The ultimate goal of curative anti-cancer therapies: inducing an adaptive anti-tumor immune response

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Despite a century of intensive biological and pharmacological research resulting in hundreds of new drugs and clinical trials, the only curative therapy of most solid tumors remains surgery of localized disease. Once metastatic cells have left primary tumors and have hidden in protective niches or nidated in distant organs, patients will eventually experience recurrence and finally death. Physical agents used in radiotherapy may delay regional spreading whereas chemical agents used in chemotherapies may induce tumor shrinking but rarely totally eradicate cancers at a systemic stage. In addition, these effects are obtained at the price of intense toxicity which hampers the treatment of older patients, at an age when most cancers occur. Targeted therapies, interfering with pathways critical for the cancer cells, which have proven efficacy in hematological malignancies, are still in their infancy for solid tumors and it becomes now evident that cancer cells are capable to develop escape mechanisms to this new class of drugs.

Immunotherapies have been for a long time a matter of hopes and disillusions. In the recent years, however, they have begun to gain their place among the therapeutic arsenal of cancer therapies. They are classically thought to work through two mechanisms, the first the direct destruction of tumor cells, the second indirect anti-cancer effects via stimulation of the immune system. The destruction of tumor cells can be achieved by monoclonal antibodies which recruit effector NK cells and macrophages and possibly neutrophils to the

tumor through their Fc portion, and trigger their Fc receptors resulting in killing of the malignant cells (Clynes et al., 1998; Carter, 2006). Several monoclonal antibodies of this type have been approved including rituximab (an anti-CD20 antibody) for B cell malignancies, cetuximab (an anti-EGF receptor antibody) for wild-type Ki-Ras colorectal cancer, or trastuzumab (an anti-HER2/neu antibody) for breast and head and neck cancers (Galluzzi et al., in press). A direct destruction of tumor cells can also be achieved by cellular therapies such as the infusion of allogeneic hematologic stem cells, from bone marrow or blood, approved for the treatment of leukemia (Ashfaq et al., 2010) or that of differentiated cytotoxic T cells for the treatment of solid tumors, although the latter are still in clinical trials (Rosenberg et al., 2011). The other approach, immunostimulation of the immune system has been historically achieved by bacteria or bacterial extracts (e.g., the Coley toxin). BCG is still used to treat superficial bladder cancer (Finn, 2008; Disis, 2010). The modern version of this approach of non-specific stimulation is represented by interleukin 2, which is approved for the treatment of metastatic melanoma and renal cancer (Rosenberg et al., 1987). Therapeutic vaccines have become a reality with the approval of Provenge as a treatment for metastatic, hormone refractory prostate cancer with autologous dendritic cells (DC) pulsed with a prostatic antigen, PSMA fused to GM-CSF (Beer et al., 2011; Gulley and Drake, 2011). PROSTVAC, a therapeutic vaccine for the same disease

which uses poxvirus as a vector and PSA as an antigen, is in advanced stage of clinical validation (Kantoff et al., 2010). The most promising agents are, again, monoclonal antibodies that modulate the immune system. Ipilimumab, an anti-CTLA-4 antibody which blocks CTLA-4/CD28 interaction and therefore unlocks a lymphocyte checkpoint, has recently been approved for the treatment of metastatic melanoma (Hodi et al., 2010). Anti-PD1 antibodies which unlock the PD1/PDL-1 checkpoint are being explored in phase II studies (Waldmann, 2006; Kline and Gajewski, 2010; Rosenblatt et al., 2011). Bevacizumab (Yang et al., 2003), an antibody which neutralizes VEGF, approved for the treatment of colorectal, lung and breast cancers, has a dual effect: it decreases the neo-vascularization of tumors but it also blocks the maturation-inhibiting activity of VEGF on DC, resulting in a decrease in regulatory T cells and myeloïd derived suppressor cells, and thus acts as an immunomodulatory agent (Tartour et al., 2011).

The last decade witnessed the development of these new therapies but also the achievement of comprehensive analyses of the immune microenvironment of human tumors that shed light on what components of the local immune infiltrate influence cancer development and how they impact various parameters of patients clinical outcome. The deepest studies were performed in colorectal cancers (Galon et al., 2006; Pagès et al., 2010; Fridman et al., 2011a,b; Mlecnik et al., 2011; Tosolini et al., 2011) and most of the conclusions reached in these

analyses were reported to apply to many other tumors, such as ovarian, lung, breast, head and neck, prostate, liver, urothelial carcinoma, or melanoma (Fridman et al., 2011b). The main finding was that infiltration of primary tumors by high numbers of memory Th1/cytotoxic T cells both in the core ("center") and the invasive margin of the tumor nests was associated with good clinical outcome (Galon et al., 2006). Pro-inflammatory cells (Th-17; Tosolini et al., 2011) or cytokines (IL-17, IL-6, etc.; Tartour et al., 1996; Tosolini et al., 2011) are associated with poor prognosis. The case of regulatory T cells is more complex: they are associated with poor prognosis in ovarian cancer (Curiel et al., 2004) and gastrointestinal sarcoma (Balachandran et al., 2011), but they constitute a predictor of favorable clinical outcome in head and neck (Badoual et al., 2006), colorectal cancers (Salama et al., 2009), and Hodgkin lymphoma (Carreras et al., 2006). What emerges from numerous studies is that, even if the density of infiltrating adaptive immune cells decreases upon tumor spreading (Mlecnik et al., 2011), their main impact is on survival of the patients. It thus raises the hypothesis that cancer therapies with long-term beneficial effects may have limited impact on local disease but should activate a relevant adaptive immune reaction that will result in control of potential metastatic spreading and establish an homeostasis which allows patients to live with a controlled disease.

Pioneering work by Laurence Zitvogel and Guido Kroemer, in mouse models, revealed that chemotherapy could retard the growth of tumors growing on immunocompetent but had no effect on tumors established on immunodeficient mice (Zitvogel et al., 2008, 2011; Galluzzi et al., 2011). Based on these results, the concept of immunogenic chemotherapy was launched hypothesizing that a drug is curative if it provokes an immunogenic death of the malignant cells, thereby inducing an adaptive immune response which clears, or maintains dormant, escaping tumor cells. The molecular mechanisms of the immunogenic cell death have been deciphered. The exposition of calreticulin on the surface of the dying tumor cells increases their uptake by DC. DC are also stimulated by HMGB1 and ATP released from dying tumor cells, which act on TLR4 (Apetoh et al., 2007) and P2RX7 (Ghiringhelli et al., 2009) among other receptors, respectively favor processing of tumor antigens and Tc1 polarization of CD8+ T lymphocytes (Ghiringhelli et al., 2009) allowing for the subsequent activation of an adaptive immune reaction. Indeed in retrospective studies, polymorphisms of TLR4 and P2RX7 were associated with survival in chemotherapy treated patients (Apetoh et al., 2007; Ghiringhelli et al., 2009). Strikingly, a recent study of DTIC treated metastatic melanoma showed that survival was indeed correlated, among other factors, with T cell infiltration in metastases (Nardin et al., 2011). In human, high T cell infiltration of hepatic metastases of colorectal cancer was a predictor of patient's response to chemotherapy (Halama et al., 2011). Thus, although drug-induced tumor shrinkage is independent of the immune reaction, patient survival may be the consequence of the induction/increase of a sustained immune reaction. In line with these results, clinical efficacy of radiotherapy also required CD8+ T cells, in preclinical models (Lee et al., 2009).

The analysis of the effects of immunotherapies leads to the same conclusion. In mouse models, it was demonstrated that although the clearance of an autologous CD20 positive lymphoma or an HER2 positive carcinoma by anti-CD20 (Abès et al., 2010) and anti-HER2 (Park et al., 2010) monoclonal antibodies respectively, requires NK cells, an equilibrium phase is established that involves an antigen-specific T cell response (Abès et al., 2010; Park et al., 2010; Abès and Teillaud, 2011; Stagg et al., 2011). A second graft of the tumor is rejected in an antigen-specific manner, without a second antibody challenge. If CD4 cells are depleted during the treatment with the therapeutic monoclonal antibody (the induction phase) such memory is not induced, and if CD8 cells are removed prior to the second graft (the maintenance phase), it is not rejected (Abès et al., 2010). In human, administration of anti-HER2/neu monoclonal antibodies also induced endogenous anti-HER2/neu humoral and cellular immune responses (Taylor et al., 2007). Thus, the long-term effects of therapeutic *anti-tumor antibodies* are also mediated by an adaptive T cell response (Abès et al., 2010; Park et al., 2010; Stagg et al., 2011).

The case of ipilimumab is even more striking. Metastatic melanoma sites either shrink, or are not modified in size or grow during antibody treatment, or even new sites appear. The only significant effect is an increase of patients overall survival, an excellent predictor of this effect being again the infiltration of metastatic sites by CD8 T cells. Treatment with anti-PD1 antibodies follows the same rules (Nomi et al., 2007). Strikingly, treatment with anti-angiogenic agents reveals a similar phenomenon. A recently published clinical trial where patients with metastatic renal cancer were treated with sunitinib (an inhibitor of VEGF receptor signaling) with or without bevacizumab (an anti VEGF-A antibody) revealed that some of them had a decrease in regulatory T cells. The patients with decreased Treg had a longer survival than the group of patients on which Treg decrease was not induced (Adotevi et al., 2010). Interestingly, the decrease of Treg did not correlate with clinical response assessed by Recist criteria but only with overall survival. In patients treated with sunitinib in a neo-adjuvant setting, i.e., before surgery, a decrease in intra-tumoral regulatory T cells was detected. Finally, it is striking that in patients presenting with metastatic prostate cancer treated with therapeutic vaccines, there was no effect of disease progression but only on overall survival (Kantoff et al., 2010; Beer et al., 2011; Gulley and Drake, 2011). It is tempting to speculate that the effect on overall (but not progression-free survival is the consequence of the induction of an adaptive immune response to the vaccine and putatively to the tumor.

From these examples, it clearly results that these are two important steps should be attained by anti-cancer therapies: the first one is to reduce the tumor burden by surgery, radiotherapy, chemotherapy, or anti-tumor antibodies. If some tumor cells escape these treatments, the cure of cancer, or at least its maintenance in an equilibrium stage, is the result of the second step, i.e., the induction of an adaptive T cell response which may be efficiently sustained by immunomodulatory agents.

To reach long-term survival and therefore clinical cure of cancerous patients, innovative treatments regimen should take into account these two steps.

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