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Short Commentary Open Access

Polysaccharide, a Potential Anti-Cancer Drug with High Efficacy and Safety

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Short Commentary

Cancer is a major public health problem worldwide and is the second leading cause of death in the world. In 2016, 1,685,210 new cancer cases and 595,690 cancer deaths are projected to occur in the United States [1]. The data also indicated that an estimated 4292,000 new cancer cases and 2814,000 cancer deaths would occur in China in 2015 [2]. So far, surgery and chemotherapy are still the main therapeutic methods of most solid tumors. However, the application of therapeutic drugs had some limitations in clinical settings, such as adverse effects, hemopoietic suppression, limited efficacy, immunotoxicity and drug resistance [3-6]. So, many researchers have been devoting to develop alternative strategies or novel potent, but low toxic anti-cancer reagents, including natural products, and high efficacy to treat cancers [7].

Immunotherapy—including vaccines and immunecheckpoint (such as cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed death-1 (PD-1)) blockade—is the newest class of systemic cancer therapies [8]. The promise of cancer immunotherapy was validated officially in March 2011 when FDA of USA approved Yervoy (ipilimumab; Bristol-Myers Squibb) for the treatment of unresectable or metastatic melanoma [9]. The success of immune checkpoint antagonists heralds the dawn of a new age in cancer therapy, in which harnessing the power of the immune system to treat cancer is becoming a key strategy for clinical management. However, there are some challenges in tumor immunotherapy. Firstly, although there are many tumor associated antigens have been identified, the weak immunogenicity of these species prevents their immune response to cancer. Secondly, off target effects lead to autoimmune responses in normal tissues. Lastly, the cost of treatment is very expensive.

Polysaccharides derived from renewable sources, including the higher plants, fungi, algae, bacteria and cell membranes of animal, belong to a structurally diverse class of biomacromolecules, in which polymers of monosaccharide residues are joined to each other by glycosidic linkages. Compared with proteins and nuclear acids, polysaccharides offer the highest capacity for carrying biological information because they have the greatest potential for structural variability. However, polysaccharides have long been underappreciated by the scientific community compared with proteins and nucleic acids. With gradually revealing the key roles of polysaccharides in a broad range of biological processes, such as inflammation, cell-cell recognition, transduction and immune responses, metastasis, and fertilization, more and more researchers wonder to uncover the mystery of polysaccharides. Actually, the anti-cancer efficacy of polysaccharides was first recognized by Nauts et al. in 1946 when it was found that certain polysaccharides could induce complete remission in patients with cancer [10]. Polysaccharides that act as adjuvant medicines are more commonly used in combination with chemotherapy/radiotherapy to treat various cancers [11-14]. Therefore, more than ten years ago, polysaccharides as a pathway to a class of new and improved therapeutics, as well as the next frontier in pharmaceutical research was proposed [15,16].

However, owing to their structural complexity and some redundancy in terms of structures that elicit a function, the therapeutic potential of polysaccharides has not been well exploited [15]. Antitumor polysaccharides differ greatly in their chemical structure and physical properties. For a long time, molecular weight (Mw) has been recognized as a critical parameter that dictates the antigenicity of a molecule [17]. Schizophyllan, a β-(1,3)-D-glucan with a β-(1,6)-glucose residue every three backbone glucose residues, shows complete inhibition of S-180 solid tumors when Mw is higher than 1×105, but almost completely losses efficacy at Mw lower than 5×104 due to disappearance of triple helical conformation [18]. Another triple helical β-(1,3)-D-glucan with two β-(1,6)-glucose residues every five backbone glucose residues (named as Lentinan) from mushroom shows high anti-tumor efficacy within Mw of 1×106, and losses when the triple helical structure is broken. A novel β-(1,6)-comb-branched β-(1,3)-D-glucan (AF1) from Auricularia auricula-judae was found to exhibit significant anti-hepatoma activities without cytotoxicity in a Mw-dependent manner, and the optimal molecular weight of AF1 was estimated to be 7.7 × 105 for the first time [19]. Taken together, the anti-tumor effect of polysaccharides shows a strong dependence on molecular weight.

As for the mechanism of anti-tumor, numerous studies have suggested that polysaccharides can inhibit tumor growth through the following common mechanisms [20]: (a) prevention of the tumorigenesis by oral administration of polysaccharides; (b) direct anti-cancer activity, such as the induction of tumor cell apoptosis, cell cycle arrest, anti-angiogenesis, depressing the synthesization of protein and nucleic acid, effect of expression of tumor suppressorgene (such as p53, Rb, p16) of tumor cells, effect of signal transfer pathway in tumor cells, and anti-radical effect; (c) immunopotentiation activity in combination with chemotherapy; (d) inhibiting tumor invasion, adhesion and metastasis. Immunoenhancement describes enhancing host immunofunction, which has been considered the main or singular mechanism of some types of polysaccharides, especially β-glucans from fungi, in order to inhibit tumor progression. Very recently, the underlying anti-tumor mechanism has been revealed that Lentinan activates immune responses to induce tumor cell apoptosis through caspase 3-dependent signaling pathway and inhibit tumor cell proliferation through targeting p53 via enhancement of p21, as well as anti-angiogenesis [21].

Taking into account the rising trend of the incidence of cancers of various organs, as well as the high anti-tumor efficacy and safety, developing polysaccharides as the effective therapies to control human malignancies is really a potential strategy. However, the problem of how to exploit the vast potential of polysaccharides in drug development involves overcoming fundamental challenges to clarify the important structure-activity relationship and the anticancer mechanisms at the molecular level, which will help scientists to design high potential antitumor drugs. Therefore, in the future, more researches should focus on the accurate and reproducible measurement of structure parameters including composition, branches, sequence, linkage, conformation and even higher structures of polysaccharides by means of high resolution instrumental methods. On the other hand, by using chemical method or molecular biology technology to control the structural characteristics, scientists can create a polysaccharide, for which a significant scope of properties can be predicted.

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