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Current trends of anticancer immunochemotherapy

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Abbreviations: MDSC, myeloid-derived suppressor cell; Treg, regulatory T cell

The paradigm of combinatorial anticancer therapy is nowadays deeply established into the clinical routine, reflecting the notion that–with a few notable exceptions–standalone chemo- or radiotherapeutic regimens are always insufficient to completely eradicate neoplastic lesions. Moreover, combining agents with distinct mechanisms of action potentially results in synergistic antineoplastic effects. This not only allows for the use of decreased drug dosages, de facto limiting the incidence and severity of side effects, but also significantly reduces the likelihood that malignant cells may become chemo- or radioresistant.

Along with the development of ever more efficient strategies to elicit or boost anticancer immunity and with the realization that most successful antineoplastic agents operate–at least in part–by (re)activating tumor-specific immune responses, great interest has been attracted by the possibility to develop combinatorial immunotherapeutic interventions and/or to combine chemo- or radiotherapeutic regimens with immunotherapy.[1–3] Thus, an ever increasing amount of literature describes preclinical and clinical studies investigating whether and under which conditions several distinct immunostimulatory agents can be combined to each other or with conventional antineoplastic regimens to obtain improved therapeutic responses and/or reduced side effects.[4–6]

Intriguingly, both immunotherapeutic regimens and antineoplastic agents that exert immunostimulatory effects can be classified based on their ability to promote anticancer immune responses by acting on cancer cells or on the immune system.[1] Thus, clinically employed and hitherto experimental agents can re(activate) anticancer immune responses by (1) altering the MHC Class I immunopeptidome or by stimulating the presentation of tumor-associated antigens on the surface of malignant cells (antigenicity); (2) by favoring the emission of danger signals with adjuvant properties by neoplastic cells, resulting in the stimulation of innate and cognate immune effectors (immunogenicity); or (3) by increasing the sensitivity of malignant cells to the cytotoxic functions of immune effectors (susceptibility).[7] Just to mention a few examples, both cisplatin (a DNA damaging agent) and gemcitabine (a nucleoside analog) have seen shown to expand the repertoire of antigens eliciting tumor-specific immune responses in vivo (increase in antigenicity);[8] anthracyclines (such as doxorubicin) reportedly cause an immunogenic variant of apoptosis that is associated with the emission of various damage-associated molecular patterns (DAMPs), some of which exert potent immunostimulatory effects (increase in immunogenicity);[9,10] and several chemotherapeutics are known to stimulate the expression of death receptors (such as CD95) or activating ligands for natural killer (NK)-cell receptors, hence increasing the propensity of malignant cells to be killed by CD95L-expressing $CD8^+$ T cells and NK cells, respectively.[11,12] Alternatively, anticancer immune responses can be (re) instated by immunochemotherapy as a result of direct stimulatory effects on (1) cognate or (2) innate immune effectors, as well as (3) following the inhibition of immunosuppressive networks, such as those established around regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs).[7] For instance, metronomic cyclophosphamide (an alkylating agent) has been shown to promote the differentiation of T_H17 cells in vivo, both among circulating and tumor-infiltrating leukocytes (activation of cognate immune effectors);[13] imatinib (an inhibitor of BCR-ABL and KIT currently employed for the treatment of chronic myelogenous leukemia and gastrointestinal stromal tumors) reportedly potentiates the effector functions of NK cells (activation of innate immune effectors);[14,15] and several chemotherapeutics including gemcitabine and cyclophosphamide have been suggested to mediate MDSC- and Treg-depleting effects in patients (relief of immunosuppressive networks).[16,17]

To get some insights into the current trends of immunochemotherapy, we have identified among the articles published in OncoImmunology from January 2012 to March 2013 (12 issues of the journal) all those describing or commenting the sequential or concomitant administration of distinct immunotherapeutic or

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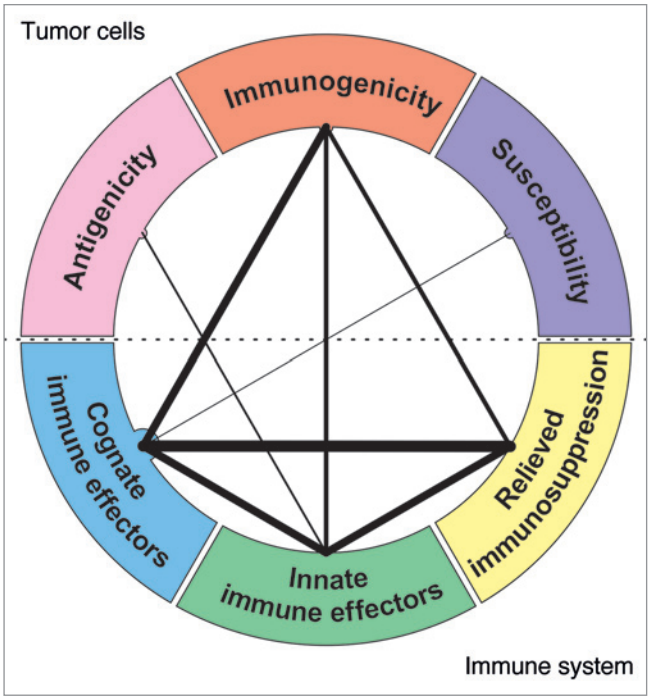

Figure 1. Current approaches of anticancer immunochemotherapy. Among the articles published in OncoImmunology from January 2012 to March 2013, all those describing or commenting the sequential or concomitant administration of distinct immunotherapeutic or chemotherapeutic regimens (both in preclinical and clinical settings) have been identified, and such combinatorial approaches have been classified based on the most prominent immunostimulatory activity of their components. The size of inward bulges and the weight of central connectors reflects the relative proportion of homologous (involving the use of two distinct molecules that exert immunostimulatory effects via the same general mechanism) and heterologous (involving the administration of two agents that promote anticancer immune responses via distinct general mechanisms) combinatorial approaches to immunochemotherapy, respectively.

chemotherapeutic regimens (both in preclinical and clinical settings) and cataloged such combinatorial approaches based on the most prominent immunostimulatory activity of their constituents. Thus, monoclonal antibodies that exert antineoplastic functions mainly by triggering complement-dependent cytotoxicity and antibody-dependent cellular cytotoxicity (e.g., the HER2-targeting drug rituximab) have been classified as means of activating innate immune effectors,[18,19] peptide-, DNA- and dendritic cell-based vaccine as maneuvers to stimulate cognate immunity,[20-22] and so on.

We next estimated the relative frequency of each possible approach to immunochemotherapy among these studies, finding that (1) heterologous strategies, that is, the combination of therapeutic agents that (re)activate anticancer immunity via distinct general mechanisms (see above), are largely preferred over homologous strategies, involving interventions that stimulate the same facet of anticancer immune responses (even when they do so via distinct molecular mechanisms); (2) the vast majority of immunochemotherapeutic regimens rely on agents that exert stimulatory effects on the immune system; (3) increasing the immunogenicity of malignant cells is the preferred approach for the (re)establishment of anticancer immune responses when tumor-targeting agents are concerned; and (4) currently, the most investigated approach to immunochemotherapy involves the use of agents that activate cognate immune effectors coupled to interventions that inhibit immunosuppressive networks (**Fig. 1**). It will be interesting to see not only how these trends evolve in the forthcoming years, but also whether any of the six major means to (re)activate anticancer immunity discussed above will turn out to constitute a conditio sine qua non for the elicitation of optimal clinical responses to immunochemotherapy.

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