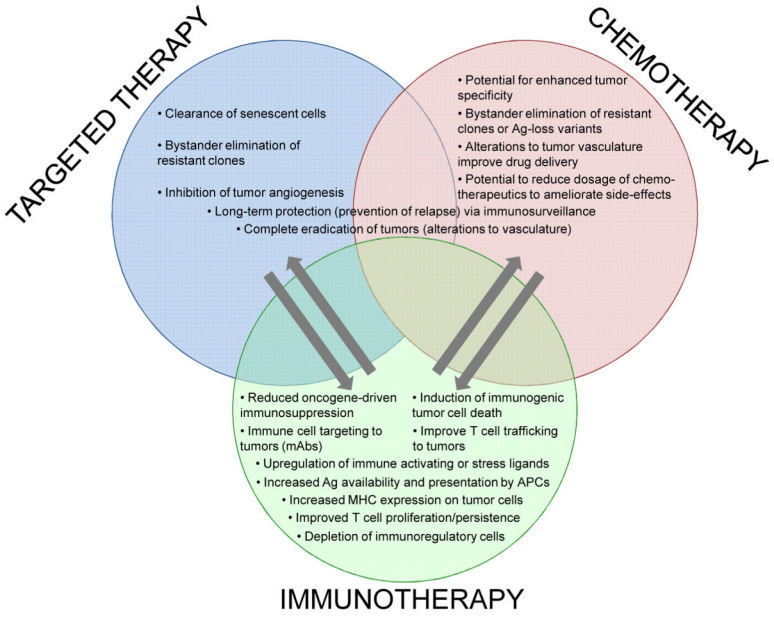

Figure 2. Combining immunotherapy with conventional cancer therapies can enhance treatment efficacy compared to their respective monotherapies

Arrows indicate potential mechanisms in which one therapy can promote (→) the efficacy of another therapy (also see recent reviews [51,52]). Importantly, while synergism between these therapies is well documented, the mechanisms of action are largely undetermined, especially in the context of different types of cancer and their unique mircoenvironments.

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Table 1

A comparison of the different mouse models of cancer

Features:	**Transplanted**	**Carcinogen- induced**	**Germline- GEM**	**Conditional- GEM**
Cancers modeled: *Examples:*	All *B16 melanoma* *EL4 lymphoma* *MC57 fibrosarcoma* *Lewis Lung carc.* *TRAMPC prostate*	Limited *MCA sarcoma* *UV fibrosarcoma* *DMBA+TPA skin carc.*	All *RIP-Tag2 pancreatic β-cell hyperplasia* *PyMT mammary* *TRAMP (Pro-Tag2) prostate*	All *$Kras^{LSL\text{-}G12D}$ lung* *$Kras^{LSL\text{-}G12D}$;$PTEN^{f/f}$ ovarian* *$Kras^{LSL\text{-}G12D}$;$p53^{f/f}$ sarcoma* *$Kras^{LSL\text{-}G12D}$ pancreatic*
Time to progression: (survival time)	0–4 weeks (after transplant)	2–4 months (after induction)	2–6 months (mouse age)	2–12 months (after induction)
Genetics alterations mimic human cancers?	Unknown/yes	Unknown/yes	Yes (some models)	Yes
Histopathology mimics human cancers?	Limited cases	Yes (limited tumor types)	Yes	Yes
Tumor initiated by transformation of normal cells?	No	Yes	Yes	Yes
Timing of tumor initiation controlled?	Yes	Partially (variable latency & penetrance)	No (empirically defined)	Yes
Location of tumor formation controlled?	Yes (orthotopic)	Yes (limited tumor types)	Yes (transgenic); No (tumor suppressor KO)	Yes (limited technology)
Tumors in natural microenvironment?	No (maybe orthotopic)	Yes (carcinogens may affect environment)	Yes (oncogenic events not restricted to tumor)	Yes
Multifocal disease?	No	Unknown	Yes	Yes
Track tumor antigen specific T cell responses?	Yes	No	Yes	Yes
Restrict tumor antigen expression to tumors?	Yes	NA	No	Possible
Regulated tumor antigen expression?	Possible	No	No	Possible