Chemistry Research Journal, 2022, 7(1):1-5

Available online www.chemrj.org

Review Article

ISSN: 2455-8990
CODEN(USA): CRJHA5

Traditional Herbs Role in Enhancement of Antitumor Responses of Agonistic CD40-Antibody by Reducing Myeloid-derived Suppressor Cells

Vishnu P. Tripathi[1]*, Roberto Jetsu[2]

[1]Department of Biotechnology, V.B.S. Purvanchal University, Jaunpur, India
[2]Professor, Department of Pharmacology, University of Verona, Italy
*Corresponding Author: Vishnu P. Tripathi, Department of Biotechnology, V.B.S. Purvanchal University, Jaunpur, India. Email: tripatipvishnu@gmail.com

Abstract The most exciting area in current cancer research is immuno-oncology, which aims to develop immunotherapy that activates the human immune system to attack cancers. However, we still lack broadly effective drugs and drug targets for this promising new cancer treatment modality. The number of tumor-infiltrating leukocytes varies between tumor type, stage as well as between individual patients. Depending on the type of immune cell and their activation state, leukocytes may have anti-tumoral effects or conversely, promote tumor growth. Tumors with high leukocyte infiltration are termed "hot" while tumors with low or no infiltration are commonly termed "cold" tumors. An alternative to these are the coined terms of inflamed, excluded and desert tumors, relating to leukocyte-infiltrated tumors, tumors with leukocytes in the border but not infiltrating into the tumor core, or tumors with no signs of immune cells within nor around them. T lymphocytes T cells arise from lymphoid progenitor stem cells in the bone marrow and are the main effector cells of the adaptive immune response. Traditional medicine towards new drug development and developed a variety of cell-based immune activity assays for identifying and characterizing novel innate immune drug targets and mechanisms are upcoming which the present review focuses.

Keywords Traditional Medicine, Agonistic CD40-Antibody, Myeloid-derived Suppressor Cells

Introduction

Cutaneous melanomas arise from pigment-forming melanocytes. Melanoma occurs mainly in white-skinned people and the incidence drops dramatically as skin pigmentation increases [1]. An estimated 80% of melanomas is caused by exposure to ultraviolet light, resulting in the highest mutational load compared to other types of cancers [2]. Melanoma is the deadliest form of skin cancer, responsible for 80% of all skin cancer related deaths [3]. The incidence of malignant melanoma is 13/100 000 per year in the European Union and there are an estimated 133 000 new diagnoses worldwide every year. Advanced metastatic Stage IV melanoma patients have a poor prognosis, with a mean survival of 8–10 months and a 5-year survival rate of less than 10% [4]. Treatment of primary melanoma is based on surgery and removal of the tumor. More advanced metastasized melanoma may be treated with targeted BRAF or C-KIT therapies in the patients who have mutations in these genes, or with antibody immunotherapy targeting PD-1 and CTLA-4, which will be discussed in more detail [5].

Urothelial carcinoma of the bladder is a common cancer with an estimated 330 000 new cases and 130 000 deaths worldwide each year [6]. Most bladder cancers are attributable to smoking or exposure to other types of carcinogens. The incidence is strongly male-biased, with three quarters of new cases diagnosed in males. At presentation, 70-80% of patients have superficial non-muscle invasive cancer, which is treated by transurethral resection followed by intravesicular chemotherapy [7]. Higher-risk muscle-invasive bladder cancer and metastatic cancer are preferentially referred to adjuvant local Bacillus Calmette-Guerin (BCG) immunotherapy [8-11]. BCG instillation into the bladder has been used since the 1970s and results in remission for 70% of patients. With these treatments, patients and healthcare are faced with an extensive follow-up screening due to the high risk of relapses. More recently, in 2016, Atezolizumab was the first immune-checkpoint antibody targeting PDL1 that gained clinical approval for patients with locally advanced or metastatic bladder cancer [12,13]. Clinical trials employing a combination of antibodies targeting PD-1 and CTLA-4, which has proven to be more effective than PD-1 alone in melanoma, are currently underway [NCT02496208, NCT02553642].

Traditional Chinese medicinal herbs in anticancer

To date, a number of Chinese medicinal herbs (both natural products and formulae) have been documented to possess anticancer activities through various potential mechanisms [14]. Meanwhile, some of the Chinese medicinal herbs can improve the therapeutic outcomes of patients when used in combination with conventional anticancer drugs due to the presence of synergetic effects, alleviation of side effects, or delaying/overcoming of drug resistance. This manuscript summarizes the anticancer drug development strategies from Chinese medicinal herbs [15]. Although abundant work about Chinese medicinal herbs have been carried out in the past decades, several points still need to be taken into consideration for future development. Firstly, an effective QC is crucial to ensure the safety and efficacy of Chinese medicinal herbs, especially for formulae. Since numerous factors influence the effects of Chinese medicinal herbs, a more comprehensive QC pattern is required. Aside from some rising chemical analysis methods, such as chromatographic fingerprint and multi-component quantification [16-17], pharmacology/biology evaluation is needed. Secondly, although Chinese medicinal herbs and formulae have been widely used in clinic, especially in China, the working mechanisms for most of them still remain to be clarified. The better understanding of the involved mechanisms will promote the discovery of more potential anticancer compounds or formulae. Thirdly, many natural products have been extensively studied and proven to exhibit anticancer effects *in vitro*, while showing poor activity *in vivo*. Such limitations may be caused by their poor bioavailability or toxicity. Thus, the implementation of some chemical and pharmaceutical methods is necessary during drug development. For those which have been proven safe and effective in vitro and in vivo, clinical trials can be considered under a good quality control. Fourthly, previous investigations mainly focused on the natural products which show high contents in Chinese medicinal herbs owing to the limitation of chemical analysis and isolation technologies. However, beside those high-content compounds, there are still many low content components existing in Chinese medicinal herbs, which also presents a huge resource for drug development.

Recent developments of traditional medicinal herbs in anticancer

With the development of more and more advanced chemical analysis technologies and screening models, those low-content compounds can be purified and identified for drug discovery. Fifthly, the microbiota of healthy human is in a state of dynamic equilibrium, and a recent study indicated that the imbalance of microbiota would be associated with various types of diseases including cancer [18-21]. Microbiota can not only promote the occurrence and development of tumor, but also exhibit inhibitory effect against tumor development in some cases. Meanwhile, it was reported that microbiota was associated with the effects of immunotherapy such as anti-CTLA4 and anti-PD-L1 therapy [22-26]. We wonder whether the anticancer effects of some Chinese medicinal herbs are related with the regulation of microbiota. Last but not least, in recent years, artificial intelligence technology has been introduced into the field of drug discovery and applied in almost all aspects of drug development, such as drug screening and target predicting [27-32]. Considering the complexity of Chinese medicinal herbs, application of artificial intelligence technology may promote the development of anticancer drugs from Chinese medicinal herbs [33].

Key mechanisms of traditional medicinal herbs:

Mechanism study is another bottleneck for the development of Chinese medicinal formulae, due to complicated components, multi-target effects, complicated interaction with organisms, etc. The traditional 'one target, one drug' mechanism study mode is unsuitable for the development of formulae. Along with the application of multi-omics, systems biology and network pharmacology have been developed rapidly and offer promising potential in the mechanism study of formulae. Realgar Indigo naturalists an effective formula used for the treatment of acute promyelocytic leukemia. the systems biology strategy based on the molecular, cellular, and organism levels evaluation in vitro and in vivo has been successfully used in its mechanism study, which demonstrated that Realgar-Indigo naturalis formula intensified degradation of promyelocytic leukemia-retinoic acid receptor alpha oncoprotein, increased reprogramming of myeloid differentiation regulators, and enhanced G0/G1 arrest in acute promyelocytic leukemia cells [34-36]. Similarly, the network pharmacology approach was also successfully applied to clarify the possible therapeutic mechanisms of Liu-Wei-Di-Huang-Wan [37-38]. The results indicated that the effects of LiuWei-Di-Huang-Wan on the "Yin deficiency" pattern in Chinese medicine was mediated by maintaining homeostasis in the endocrine system, the immune system.

Conclusion

Chinese medicinal herbs provide abundant resource library for drug development. It is extensively potential to discover more anticancer drugs from both natural products and traditional formulae. In this review, we documented the current progression on development of anticancer drugs from Chinese medicinal herbs including the natural products and formulae, along with the defects and obstacles remain to be overcome. A series of drug development strategies and technical approaches that suitable for discovery and development of anticancer drugs from Chinese medicinal herbs have been summarized and discussed.

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