Progressively growing tumors emerge from a unique environment, in which the interactions between tumor cells, the surrounding stroma and infiltrating immune cells result in tumor progression. Over the past two decades a tremendous amount of work has been put into dissecting the cellular composition and activation state of immune cells in tumors in order to understand their contribution to tumor growth and escape. Since tumor cells often express altered or neo-antigens, it is not surprising that the host immune system senses and reacts to them [Reviewed in 1]. However, why such responses rarely result in tumor eradication is still not clear. To address this question, we searched for circumstances in which the net interactions in the tumor microenvironment promote effective immunity and tumor eradication rather than tumor escape.

One such circumstance occurs when tumors are transferred from their natural autologous setting into an allogeneic setting. Much like transplanted allogeneic organs, allogeneic tumors are reliably rejected by host T lymphocytes, even when the tumor and host share the same major histocompatibility complex alleles, the most potent determinants of transplant rejection. Nonetheless, it is not clear why allogeneic tumors, which differ only in their minor antigens, are rejected whereas autologous tumor cells, which express neo-antigens, keep growing. The process responsible for initiating tumor-eradicating immunity in the allogeneic setting has recently been elucidated by our group, and the findings provided a roadmap for the subsequent discovery of a method for inducing similar tumor-eradicating responses against naturally arising autologous tumors.

We discovered that most mice and humans have high titers of naturally occurring IgG antibodies that can bind to cell-surface proteins on allogeneic but not autologous tumors. We further showed that in mice inoculated with an allogeneic tumor, tumor rejection is initiated by these tumor-binding IgG antibodies (termed alloIgG), which enable tumor antigen uptake by resident DC via their Fc receptors. Once the DC acquire tumor antigens, they process and present them to T cells in a stimulatory context. The unique capacity of DC to determine the type and intensity of immunity that develops in response to the antigens they present have made these cells attractive targets for therapeutic manipulation [Reviewed in 4,5].

However, administration of alloIgG to mice bearing established syngeneic tumors had no therapeutic benefit. This result may not be surprising in light of the immunosuppressive microenvironment in autologous tumors. Indeed, analysis of tumor-associated DC from dozens of tumors indicated that they cannot respond to immune complexes (IC) unless additional stimulatory signals from molecules such as TNFα and CD40 agonist are also provided. Importantly, when alloIgG was injected into autologous tumors in combination with such DC stimulating molecules, the combination overcame tumor-mediated suppression and led to DC-dependent, T cell-mediated tumor eradication. A wide range of tumors in mice, including melanoma, pancreas, lung, colon and breast cancer, were cured with this approach. Moreover, treatment of primary tumors led to eradication of distant tumors and metastases and proved effective in models in which a checkpoint inhibitor, anti-PD-1 antibody, had little effect. Finally, other than transient inflammatory reactions at the injection site and local viti151gido, there was no evidence of systemic toxicity or autoimmunity.

Our findings contrast with some prior studies of the effects of tumor-binding antibodies. For example, circulating antibodies against p53 are associated with a poor prognosis in a variety of human cancers [reviewed in 6]. Additionally, vaccination of μMT mice that lack B cells with irradiated tumor cells promoted a protective Th1-biased immune response, while vaccination of wild-type animals generated a poorly protective Th2-biased response [7]. In other studies tumor-binding IgG was shown to promote tumor progression through the induction of regulatory macrophages and release of proangiogenic and growth factors from mast cells [8,9]. On the other hand, tumor-binding IgG can kill tumor cells by fixing complement or inducing antibody-dependent cell-mediated cytotoxicity. Moreover, engagement of Fc receptors on DC by IC is known to promote their activation and cross presentation of internalized antigens, including tumor associated antigens [reviewed in 10].
Our findings provide an explanation for these seemingly contradictory observations. In the presence of an immunosuppressive environment, most tumor-binding antibodies have little therapeutic effect and can potentially promote tumor growth via a variety of mechanisms. However, as demonstrated in our study, in an immunostimulatory environment these antibodies can induce a potent antitumor response.

To assess the potential clinical relevance of these findings, we studied tumors and immune cells from patients with lung cancer. T cells from these patients failed to respond to their own tumor antigens, in vitro, even in the presence of activated DC, but when IgG antibodies pooled from healthy blood donors were used to form tumor cell-IC before addition to these cultures, the same T cells responded vigorously to the tumor antigens, thus recapitulating the findings in mice. A schematic depiction of the mechanistic steps involved in this process is shown in Figure 1. As this treatment enables recipient DC to acquire and present a wide range of tumor antigens, its potency is greatly enhanced relative to therapies that target a single tumor associated antigen. Moreover, as polyclonal alloIgG binds a wide range of tumors, a single combination of such antibodies with DC-stimulating agents could prove broadly efficacious. Taken together, these findings show that in an immunostimulatory milieu, tumor-binding alloantibodies can induce powerful antitumor immunity that can potentially be exploited for the treatment of patients with cancer.

Disclosure of potential conflicts of interest
No potential conflicts of interest were disclosed.

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