Editorial

Cancer immunotherapy: accelerating the immune response without releasing the brakes

Luis I. Terrazas, Felipe Vaca-Paniagua

Unidad de Biomedicina and Laboratorio Nacional en Salud, Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Avenida de los Barrios 1, Los Reyes Iztacala, Tlalnepantla, Estado de México, México

Correspondence to: Luis I. Terrazas. Unidad de Biomedicina and Laboratorio Nacional en Salud, Facultad de Estudios Superiores Iztacala, Universidad Nacional Autónoma de México, Avenida de los Barrios 1, Los Reyes Iztacala, Tlalnepantla, Estado de México, México. Email: literrazas@unam.mx.

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Immuno-oncology, or oncoimmunology, is an area of research that has developed rapidly in recent years. This development has been fueled by the deep basic knowledge generated by studying immune regulation to induce positive or negative signals to improve immune responses or stop those responses when necessary. On the other hand, multiple mechanisms of escape, as well as basic knowledge on carcinogenesis and metastasis, have also reached new heights, so that putting such knowledge together may help to fight against different types of cancer.

In recent years, an increasing amount of scientific research has been focused on how to manipulate the immune system in order to improve anticancer response at both preclinical and clinical levels. There are two main strategies: (I) looking for ways to block the checkpoints of immune responses (antagonists or antibodies such as anti-CTLA4, anti-PD-1 or anti-PD-L1) during tumor development and (II) fueling the immune response by using agonists (antibodies or ligands) that improve the immune response during tumor development. Simply put, on one side we release the brakes of the immune system, and on the other side we push the accelerator to improve the immune response. Both strategies have their pros and cons, and both are focused on how to adequately modify the features of the tumor microenvironment (usually immunosuppressive) to improve clinical responses against cancer.

In a recent paper published on January 31, 2018, Sagiv-Barfi and colleagues from Stanford University (1) developed an innovative strategy to induce the clearance of previously established tumors. Usually, anticancer treatments entail the administration of the drugs in a systemic pathway, mainly I.V., far from where the tumor is growing. In their work, Sagiv-Barfi *et al.* used an interesting model; they subcutaneously implanted tumor cells in two different sites of the abdomen (left and right), and once the tumors were palpable they employed a local delivery system that consisted in the inoculation of the innate activator of the immune system, the non-methylated CpG oligodeoxynucleotide (a ligand for TLR9) in just one of the two tumor nodules. Such stimulation altered the tumor microenvironment by inducing the expression of OX40 on T cells, indicating immune activation. OX40 is a member of the tumor necrosis factor (TNF) receptor family and has been previously reported as a potent T cell activator when it is engaged with its ligand (OX40L), favoring T cell proliferation and cytokine production (2). To take advantage of the OX40 induction, this group further fueled the local immune response by injecting, concomitantly with CpG, a low dose of an agonist antibody against OX40, thus simulating a natural OX40-OX40L interaction. Interestingly, the local microenvironment in the tumor that was injected displayed significant modifications, such as local cytokine production (IL-12, IFN-γ and TNF-α) and local T cell activation. In contrast, the contralateral tumor, which was receiving only the vehicle, did not show any modification in its microenvironment, indicating a localized effect of this treatment. Moreover, the tumors that received the concomitant inoculation of CpG + OX40 agonist displayed a complete regression in a few days. Extraordinarily, approximately 2 weeks later, the other, non-injected tumor

also showed a complete remission. Mice receiving such treatment were free of tumors and survived for more than 100 days, while control mice (vehicle) succumbed as early as 20 days after tumor implantation. These authors tested their combined therapy in three different orthotopic models of cancer, including breast cancer, melanoma and colon cancer; a successful tumor rejection was reported in these neoplasms. Some low recurrence was observed, but only 3 of out 90 mice treated had new tumorigenesis, which was reverted with a second round of the combined therapy (CpG + OX40 agonist). These data indicate that this innovative treatment can induce long-lasting protection.

Notwithstanding these remarkable results, the authors decided to challenge their local therapy with a model of spontaneous tumorigenesis using female mice of the strain PyVT/PyMT; these mice are known to develop highly invasive mammary ductal carcinomas in all their 10 mammary fat pads and usually experience metastasis to the lungs. The researchers allowed the first tumor to reach a considerable size (50 to 75 mm^3) and then started the local intra-tumor treatment in just the first tumor (only 3 doses in total, every other day). Surprisingly, the tumorigenesis in all the other mammary fat pads was dramatically reduced. Additionally, metastasis to the lungs was practically eliminated, and more than 65% of the mice survived for at least 25 weeks without recurrence of breast tumors. This tumor regression was associated with higher percentages of memory $CD8^+$ T cells producing IFN-γ. Further immunological analysis from cells present in the tumor microenvironment demonstrated that this combinatory therapy was able to reduce the number of Treg cells while increasing the percentage of $F4/80^+CD11b^+$ myeloid cells, natural killer (NK) cells and $CD8^+$ cells. This observation is key because this treatment was able to activate innate cells and antitumor specific T cells and was able to down-modulate, through the OX40 ligation, the presence of Treg cells, which have been demonstrated to be deleterious in different types of cancer (3). Moreover, by translating these findings to humans, they found that the exposure of tumors (B cell lymphoma) to CpG *in vivo* and *in vitro* induced the expression of OX40 on $CD4^+$ T cells infiltrating the tumors.

This interesting *in situ* or local therapy strategy involves the activation of T cells and NK cells already present in the tumor microenvironment, together with innate cells, hence resembling the use of adjuvants in vaccines. Thus, CpG activates innate cells, perhaps myeloid cells, which may induce IL-12 and TNF-α production, whereas the anti-OX40 agonist antibody reignites the antitumor specific $CD4^+$ and $CD8^+$ cells already infiltrating the tumor; such change in the tumor microenvironment may favor a rapid anticancer response in already established tumors.

This innovative action is in contrast with the canonical systemic therapy usually applied via I.V. It also contrasts with most of the authorized treatments to modulate the immune response in cancer, which are focused on the blockade of the inhibitory signals of the PD-1 and PD-L1 pathways, as well as the blockade of the suppressor molecule CTLA4. All these therapies were rapidly approved (from 2011 to 2017) for human use in different types of malignancies (4). This haste to approve effective anticancer immunotherapy has begun to demonstrate the complexity and drawbacks of modulating the immune response by systemic treatments, as every month there are reports in the literature that detail severe side effects in patients that oblige the suspension of the therapeutic regimen. Many patients treated with either anti-PD-1, anti-PD-L1 or anti-CTLA4 antibodies have shown illness associated with excessive unspecific immune responses, ranging from light symptoms to death by autoimmune myocarditis and hepatitis (5,6). Thus, it now looks as if clinicians will have a choice: push the accelerator to make the immune response go faster, but leave the brakes intact (CpG + OX40 agonist), or fully release the brakes of the immune system (blocking PD-1, PD-L1 or CTLA-4). In both cases the immune response is activated, but in the first one the brakes are ready to stop excessive responses, in the second case the absence of brakes may be a serious disadvantage. Perhaps the collateral damage is worth it if it is timely controlled. This combination of local therapy has initiated a new boom in the oncoimmunology field; as reported in a recent work, concurrent treatment with OX40 agonist antibodies and PD-1 blockade is able to induce breast-tumor regression in approximately 30% of experimental mice (7), whereas the same team at Stanford University, by using pluripotent stem cells activated with CpG as a vaccine (or adjuvant), demonstrated that this combined treatment was able to protect against both breast cancer and melanoma in mice (8). As noted by Sagiv-Barfi *et al.*, the distant immunogenic capacity of local treatment may be exploited in patients with high-risk of recurrence or metastasis (such as *BRCA1/2* germline mutation carriers) independently of their tumor type, by performing the *in situ* immune activation before the surgery. The low-dose needed to activate the tumor microenvironment may potentially reduce the risk of autoimmune reactions and the low number of doses needed may lessen costs and maximize the effectivity.

Taken together, these findings indicate a new era for cancer immunotherapy, in which immune activation is achieved by the local co-injection of immunomodulatory agents that act like adjuvants and the vaccine (and therapeutic value) is provided by the tumor itself, by the expression of specific neoantigens.

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