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Review

Immunological Effects of Conventional Chemotherapy and Targeted Anticancer Agents

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The tremendous clinical success of checkpoint blockers illustrates the potential of reestablishing latent immunosurveillance for cancer therapy. Although largely neglected in the clinical practice, accumulating evidence indicates that the efficacy of conventional and targeted anticancer agents does not only involve direct cytostatic/cytotoxic effects, but also relies on the (re)activation of tumor-targeting immune responses. Chemotherapy can promote such responses by increasing the immunogenicity of malignant cells, or by inhibiting immunosuppressive circuitries that are established by developing neoplasms. These immunological "side" effects of chemotherapy are desirable, and their in-depth comprehension will facilitate the design of novel combinatorial regimens with improved clinical efficacy.

Cancer is historically conceived as a cell-autonomous disease driven by the activation of (proto)oncogenes or the inactivation of oncosuppressor genes (Hanahan and Weinberg, 2000). Logically, the ultimate goal of anticancer therapy consists of the destruction of malignant cells. This can be attained with cytotoxic drugs that target rapidly proliferating cells, especially when these cells, like cancer cells, are particularly vulnerable because of aberrations in the mechanisms that control adaptive stress responses and cell death (Fulda et al., 2010; Solimini et al., 2007). Based on their principal mechanism of action, conventional chemotherapeutics can be broadly subdivided into: (1) alkylating agents, which provoke inter- or intra-strand DNA crosslinks that destabilize DNA during replication (e.g., cyclophosphamide); (2) antimetabolites, which inhibit the synthesis of DNA, RNA, or their building blocks (e.g., 5-fluorouracil [5-FU]); (3) topoisomerase inhibitors, which impede the correct unwinding of DNA during replication and transcription (e.g., irinotecan); (4) microtubular poisons, which interfere with the polymerization or depolymerization of tubulin, hence inhibiting the mitotic spindle (e.g., paclitaxel); and (5) cytotoxic antibiotics, which exert antineoplastic effects by various mechanisms, including DNA intercalation and overgeneration of reactive oxygen species (e.g., bleomycin). Alternatively, neoplastic cells can be targeted with molecules that are tailored on cancer-specific alterations (e.g., oncogenic signaling pathways, mechanisms of non-oncogene addiction), a therapeutic paradigm that follows the precepts of "precision medicine" (Werner et al., 2014). The use of both conventional and targeted chemotherapeutics has been successfully implemented in the clinical praxis, seemingly comforting the cell-autonomous perception of cancer that has been driving the development of antineoplastic agents over the past 50 years.

Yet another treatment modality recently unveiled a tremendous clinical potential: the so-called immune checkpoint blockers (ICBs) (Lesokhin et al., 2015). No less than three distinct ICBs are currently approved by the US Food and Drug Administration (FDA) and other equivalent agencies worldwide for anticancer therapy: (1) ipilimumab (Yervoy), a monoclonal antibody (mAb) blocking cytotoxic T lymphocyte-associated protein 4 (CTLA4), which is licensed for use in patients with unresectable or metastatic melanoma; (2) pembrolizumab (Keytruda), an mAb blocking programmed cell death 1 (PDCD1, best known as PD-1), which is approved for use in individuals with unresectable or metastatic melanoma experiencing disease progression on ipilimumab or targeted anticancer agents; and (3) nivolumab (Opdivo), a PD-1-targeting mAb licensed for use in subjects with unresectable or metastatic melanoma that no longer responds to other drugs, as well as in patients with advanced or metastatic non-small cell lung carcinoma (NSCLC) progressing on or after platinum-based chemotherapy (Lesokhin et al., 2015). These and other ICBs are expected to obtain regulatory approval for an expanding panel of oncological indications based on impressive results from several, randomized clinical studies (Ansell et al., 2015; Westin et al., 2014). The clinical success of ICBs demonstrates that cancer can be efficiently treated by targeting immune, rather than malignant, cells,

spurring renovated interest in the immunosurveillance theory. According to this concept, tumors can only originate and progress in the context of failing immune responses (Schreiber et al., 2011; Zitvogel et al., 2006). This implies that (one of) the goal(s) of cancer therapy should consist in reinstating the immunological control of tumor growth (Schreiber et al., 2011; Zitvogel et al., 2006). Thus, the mechanistic rationale behind the development of anticancer immunotherapies is completely different from that subjacent to conventional and targeted antineoplastic agents.

Preclinical and clinical data accumulating over the past decade have begun to erode the frontiers between a purely cell-autonomous and a purely immunological approach to the development of anticancer drugs. For instance, it became clear that the density, composition, localization, and function of tumor-infiltrating lymphoid and myeloid cells, the so-called immune contexture, has a major prognostic and predictive value in patients with cancer treated with conventional or targeted anticancer agents (Table 1) (Fridman et al., 2012). Thus, the immune contexture determined at diagnosis influences the prognosis of individuals affected by virtually all solid neoplasms, including colorectal carcinoma (Anitei et al., 2014), breast carcinoma (Ascierto et al., 2013), NSCLC (Remark et al., 2015), ovarian carcinoma (Nelson, 2015), and prostate cancer (Ness et al., 2014). Moreover, it turned out that widely used conventional chemotherapeutics as well as target anticancer agents modulate the composition and functionality of the tumor infiltrate, and this affects disease outcome (Senovilla et al., 2012a). Thus, an increased amount of intratumoral immune effectors (alone or coupled to a decreased abundance of immunosuppressive cells) in response to treatment was shown to correlate with pathological complete response as well as progression-free and overall survival in patients with breast carcinoma treated with anthracycline- or taxane-based neoadjuvant chemotherapy (Issa-Nummer et al., 2013; Senovilla et al., 2012b). Similarly, the tyrosine kinase inhibitor (TKI) imatinib mesylate (see below) was shown to increase the abundance of $CD8^+$ cytotoxic T lymphocytes (CTLs) and natural killer (NK) cells within gastrointestinal stromal tumors (GISTs), and this correlated with disease outcome (Rusakiewicz et al., 2013). Genetic and epigenetic determinants of the functionality of circulating and tumor-infiltrating NK cells also affect the prognosis of GIST patients treated with imatinib (Delahaye et al., 2011), corroborating the notion that the therapeutic effects of targeted anticancer agents rely (at least in part) on the (re)activation of a tumor-targeting immune response. Preclinical data obtained in mice in which distinct immune effectors were ablated or, on the contrary, specific immunosuppressive circuits were inactivated demonstrate that many chemotherapeutic agents that were initially developed according to a purely cancer cell-autonomous logics mediate antineoplastic effects via immunological mechanisms (Galluzzi et al., 2012; Zitvogel et al., 2013).

Here, we examine the provocative hypothesis that the clinical activity of most, if not all, conventional and targeted antineoplastic agents currently licensed for use in humans can be attributed to the reestablishment of immunosurveillance, and we discuss prospects to develop combinatorial regimens with improved therapeutic profile.

Principles of Anticancer Immunosurveillance

The presence of leukocytes within and around tumors has an ambiguous connotation. On one hand, specific immune effectors (mostly CTLs and NK cells) can eliminate premalignant and malignant lesions, at least under some circumstances (Schreiber et al., 2011). On the other hand, various myeloid and lymphoid cells including specific subsets of tumor-associated macrophages and $CD4^+CD25^+FOXP3^+$ regulatory T (T_{REG}) cells can inhibit tumor-targeting immune responses as they mediate robust immunosuppressive effects (Gabrilovich et al., 2012). Moreover, chronic inflammation (mostly supported by myeloid cells) can stimulate carcinogenesis (Coussens et al., 2013). Hence, an exhaustive molecular and cellular profiling is required to evaluate the functional significance of the tumor infiltrate. Preclinical data obtained in rodent models point to the existence of a process whereby the immune system, in the absence of external manipulations, both protects the host against oncogenesis and sculpts the immunogenicity of developing tumors (Schreiber et al., 2011). Such a natural immunosurveillance process, which is also known as immunoediting, consists of three phases (Figure 1): (1) eradication of forming malignant cells by the immune system (elimination); (2) failure of the elimination phase, resulting in tumor dormancy (equilibrium) as well as in the establishment of an immunological pressure that sculpts genetically unstable cancer cells (editing); and (3) selection of cancer cell variants that are not recognized or eliminated by the immune system, which can manifest clinically (escape) (Schreiber et al., 2011). Systemic analyses of human neoplasms have confirmed the clinical relevance of the immunosurveillance theory (Rooney et al., 2015).

The capacity of any cell to elicit an immune response (immunogenicity) relies on a combination of two factors: antigenicity and adjuvanticity (Matzinger, 1994). For example, virus-infected cells are recognized by the immune system because viral peptides are presented in association with major histocompatibility complex (MHC) proteins on the cell surface. These alien epitopes determine an increase in the antigenicity of infected cells, but are not sufficient for the activation of a robust immune response. Indeed, viral infection also induces an adaptive stress response that can be followed by cell death. In the course of adaptation as well as upon the permeabilization of the plasma membrane (an inevitable consequence of cell death) (Galluzzi et al., 2015), cells emit several signals (in the form of soluble or plasma membrane-associated molecules) that alert the organism of a potential harm (Brenner et al., 2013). Such "danger" signals, which are also known as damage-associated molecular patterns (DAMPs) bind to pattern recognition receptors (PRRs) on the surface of myeloid and lymphoid cells, thereby attracting them and initiating signaling pathways that are required for the activation of efficient immune responses (Chow et al., 2015).

Similar to virus-infected cells, cancer cells must differ antigenically from their normal counterparts and emit danger signals to be recognized by the immune system. Contrary to previous beliefs, malignant cells often display an increased antigenicity because (1) they are very prone to accumulate genetic mutations, implying that they have a relatively high chance to produce and present on MHC molecules mutant antigenic determinants (Gubin et al., 2014); and (2) they ectopically express "cancer/testis" or "oncofetal" antigens, i.e., proteins that are expressed