



The new revolution of immunotherapy: is it time to pair it with the old one? —Yellow Leader as a candidate

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Abstract: With the advent of immunotherapy in cancer treatment, the natural history of this disease has changed. The immune checkpoint therapies have shown great promise in this setting, by potentiating the body's natural immune response against tumor cells. Checkpoint inhibitors (CPIs) have definitively consolidated the target of reversing the immunoevasion as one of the most universal strategies to change the natural evolution of advanced oncological diseases, and to maximize CPI treatment efficacy, synergies in immune system modulation must be seriously considered. In the field of Integrative Oncology, Chinese medicinal mushrooms have been increasingly promoted as excellent anticancer immunoenhancers. However, many plants of traditional Chinese medicine have been less visible, but—as scientific literature reveals—not less powerful as antitumor immunomodulators. Astragalus membranaceous root is a venerated plant as a tonic in traditional Chinese pharmacopoeia. This is known to be beneficial to relieve mild disorders and to help in more serious diseases, such as cancer. For this great restorative capacity was why it won the name of Huang Qi, “leader of all tonics”, or Yellow Leader, because of its colour. Astragalus root contains a variety of immunoactive constituents. Its power as an antitumor root is not only due to its immunomodulatory activity; it is able to modulate several apoptotic and antiangiogenic signaling pathways and interact with specific transcription molecules. We propose a rational model of the combination of CPI with Astragalus root chosen as representative of traditional immunotherapy, to set a paradigmatic frame to develop novel target-specific combinations with natural immunomodulators. We are convinced that by combining these two strategies in immunotherapy—the new one and the old one—we can definitely overcome immune cell exhaustion, boost the response to immuncheckpoint treatment, and minimize side effects, to get better and more efficient results in cancer immunotherapy.

Keywords: Immunotherapy; checkpoint inhibitor (CPI); astragalus

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The revolution of immunotherapy in oncology: the anti PD-L1/PD-1

With the advent of immunotherapy in cancer treatment, the natural history of this disease has taken a 380-degree turn, both in survival and in the quality of life of the affected people. It has been only seven years since the first clinical trials were published with checkpoint inhibitors (CPI), to block the immunosuppressive signal dependent on the PD-1 and its PD-L1 ligand pathway, which have shown

unprecedented results in a wide variety of tumors (1).

A key point in the mechanism of action of PD-1/PD-L1 pathway inhibitors is that they enhance the antitumor capacity of T cells, reversing the immunoevasion phenomenon (2-4). There are several CPIs which are already in clinical use: pembrolizumab, nivolumab, atezolizumab, durvalumab and avelumab. Lethal and devastating tumors such as lung cancer or melanoma have gone from months of survival—also with very poor tolerance to conventional cancer treatment (mainly chemotherapy)—to years of

quality living. Other cancers such as sarcoma, renal tumor, hepatocellular carcinoma, bladder tumor and breast cancer, have been added to the list of beneficiaries of immunotherapy (5-10). Thus, CPIs have definitively consolidated the target of reversing the immunoevasion as one of the most universal strategies to change the natural evolution of advanced oncological diseases.

The PD-1/PD-L1 pathway: between the immunocompetence and the immunotolerance

PD-1 is a protein that is normally expressed in the immune system cells, when they are activated: natural killer (NK) cells, myeloid cells, B and T lymphocytes. Two ligands have been identified for PD-1: PD-L1 and PD-L2. These two ligands are expressed by different cells in our body. In normal physiological conditions, The PD-L1/PD-1 interactions are key in the regulation of immunotolerance against autoantigens (11,12). When the immuncheckpoint pathway becomes dysfunctional, it contributes to the development and maintenance of pathologies such as chronic viral infections and autoimmune diseases, leading to the T cells depletion (13,14).

In cancer, it has been shown that practically all tumors overexpress the ligand PD-L1. The tumor cell PD-L1 binds to the lymphocyte PD-1 receptor, draining T cells by inhibiting their proliferation and activation; it dramatically enhances the immunoevasion phenomena in the tumor (15). Therefore, the PD-L1 overexpression in tumors is considered a worsening indicator and poor prognosis item, it is a dysfunctional antitumor immune barrier marker (16). Recent research shows that PD-L1 is able to send signals to the cancer cells directly to make them grow without needing the immune system as an intermediate step (17).

Immunoevasion in cancer: beyond the PD-1/PD-L1 pathway

Although PD-1/PD-L1 pathway is considered one of the essential points of immune checking modulating T cells response, it is not the only one. Although T cells are the main acquired immunity cells involved in tumor surveillance, other collaborators are needed for T cells to be efficient.

In order to recognize the antigenic peptides against which they will react, these peptides must be presented to T cells in advance; as do the antigen-presenting cells [dendritic cells (DCs) and macrophages]. The presented peptides must

bind to the major histocompatibility complex molecules (MHC) of the cell surface to be duly recognized by T cell receptors and form the anchorage T cell receptor-peptide-MHC.

Moreover, T cells in order to be properly activated and proliferate they require a process called “co-stimulation”, a number of cascade immune cell activations where antigen presenting cells are also involved (18).

During cancer process, all of these immune agents are somewhat partners of the immunotolerance event carried out by the immuncheckpoint pathway; that is called “immunoediting”. Immunoediting is the ability of the immune system to maintain a dynamic equilibrium over time between malignant cells recognition and destruction, and tumor development. As cancer progresses, the immune system displays a bipolar behavior in their ability to promote or suppress tumor growth. As long as the number of cancer cell divisions are increasing, genetic instability and other aberrant events such as neoangiogenesis are taking place. This phenotype promotes a reduced tumor cell immunogenicity that allows them to escape from detection and elimination by the immune system (19).

It is important to highlight at least 3 events that take place during the immunoediting process. One of them is the suppression by the myeloid-derived suppressor cells (MDSCs). During the time of tumor growing, the innate and adaptative immunity that is supposed to destroy it, may be impeded by the suppressive action of MDSCs.

The MDSCs are a heterogeneous group of immune cells (immature macrophages, granulocytes, DCs) that come from the bone marrow in response to several tumor microenvironment stimuli. Once MDSCs reach the tumor bed, they are able to inhibit the function of local NK and T cells. The so called “tumor-associated macrophages” (TAMs) are also a type of macrophages belonging to MDSCs; they acquire a protumoral phenotype (M2) able to deactivate T cells and stimulate tumor growth, invasion and angiogenesis (20-24).

Another abnormality that may occur in this context is a failure in the antigens presentation system. MHC antigens I and II facilitate the recognition of tumor cells by cytotoxic T lymphocytes and NK cells through presentation of tumor antigens to such immune cells. Eventually, the tumor and immune cells conforming tumor microenvironment, instead of expressing the functional MHC can overexpress human leukocyte antigens (HLAs) and natural killer antigens (NKAs), which cause cytotoxic T cells and NK cells apoptosis and therefore immunosuppression (25).

A Yellow Leader to fight the immunoevasion: Astragalus root

Astragalus membranaceus grows in high areas of China. His Chinese name is Huang qi, which means Yellow Leader. It is popularly known as the “Root of Astragalus” because the part of the plant used is the dried root. Being a member of the Fabaceae family, there are many types of *Astragalus*. The most common genus is the *Astragalus membranaceus* variety *Mongolicus*, sometimes also called *Astragalus propinquus* (26).

Venerated plant as a tonic in traditional Chinese pharmacopoeia for more than 2,000 years ago, *Astragalus radix* is known beneficial to relieve multiple disorders: insomnia, anxiety, fatigue, impotence, infertility, allergies, eczema, diarrhea, herpes, colds, even more serious diseases such as diabetes, lupus, heart disease, cancer, etc. For this great restorative capacity was why it won the name of Huang Qi, “leader of all tonics” (27,28). Such ancestral properties have aroused great interest among the scientific community, and in recent decades *Astragalus* has been a subject of research, positioning it as a plant with promising active principles.

In the field of Integrative Oncology, Chinese medicinal mushrooms have been increasingly promoted as excellent anticancer immunoenhancers (29,30). For this reason, many plants of traditional Chinese medicine are less visible, but—as scientific literature reveals—not less powerful as antitumor immunomodulators (31). Examples such as ginseng root, capable of blocking the immunosuppressive action of MDSCs, or *Scutellaria baicalensis*, which can reprogram the protumoral (M2) phenotype of TAM macrophages to antitumor (M1) macrophages, are very representative (32-34).

It is not our purpose here to carry out an exhaustive review of the whole promising immunobotanical arsenal in cancer, but quite the opposite. The objective is to make a scope, and to propose a rational model of the combination of CPI with a single plant, in this case *Astragalus* root, chosen as representative of traditional immunotherapy. From here we suggest the reader to open their mind to consider other possible combinations from this paradigmatic frame, and encourage them to develop novel target-specific combinations with natural immunomodulators to enhance effective therapeutic results without major systemic side effects.

The immunomodulatory activity of *Astragalus* makes it an excellent plant—not only as an anti-infectious (35)—

but as a basis for improving the pathophysiology of degenerative diseases such as diabetes, premature aging and cancer (36,37).

Astragalus root contains a variety of immunoreactive constituents, the most studied ones, the polysaccharides. Recently, other *Astragalus* compounds have been tested such as isoflavonoids, coumarins and especially saponins (astragalosides), and they show good immunoregulatory activity (38-41). The best-known fraction of *Astragalus*—the polysaccharide one—contains mannose, D-glucose, D-galactose, xylose and L-arabinose. These macromolecules exhibit several pleiotropic effects on the immune system: clearance of the immunocomplexes to facilitate the immunological activity, increase in the number of bone marrow stem cells, stimulation of T lymphocytes transformation, macrophages, DCs, NK cells and B lymphocytes activation, inhibition of CD4 T cells negative immunoregulation, etc. (42-47). At high doses, the polysaccharide fraction seems to enhance the antigen presentation faculty, increasing the class II MHC antigens expression (48,49). Therefore, when *Astragalus* polysaccharide fraction is co-administered with vaccines it proves to be a potent immunogenic adjuvant (50-53).

Immunoregulatory action of Astragalus in cancer

The power of *Astragalus* as an antitumor root is not only due to its immunomodulatory activity; it is able to modulate several apoptotic and antiangiogenic signaling pathways and interact with specific transcription molecules (54-59). In clinical setting, a meta-analysis of randomized trials evaluating the benefits of *Astragalus* based Chinese treatment mixtures combined with chemotherapy for non-small cell lung cancer (NSCLC), showed benefit increasing effectiveness and reducing toxicity of chemotherapy (60).

The main actions of *Astragalus* antitumor immunomodulator can be summarized in the following (according to the available studies):

- ❖ Potentiating therapeutic efficacy of chemotherapy by reducing myelosuppression (36,61);
- ❖ Stimulating hematopoietic factors and interleukin (IL) production (62);
- ❖ Potentiating anti-tumor activity of recombinant lymphokine-activated killer (LAK) cells by means of tumor necrosis factor (TNF) and cytotoxic cells (with LAK-like activity) production (63,64);
- ❖ Enhancing immune defense (65);
- ❖ Increase in number of stem cells in bone marrow and

- lymphatics (66);
- ❖ Stimulating NK cell activity (67);
- ❖ Activating proliferation and increase cytokine production of macrophages (68,69);
- ❖ Antagonizing the leukopenic effect of immunosuppressants (70);
- ❖ Increase in proliferation and antibody production from T and B lymphocytes (71);
- ❖ Stimulating DCs maturation by regulating toll-like receptor 4 (TLR4) (72);
- ❖ Inducing overexpression of MHC in tumor membranes (73).

Can the Astragalus root influence the expression of PD-1/PD-L1?

Recently, one study found that Astragalus polysaccharide could decrease the expression of both PD-L1 protein and PD-L1 mRNA in melanoma. By regulating PD-1/PD-L1 pathway, Astragalus is able to enhance the antitumor immune activity of T lymphocytes (74). Another study investigated the antitumor effect of a traditional Chinese medicine formula that contains astragalus [Bu-Fei Decoction (BFD)] on NSCLC. BFD interrupted the link between TAMs and cancer cells by inhibiting the expression of IL-10 and PD-L1 *in vitro* and *in vivo*. TAMs and IL-10 promoted the mRNA and protein expression of PD-L1 in NSCLC cells (75).

Three reasons to combine immunotherapy with Astragalus root

First and foremost, to be effective, immune checkpoint (ICP) immunotherapy requires the integrity of much of the rest of the stroma immune system. Different studies have verified that the ICP activity depends on the positive activity of CD8, together with a limited activation of regulatory T cells (TReg) (76,77). This fact seems crucial to predict good response to this treatment (78). As we have seen, some botanicals (79) and more specifically the root of Astragalus can modulate the immune microenvironment to align it in a synergistic action together with the IPC, for the sake of a longer and more lasting response to immunotherapy.

Secondly, cancer patients will need at some point in their illness corticosteroids to modulate any disease related problems such as: brain metastases, cancer pain, vomiting, etc., but above all to control ICP iatrogenic effects. As expected mechanistically, one of the most

frequent and limiting side effects of the ICP therapy is the inflammation due to the reactivation of the immune fight in the tumor, and also in other parts of the body. This causes two problems: first, the difficulty in assessing the treatment response (80,81), thus appearing what are called “pseudoprogession” which confuse some when it comes to the decision on whether to continue the treatment or not, and can also cause clinical worsening (82,83); second: the onset of persistent arthritis (84,85) that can become limiting and end up forcing the use of corticosteroid therapy, even at low doses or at intervals. Logically, the use of corticosteroid therapy in these patients is contraindicated, since its immunosuppressive effect could interfere with the response (86,87), but also encourage the growth of the disease itself (88). As we have previously read, the polysaccharides and the other compounds of many of the immunomodulatory plants can offer an excellent balance between their immunoactivating capacity and their inflammation modulator action, becoming an ideal substitute for corticosteroids.

Finally, the use of botanicals as synergists in the conventional treatment of cancer has always been overshadowed by the risk of pharmacokinetic interactions, especially with regard to liver metabolism of both, drugs and plants. This is not the case of ICP molecules, as they suffer intracellular catabolism by lysosomal degradation (89).

Conclusions

The ICP therapies have shown great promise in the treatment of cancer by potentiating the body's natural immune response against tumor cells. For this reason, to maximize treatment efficacy, synergies in immune system modulation must be considered. Cytotoxic T cells, as well as other cell types in tumor microenvironment—such as suppressive Tregs and stimulatory T-helper cells—also affect the efficacy of ICP therapy. Additionally, the role that innate immune system plays in potentiating the anti-tumor immune response seems more important than previously realized.

In the view of these facts, and having seen the impressive effect of Astragalus by modulating the immune system in cancer, we are convinced that by combining these two strategies in immunotherapy—the new one and the old one—we can definitely overcome immune cell exhaustion, boost the response to immunocheckpoint treatment, and minimize side effects, to get better and more efficient results in cancer care.

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Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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