Targeting of growth factors in the treatment of hepatocellular carcinoma: The potentials of polysaccharides (Review)

XUAN WANG[1], JIEYU DING[1], YUANYUAN FENG[2], LINGLING WENG[1], GUANGQIANG ZHAO[1], JIANFENG XIANG[1], MINGUANG ZHANG[1] and DONGWEI XING[1]

[1]Radiology Department, Shanghai Municipal Hospital of Traditional Chinese Medicine Affiliated to Shanghai University of Traditional Chinese Medicine, Shanghai 200071; [2]Oncology Department, Shuguang Hospital, Shanghai University of Traditional Chinese Medicine, Shanghai 200021, P.R. China

Abstract. Hepatocellular carcinoma (HCC) has become a leading cause of cancer-associated mortality worldwide and is thus of great concern. Although various chemotherapeutic drugs are currently used for the treatment of HCC, severe side effects associated with these treatments have prompted interest in novel therapies, including the use of certain biological macromolecules such as polysaccharides. Several studies have shown that polysaccharides have anticancer and antiproliferative effects on HCC. Vascular endothelial growth factor, transforming growth factor β, epidermal growth factor and fibroblast growth factor may be effective targets for polysaccharides and may modulate tumor growth and immunity through increasing the expression levels of cytokines. The present review focuses on the ways in which growth factors contribute to the development of HCC, and on the anti-growth factor activities of natural and synthetic polysaccharides, as well as their effect on proinflammatory cytokines.

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Correspondence to: Professor Minguang Zhang or Dr Dongwei Xing, Radiology Department, Shanghai Municipal Hospital of Traditional Chinese Medicine Affiliated to Shanghai University of Traditional Chinese Medicine, 274 Zhijiang Road, Shanghai 200071, P.R. China
E-mail: mgzhang09@163.com
E-mail: szyxingdongwei@163.com

1. Introduction

Hepatocellular carcinoma (HCC) is the second leading cause of cancer-associated mortality worldwide (1). HCC represents the most common histological type of liver cancer, accounting for 70-85% of cases (2). Its treatment may include local ablation, surgical resection, trans-catheter arterial chemo-embolization and the administration of chemotherapeutic agents (3,4). However, at the time of their diagnosis, HCC tumors may be too large or may have expanded into nearby major blood vessels or metastasized, rendering the majority of HCC patients unsuitable for treatment by surgical resection (5). In addition, chemotherapy provides only a modest improvement to the overall survival time of patients due to the lack of specificity of the agent as well as the intolerable side effects that are often induced (6). Thus, novel anticancer therapeutic agents for use in the treatment of HCC are urgently required. In this regard, polysaccharides may be promising candidates. Numerous studies have reported that polysaccharides have antitumor activities and that polysaccharides from different herbs have different roles (7-10).

Normal cells in multicellular organisms constantly signal to one another via molecules called growth factors and cytokines. The signals conducted by growth factors and cytokines can inform individual cells whether to divide or not (11). According to Hanahan and Weinberg (12), the cell surface receptors that transduce signals into the cell are targets that can lead to dysregulation during tumor progression, resulting in self-sufficiency in growth signaling, one of the major hallmarks of cancer cells. Growth factor receptors are overexpressed in numerous types of cancer, and may enable the cancer cells to become hyper-responsive to ambient levels of growth factors and even ligand-independent signaling (13). This observation provides the rationale for research into the development of anti-growth factor compounds. The present study reviews the mechanisms that underlie the growth factor-mediated growth, proliferation, angiogenesis and metastasis of HCC cells, how they may be targeted by polysaccharides, and the current research being conducted into the use of these polysaccharides for the treatment of HCC.
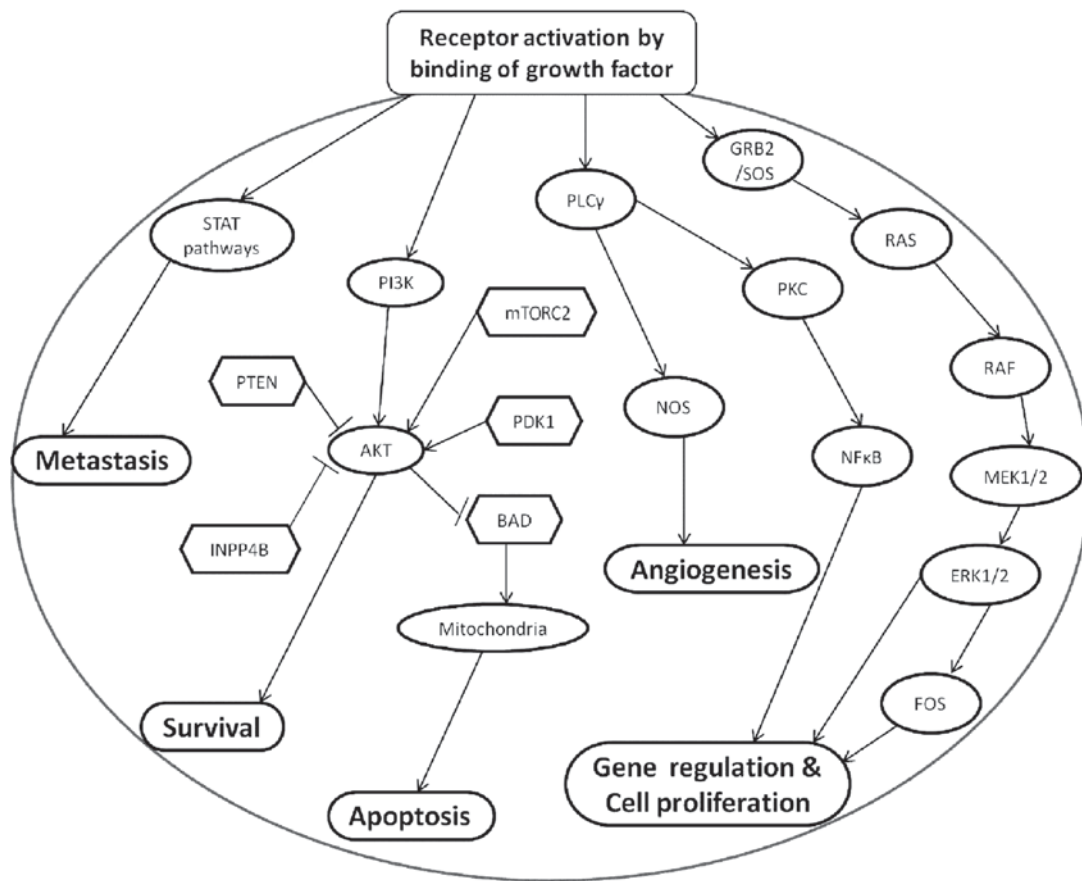
Figure 1. Tumorigenesis, mediated by growth factors. Growth factors activates their corresponding receptors, leading to the subsequent activation of four pathways: PI3K/AKT/mTOR pathway, Ras/Raf/MAPK pathway, NOS pathway and STAT pathway. These four pathways can induce cell proliferation, survival, angiogenesis and metastasis. PI3K, phosphoinositide 3-kinase; AKT, protein kinase B; mTOR, mammalian target of rapamycin; MAPK, mitogen-activated protein kinase; NOS, nitric oxide synthase; STAT, Signal Transducer and Activator of Transcription; GRB2/SOS, growth factor receptor-bound protein 2/Son of Sevenless; PLCγ, phospholipase Cγ; PKC, protein kinase C; PTEN, phosphatase and tensin homolog; mTORC2, mTOR complex 2; PDK1, pyruvate dehydrogenase kinase 1; BAD, Bcl2-associated agonist of cell death; INPP4B, inositol polyphosphate-4-phosphatase type II B; NFκB, nuclear factor κB; MEK1/2, MAPK kinase 1/2; ERK1/2, extracellular signal-regulated kinase 1/2.

2. Involvement of growth factors in HCC

Upon response to their specific ligands, growth factor receptors mediate tumorigenic activity through a variety of signaling pathways (14). A large number of growth factors are produced in the human liver during the foetal stage, including epidermal growth factor (EGF), insulin-like growth factors (IGFs), hepatocyte growth factor (HGF), vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), transforming growth factor (TGF)-α and TGF-β. However, the production of many of these growth factors decreases or is absent in the normal adult liver (15-17). On the other hand, following injury or damage, when liver regeneration is required, adult hepatocytes are able to upregulate the production of particular growth factors, including EGF, TGF-α, IGF and VEGF (18). This normal, transient upregulation is dysregulated in the chronically injured liver, and such dysregulation of growth factor production and growth factor receptor signaling in adult hepatocytes serves an important role in hepatocarcinogenesis (19) (Fig. 1).

VEGFs, prominent factors associated with aggressive tumor behavior, belong to the PDGF supergene family (20,21). VEGF-A, the major factor for angiogenesis, binds to two

tyrosine kinase receptors, namely VEGF receptor (VEGFR)-1 and VEGFR-2. VEGFR-1 is a trans-membrane receptor and is responsible for mediating angiogenesis and inflammatory responses. VEGFR-2 serves important roles in physiological and pathological angiogenesis and regulates the proliferation and migration of endothelial cells (22,23). Previous studies have indicated that high serum levels of VEGF have significant predictive ability for the estimation of survival in HCC patients treated by hepatic resection, radiofrequency ablation or trans-catheter arterial chemoembolization (24,25). In HCC, VEGF expression is increased through the expression of hypoxia-inducible factor-1α. In hypoxic conditions, VEGF and VEGFR trigger the angiogenic cascade and promote endothelial cell migration and proliferation. Thus, VEGF blockade may be an effective target for HCC treatment (26,27). Curcumin and Bevacizumab (VEGF blocker) can independently inhibit HCC progression through the regulation of the VEGF/VEGFR/K-ras pathway (28).

TGF-β1 is commonly recognized as a hallmark of HCC and represents one of the most important pathways to be targeted (29). TGF-β induces the epithelial-mesenchymal transition (EMT), which is involved in hepatocarcinogenesis and HCC metastasis (30). Stimulation of TGF-β1 leads to the activation of phosphoinositide 3-kinase (PI3K)/protein

kinase B (Akt), whereas inhibition of PI3K/Akt activation represses EMT and invasion of HCC cells (31).

EGF interacts with the EGF receptor (EGFR) to stimulate cell growth, proliferation and differentiation, and EGFR overexpression, which is known to be associated with tumorigenesis, occurs in 40-70% of cases of human HCC (32). In addition, FGF and HGF, which are heparin-binding growth factors, act as a potent mitogens for HCC (33). In summary, all of the aforementioned factors are associated with tumor growth and development, and the control of the expression of these growth factors can serve an important role in producing antitumor effects.

3. Growth factor signaling as a therapeutic target in HCC: Potential of polysaccharides

Clinical trials indicate that growth factor receptors and their associated signaling pathways are important in HCC cancer etiology and progression (34). Hence, growth factors, their receptors, and signaling pathways mediated by these growth factors are interesting targets for future therapeutic approaches. A number of strategies, including inhibition of receptor expression using gene therapy (antisense approach), antagonistic monoclonal antibodies that prevent the binding of ligands to receptors, or pharmacological (low-molecular-weight) receptor-selective tyrosine kinase inhibitors have already been evaluated for their potency in inhibiting the activity and downstream signaling cascades of these receptors in HCC (34).

Initial clinical trials have also demonstrated that multi-kinase inhibition is an effective novel treatment strategy in HCC (35). In this respect, sorafenib, an inhibitor of Raf, VEGF and PDGF signaling, is the first multi-kinase inhibitor that has been approved by the Food & Drug Administration for the treatment of advanced HCC (35). Sorafenib administration is an effective treatment for advanced HCC and can increase the survival rate of these patients. Sorafenib inhibits the growth of hepatoma cells by interfering with the secretion of IGF-1 (36). In addition, linifanib, a multi-targeted receptor tyrosine kinase inhibitor, can inhibit members of the VEGF and PDGF receptor families (37).

However these drugs have their own disadvantages with regard to side effects, drug intolerance and resistance. Although sorafenib has shown promising therapeutic effects, primary and acquired resistance to the drug has been reported in numerous studies (38,39). Furthermore, the overall survival time of HCC patients who responded to sorafenib improved by only ~2 months (40,41). In this setting, polysaccharides may be a good option. Many polysaccharides and polysaccharide-protein complexes have been isolated from mushrooms, fungi, yeast, algae and plants. Polysaccharides have a broad spectrum of biological effects, such as antibiotic, antioxidant, anti-mutant, anticoagulant, immunomodulating and anticancer activities (42-48). The antitumor ability depends on a number of properties, such as structure, dose, mechanism of action, and site of activity (49). Several studies have demonstrated that polysaccharides may have roles in the prevention of tumorigenesis and induction of tumor cell apoptosis, immunomodulation during chemotherapy, and inhibition of tumor metastasis (50). Further research into

how polysaccharides may act via growth factors, cytokine networks and signaling pathways, and their roles and mechanisms in cancer regulation is required.

Sources of polysaccharides targeting growth factors in HCC. Polysaccharides are the most abundant group of biopolymers and, due to their biocompatibility, biodegradability and non-toxicity, many studies have been conducted to evaluate their therapeutic effects (51-53). A large variety of polysaccharides can be isolated from plants (dietary fibers, herbs and wood plants), algae, lichen, microorganisms (fungi, yeasts and bacteria) and animals. Research has been conducted to characterize the constituents of these polysaccharides; however these kinds of studies are strikingly limited.

A study by Lv *et al* (54) found that polysaccharides isolated from tea were hetero-polysaccharides which consisted of mannose, ribose, rhamnose, glucuronic acid, galacturonic acid, glucose, xylose, galactose and arabinose with molar contents of 16.3, 10.3, 47.1, 5.6, 24.0, 128.4, 25.0, 101.4 and 71.1 μM, respectively (54). Another study demonstrating the hepatoprotective effect of polysaccharides from Huangshan Maofeng green tea also found that the main monosaccharide components of this polysaccharide were galactose (mol.%, 35.0%), arabinose (28.9%) and galacturonic acid (11.3%) (55). Capillary zone electrophoresis analysis showed that polysaccharide isolated from *Gynostemma pentaphyllum* Makino consisted of glucose (23.2%), galactose (18.9%), arabinose (10.5%), rhamnose (7.7%), galacturonic acid (4.7%), xylose (3.9%), mannose (3.1%), and glucuronic acid (1.2%) (56). Characterization of polysaccharides from two *Pleurotus* mushrooms, *P. eryngii* and *P. ostreatus,* found that they were mainly composed of mannose, along with other monosaccharides, including glucose, galactose, xylose and rhamnose (57,58). The monosaccharide constituents of *Lentinus edodes* polysaccharide have also been characterized (59).

However, although many studies have found that, grossly, these polysaccharides have potent antitumor activities in HCC, it has not been determined which components of the polysaccharides are responsible for such effects. Furthermore, synthetic polysaccharides are often used in association with chemotherapy (60-62). Traditional Chinese medicine (TCM) and certain herbal medicines have been used in the treatment of cancer for thousands of years in China, Japan and South Korea, as well as some other Asian countries (63). As adjunct anticancer agents, TCMs can have important anticancer roles in inducing apoptosis and differentiation, improving the immune system, inhibiting angiogenesis, and also in increasing the sensitivity to and reducing the side effects of chemotherapeutics, and improving patient survival time (64). For example, naturopathic therapy using *Cordyceps sinensis* can prolong the survival time of patients with HCC (65). Studies have demonstrated that their roles in HCC are associated with the regulation of growth factors and cytokines. The names, sources and specific targets of polysaccharides are given in Table I.

Polysaccharides targeting a single growth factor. Pleurotus mushroom polysaccharide-protein complex (PP) has shown anticancer activities against liver cancer cells *in vitro* and

Table I. Names of polysaccharides with their sources and potential targets.

A, Polysaccharides from natural sources

Source and name	Targets
Traditional Chinese medicine	
Aconitum koreanum polysaccharides	IL-2, TNF-α, IFN-γ
Salvia miltiorrhiza polysaccharides	TNF-α
Radix Glycyrrhizae polysaccharide	IL-10, TGF-β, IL-2, IL-12p70
Astragalus polysaccharides	IL-1α, IL-2, IL-6, TNF-α, IL-10
Exopolysaccharide fraction from *Cordyceps sinensis*	TNF-α, IFN-γ
Plant-derived	
Tea carbohydrate polymers	IFN-γ, TNF-α, VEGF
Dihydromyricetin	TGF-β
Corn silk polysaccharides	IL-2, IL-6, TNF-α
Gynostemma pentaphyllum Makino polysaccharide	IL-2, TNF-α, IFN-γ
Artemisia apiacea polysaccharide	IFN-γ, IL-4
Dietary	
Pleurotus mushroom polysaccharide	VEGF
Tricholoma matsutake polysaccharide	TNF-α, IFN-γ, IL-2
Lentinus edodes polysaccharide	TNF-α, IFN-γ, IL-2

B, Synthetic polysaccharides

Name	Targets
Low molecular weight chitosan	VEGF
Chitosan nanoparticles	VEGFR-2
Galactose modified trimethyl chitosan-cysteine nanoparticles	VEGF

C, Others

Name	Targets
HS mimetic PI-88 series	FGF1, FGF2
HS mimetic PG500 series	FGF1, FGF2, VEGF

HS, heparan sulfate; IL, interleukin; TNF, tumor necrosis factor; IFN-γ, interferon-γ; FGF, fibroblast growth factor; TGF-β, transforming growth factor-β; VEGF, vascular endothelial growth factor; VEGFR-2, VEGF receptor 2.

in vivo (66). PP inhibits proliferation by inactivation of PI3K/Akt signaling (67). Studies have suggested that, in HCC, PP reduces the expression of secretory VEGF, which in turn mediates autocrine regulation of PI3K/Akt signaling in xenograft BALB/c nude mice. PP can also enhance sensitivity to the chemotherapeutic drug cisplatin (68).

Tea carbohydrate polymers are natural polymers with antioxidant, hepatoprotective and antitumor activities (69). These have exhibited strong antitumor activity in experimental HCC animals. It was found that administration of tea carbohydrate for 40 days could significantly inhibit tumour growth and that three different doses of carbohydrate treatment (100, 200 and 300 mg/kg body weight/day) significantly decreased microvessel density in a dose-dependent manner. During this period, a significant enhancement in the serum white blood cell count and interferon (IFN)-γ and tumor necrosis factor α (TNF-α) levels, and a decrease in the expression of VEGF and proliferating cell nuclear antigen were found in H22 tumor tissues (70). Tea carbohydrates were also found to augment the antitumor activity of doxorubicin (71).

Radix Glycyrrhizae polysaccharide (GP) is a major active compound extracted from Radix Glycyrrhizae, a commonly used traditional herbal medicine. In a study of tumor-bearing mice, the effect of GP on tumor growth inhibition was determined to be likely caused by the to upregulation of the Th1/Th2 cytokine ratio in serum by the decrease in the transcription factor Foxp3, interleukin (IL)-10 and transforming growth factor (TGF)-β levels (P<0.01), and the increase in IL-2 and IL-12p70 levels in serum (P<0.01) (72).

Dihydromyricetin (DHM) is the active component in extracts of *Ampelopsis grossedentata*. The principal anticancer mechanism of DHM is via the induction of p53-dependent apoptosis (73-75). A previous study demonstrated that DHM enhances chemosensitivity to nedaplatin (a platinum-containing chemotherapeutic drug) by activating the p53/B-cell lymphoma 2 (Bcl-2) signaling pathway, which resulted in mitochondrial dysfunction and induced cell death and growth inhibition in HCC cells (76). Furthermore, it has also been reported that induction of cell apoptosis by DHM is regulated via the TGF-β/Smad3 signaling pathway and that TGF-β expression is decreased in the mouse HCC cell line Hepal-6 (77).

Polysaccharides targeting multiple growth factors. Cell surface/extracellular matrix heparan sulfate (HS) glycosaminoglycans are complex polysaccharides, and HS mimetics function by blocking these interactions and inhibiting processes crucial to tumor progression, and could therefore be considered as a novel class of cancer therapeutics (78,79). The HS mimetic PI-88 acts as an inhibitor of heparanase and angiogenesis in HCC. A series of PI-88 analogs with augmented chemical and biological properties are composed of single, defined oligosaccharides with specific modifications and can inhibit heparanase and FGF1, FGF2 and VEGF, and thus can act as potent inhibitors of growth factor-induced endothelial cell proliferation (80). The PG500 series of HS mimetics have high affinity for growth factors; however, their affinity is lower compared with the PI-88 series. A previous study showed that PG500 compounds containing a larger lipophilic moiety had reduced anticoagulant activity compared with PI-88 (81). However, the selected PG500 series compounds all inhibited FGF1, FGF2 and VEGF-induced endothelial cell proliferation. In a tube formation assay, it was found that certain of the PG500 series compounds (PG536, PG537, PG545 and PG562) inhibited tube formation by >90% at a concentration of 10 μM. Furthermore, in a rat aortic assay of angiogenesis, it was found that PG536, PG545 and PG546 inhibited angiogenesis by >80% following daily administration of 10 μM for 6-8 days. Treatment with PG545, PG546 and PG547 also potently inhibited the development of metastatic nodules when administered at 10 mg/kg. Finally, PG545 was found to significantly inhibit tumor development in a xenograft model (HT29 colon adenocarcinoma cells) (81).

Polysaccharides targeting pro-inflammatory cytokines. Cytokines are a subtype of growth factors that are produced by hematopoietic and immune cell types, and include IFNs and ILs. Cytokines normally function to stimulate a host response to control cellular stress and minimize cellular damage. Cytokines produced by CD4+ T-helper (Th) cells are categorized as Th1 or Th2; Th1 cytokines (e.g., IL-1α, IL-1β, IL-2, IL-12p35, IL-12p40, IL-15, TNF-α and IFN-γ) and Th2 cytokines (e.g., IL-4, IL-8, IL-10, and IL-5) are generally referred to as proinflammatory and anti-inflammatory cytokines, respectively (82). In the liver, cell damage and regeneration mediated by viral hepatitis-induced immune responses can cause dysregulated hepatocyte proliferation, which may accelerate the development and progression of hepatic cancer through transcription and activation of cytokines and growth factors, oxidative DNA damage, DNA methylation, and hepatocyte injury (83-86). Increasing evidence indicates the involvement of cytokines in hepatocarcinogenesis [reviewed by Bishayee (87)].

On the other hand, numerous studies have demonstrated that cytokines have broad antitumor activity. Accordingly, proinflammatory cytokines, including TNF-α, IL-6 and IL-1β, and transcription factors that are required for signaling by these cytokines, including NF-κB and STATs, are emerging as potential targets for anticancer therapy (88). Serum cytokines play important roles in suppressing tumor growth (89). IL-1α, IL-2 and IL-6 are capable of inducing the proliferation of responsive T-cells (90). Wnt/β-catenin and EGFR signaling are the major cascades that are activated through proinflammatory cytokines and involved in the progression of epithelial tumors (91). IL-10 inhibits the synthesis of IL-2 and TNF-α (92).

Several *in vivo* experiments have demonstrated that polysaccharides from various sources have the ability to modulate tumor growth and immunity. Most affect tumor growth and immune functions in hepatocarcinoma tumor-bearing mice by increasing the expression levels of IL-2, IL-6 and TNF-α, and can inhibit the growth of hepatoma and prolong the survival time of these mice. These polysaccharides include those from Corn silk (*Zea mays* L.) (93), *Aconitum koreanum* and *Salvia miltiorrhiza* (94).

Polysaccharides from *Astragalus membranaceus* (APS) have been widely studied for their anticancer potential. APS was found to exert antitumor effects in H22 tumor-bearing mice and also enhanced chemosensitivity to adriamycin (ADM). The antitumor and synergistic activity of APS may be associated with its effect of increasing the expression levels of IL-1α, IL-2, IL-6 and TNF-α and decreasing IL-10 levels. APS was also found to downregulate multidrug resistance 1 mRNA and P-glycoprotein expression levels, which may be related to other anticancer effects (10,95). Several studies aimed to assess the antitumor potentials of polysaccharides from different sources and found that their anticancer effects are mediated by the secretion of INF-γ. These included polysaccharides obtained from *G. pentaphyllum* Makino (96), a polysaccharide isolated from *Artemisia apiacea* (97), and oral administration of *A. coreanum* (98). Polysaccharides obtained from cultured *Cordyceps* fungus have also been shown to have pharmacological efficacy; specifically, the exopolysaccharide fraction from *Cordyceps sinensis* was found to significantly inhibit HCC tumor growth and lead to elevated TNF-α and IFN-γ mRNA expression of splenic lymphocytes (99). Collectively, these data indicate the increasing contribution to therapeutic effects of these polysaccharides.

Combination of polysaccharides. 5-fluorouracil (5-FU) is a chemotherapeutic drug that is commonly used in HCC treatment. Chemotherapeutic drugs combined with polysaccharide may act more effectively together; thus, a combination of polysaccharides can be used with chemotherapeutic drugs like 5-FU to enhance H22 cell growth inhibition. A previous study found that polysaccharides from *Tricholoma matsutake* (PTM) could activate splenic lymphocytes, and another study demonstrated that polysaccharides from *Lentinus edodes* (PL) had antitumor bioactivities at concentrations ranging from

50 to 500 μg/ml, with maximum inhibition occurring at a concentration of 200 μg/ml between 36 and 48 h (100,101). Notably, *in vivo* experiments revealed significant increases in the cytotoxic T lymphocyte and natural killer cell activities, the frequencies of CD4+ and CD8+ T cells in the spleen, and the serum levels of TNF-α, IL-2 and IFN-γ in mice treated with 5-FU+PTM+PL when compared with mice treated with 5-FU, PTM or PL alone, 5-FU+PL, or 5-FU+PTM (102).

Helper polysaccharides. Polysaccharides have been studied for their roles in facilitating successful drug delivery, and it was demonstrated that certain polysaccharides are important in this regard.

In certain experimental tumor models, VEGF silencing by RNA interference (RNAi) has been attempted and has achieved positive results (103,104); however, due to the poor stability of small interfering RNA (siRNA) molecules *in vivo* and the low cellular uptake, a safe and efficient carrier is required for therapeutic RNAi applications (105). Chitosan is a natural polysaccharide composed of randomly distributed β-[1-4]-linked D-glucosamine and N-acetyl-D-glucosamine. Low molecular weight chitosan (LMWC) can be used as a carrier for RNAi drugs directed against VEGF (106). It was found that LMWC/VEGF shRNA complexes could be efficiently transfected into murine hepatocarcinoma Hepa1-6 cells and that this could inhibit VEGF expression and suppress tumor angiogenesis (106). In another study, chitosan nanoparticles (CNP) were shown to significantly inhibit tumor growth and induce tumor necrosis in model mice xenografted with HCC (BEL-7402) cells. The dose-dependent tumor suppression by CNP was associated with the inhibition of tumor angiogenesis. Further mechanistic evidence suggested that this inhibition of tumor angiogenesis was linked to altered levels of VEGFR-2 (107).

In another study, tumor-bearing mice were orally administered with VEGF siRNA and pDNA expressing shRNA specific for survivin (a member of the inhibitors of apoptosis family) loaded onto galactose-modified trimethyl chitosan-cysteine nanoparticles with various degrees of galactosylation. The loaded nanoparticles could effectively accumulate in the tumor tissues, resulting in the downregulation of antiapoptotic survivin, which acted synergistically with the siRNA-mediated inhibition of angiogenic VEGF. This ultimately led to increased apoptosis and inhibition of angiogenesis in hepatoma (108).

4. Conclusion and future perspectives

To date, a number of standard therapies have been shown to result in modest improvements to the overall survival and quality of life of HCC patients. However, they are associated with significant toxicities. Furthermore, the ability of solid tumors to develop multiple invasion and resistance pathways that allow them to circumvent inhibition by a single signaling pathway is becoming increasingly evident (109). Expanding knowledge of the molecular signaling that underlies tumor cell resistance and the poor survival of patients with HCC can facilitate the development of new drugs with better safety profiles. Furthermore, resistance is less likely to arise in response to natural compounds (110).

As reviewed by Zong *et al*, the anticancer efficacy of polysaccharides was first recognized in 1946 (44). Since then numerous studies have suggested that polysaccharides can be utilized as key ingredients for bio-based materials in life sciences, including pharmaceuticals, and many polysaccharides have demonstrated potential as anticancer agents (96-99). With regard to drawbacks, such as low safety profiles and resistance of current therapies, the development of polysaccharides as treatment strategies for HCC is necessary.

Although there is potential for the use of these kinds of polysaccharides against HCC, research into these polysaccharides is limited. Regarding self-sufficiency in growth signaling, a major hallmark of cancer, polysaccharides have been shown to have good activity; as discussed in the present study, polysaccharides from different sources have shown moderate anticancer activity in HCC by targeting growth factors. However, an active area of research should be dedicated to the development of more efficient and economic approaches for the preparation and modification of polysaccharides, and to elucidating the structure-activity association. The active component of these polysaccharides must be identified to better understand their anticancer mechanism in HCC, and it is also important to pay attention to the signaling pathways that are modified by the use of polysaccharides. Furthermore it is essential that *in vivo* studies are performed to confirm the results obtained *in vitro*, and these polysaccharides must also be tested in a clinical setting.

Considering the limited therapeutic options available to treat HCC, studies investigating polysaccharides may provide a rationale for the translation of these compounds into potential therapeutics against HCC. Overall, recent discussion is indicating a bright future for polysaccharides targeting growth factors in HCC.

Acknowledgements

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