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Contents

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EDITORIAL

ORIGINAL ARTICLE

Retrospective Study

Clinical Trials Study

Observational Study

Basic Study

LETTER TO THE EDITOR

ABOUT COVER

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LETTER TO THE EDITOR

Calculus bovis hijacks the tumor microenvironment in liver cancer cells in a multifaceted approach: A falling row of dominoes

Said G Farhat, Karam Karam

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Abstract

Calculus bovis (*C. bovis*) is widely used in traditional Chinese medicine due to its anti-tumor effects. *C. bovis* shifts liver cancer tumor microenvironment towards regression by hindering tumor-associated macrophages polarization. Huang *et al* have demonstrated in their study that *C. bovis* inhibits M2-tumour-associated macrophages (TAM) polarization by halting the Wnt/β-catenin pathway. The mechanism of action by which *C. bovis* exerts its anti-tumor effects is multifaceted and includes network pharmacology, transcriptomics and molecular docking. *In vitro* assays demonstrated that *C. bovis*-containing serum inhibited M2-TAMs polarization in human hepatocellular carcinomas cells. *C. bovis* was found to have 22 active components of which 11 were detected in the bloodstream. The anti-neoplastic activity of *C. bovis* lies in suppressing M2-TAM polarization by modulation of the Wnt/B-catenin pathway. *In vitro* and *in vivo* experiments have shown that *C. bovis* suppresses M2-TAM polarization and halts the Wnt signaling pathway. The inhibitory effect of *C. bovis* on M2-TAM was reversed by SKL2001, a Wnt agonist, which highlights *C. bovis*'s selectivity and specificity. *C. bovis* inhibits M2-TAM polarization by modulating the Wnt/ β-catenin pathway, thus impeding liver cancer growth. Owing to the "cross-talk" between transforming growth factor-β (TGF-β) signaling pathways, this paper highlights the potential significance of *C. bovis* in controlling the tumor microenvironment not only through hindering the polarization of M2-TAMs *via* the Wnt signaling pathway, but also by downregulating TGF-β. Therefore, *C. bovis* serves as an igniter to fuel a cascade of signaling events that culminates in the regression of the tumor microenvironment by compromising oncogenesis and angiogenesis. TGF-β is also

known for its pro-fibrotic properties. Therefore, *C. bovis* may play a pivotal role in treating liver fibrosis by downregulating TGF-β, thus hindering oncogenesis, angiogenesis and liver fibrosis. Hence, the "domino effect".

Key Words: *Calculus bovis*; Wnt/β-catenin signaling pathway; M2-tumor-associated macrophages; Liver cancer; Transforming growth factor-β; Angiogenesis; Liver fibrosis

Core Tip: *Calculus bovis* (*C. bovis*) is an herb used in traditional Chinese medicine known for its various anti-inflammatory and anti-tumorigenic effects. *C. bovis* influences the tumor microenvironment by targeting immune-related pathways. Transcriptome sequencing revealed that *C. bovis* plays a crucial role in the regulation of M2-tumor-associated macrophages polarization and halting the Wnt/β-catenin pathway. This study provides a solid and promising evidence concerning potential drug therapy in the treatment of liver cancer. In this paper, we shed light on the inevitable "cross talk" between the Wnt and transforming growth factor-β signaling pathways, thus connecting angiogenesis, oncogenesis and liver fibrosis. *C. bovis* is deemed a priming molecule that sets the stage for a series of related and inter-connected events, such as angiogenesis, hepatocarcinogenesis and hepatic fibrosis. This process brings about the "domino effect" whereby one event uncovers another related event as a falling row of dominoes.

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TO THE EDITOR

Liver cancer ranks 6th in prevalence and 4th in cancer-related mortality worldwide[1]. Liver cancer is malignant, rapidly progressive and is associated with poor prognosis with a 5-year survival rate of 3%[2]. Surgical resection, liver transplantation, interventional modalities, local ablation and targeted immunotherapies are the main treatment modalities for liver cancer[3]. These therapeutic options have their limitations as the survival rate remains low in patients undergoing treatment for liver cancer due to liver cancer cells resistance to treatment, tumor relapse, organ toxicity and metastasis[3]. This fact obviates the need for the advent of novel pharmacotherapies by gaining insights into the molecular pathogenesis of liver cancer. Traditional Chinese medicine is deemed to have multi-component and multi-target abilities as it influences Tumor microenvironment (TME) in liver cancer, thus offering a new perspective for the treatment of liver cancer[4]. Huang *et al*[5] have successfully elucidated the mechanism of action by which *Calculus bovis* (*C. bovis*) induces TME regression at the molecular level[5]. TME harbors a myriad of cells whereby macrophages play a pivotal role in controlling the microenvironment. Tumor-associated macrophages (TAMs), derived from circulating monocytes, can adopt either the M1 or M2 phenotypes. M1-TAM is a tumor-regressing phenotype, whereas M2-TAM is a tumor-promoting phenotype. Different cytokines and growth factors dictate the phenotypic switch of macrophages to an M1 or M2 phenotypes[5]. For instance, M1-TAMs are anti-tumor macrophages regulated by interferon-gamma and tumor necrosis factor-α, whereas M2-TAMs are tumorigenic macrophages regulated by nuclear factor kappa-B, interleukin-6/signal transducers and activators of transcription-3 and Wnt/β-catenin pathways[6]. Furthermore, the molecular pathways that control M2-TAM polarization foster proliferation, migration, invasion and angiogenesis[7]. Thus, reversing TAM polarization and halting the Wnt/β-catenin signaling molecular pathway provide promising venues for the treatment of liver cancer by shifting TME into regression.

Insights into the mechanism of action of C. bovis at the molecular level

C. bovis is a valuable herb used in traditional Chinese medicine due to its anti-tumor effects in various models[8]. The influence of *C. bovis* on TME remains elusive and an area of active research due to the heterogeneity of TME. Understanding the heterogeneity of TME lies in deciphering its composition and constituents. The study of Huang *et al*[5] opens new therapeutic venues as it revealed that *C. bovis* exerts its anti-neoplastic effect on M2-TAM polarization *via* the Wnt/β-catenin pathway. TAMs, key players in TME, exhibit phenotypic plasticity as they can either adopt a tumor-promoting phenotype (M2-TAM) or a tumor-regressing phenotype (M1-TAM). In light of this, *C. bovis* hinders M2-polarized TAM differentiation by modulating the Wnt/β-catenin molecular pathway[5]. *In vitro* and *in vivo* assays have demonstrated that *C. bovis* effectuates its anti-cancer activity through its active constituents, cellular targets and signaling pathways[5]. *C. bovis* plays a regulatory role in macrophage phenotypic plasticity and Wnt/β-catenin pathway within TME[5]. This study lays a foundation for developing *C. bovis*-derived anti-neoplastic therapeutic modalities for liver cancer. *C. bovis* mitigates the proliferative and migratory properties of liver cancer cells by hindering M2-TAM polarization *via* the Wnt signaling pathway. Modulating TME by shifting it into regression constitutes a new perspective for the treatment of liver cancer. The immunomodulatory and anti-inflammatory effects of *C. bovis* are well-documented

in medical literature[9]. The mechanism of action of *C. bovis* involves the Wnt/β-catenin signaling pathway that is always involved in the pathogenesis of liver cancer[10]. *C. bovis* impedes tumor progression by altering M2-TAM polarization *via* Wnt pathway.

Cross-talk between signaling pathways, liver fibrosis, angiogenesis and future directions

Serum analysis revealed 11 bioactive compounds for *C. bovis*. Bilirubin is one of the bioactive compounds of *C. bovis* that is known for its anti-oxidant, anticancer and anti-inflammatory effects[11]. Another bioactive compounds derived from *C. bovis* are acid esters and bile acid-like components known for their enterohepatic circulation and anti-tumor effects[12]. Hence, *C. bovis* has a hepatoprotective profile in addition to its anti-tumorigenic profile. For instance, the Wnt pathway drives the upregulation of transforming growth factor-β (TGF-β), which connects inflammatory, fibrotic, angiogenic and oncogenic processes. Enhancing our understanding about the pharmacology of *C. bovis* can offer promising treatment options for liver fibrosis and liver cancer. Therefore, *C. bovis*'s regulatory effect on TGF-β needs to be evaluated in future studies to elucidate a potential therapeutic effect of *C. bovis* in liver fibrosis. TGF-β signaling induces cell plasticity in liver fibrosis and hepatocarcinogenesis[13]. TGF-β is considered a pro-fibrotic mediator through the activation of quiescent hepatic stellate cell (HSC) to a myofibroblast (MFB) phenotype[14]. MFBs potentiate extracellular matrix (ECM) accumulation, which drives fibrogenesis. Furthermore, TGF-β stimulates an epithelial-to-mesenchymal transition in hepatocytes, thus aggravating fibrogenesis[15]. TGF-β also has a pro-tumorigenic effect by potentiating the pro-migratory and invasive potential of hepatic tumor cells. TGF-β enhances tumor cell plasticity by conferring properties of migratory tumor initiating cells[16]. Thus, TGF-β is both pro-fibrotic and pro-tumorigenic. TGF-β signaling pathway "cross-talks" with other signaling pathways, such as the Wnt signaling pathway. *C. bovis* suppresses M2-TAM polarization by halting the Wnt pathway, which downregulates TGF-β. Thus, *C. bovis* is deemed to harbor not just anti-tumor properties, but also anti-fibrotic potential, which lays a new foundation in treating both liver fibrosis and hepatocarcinogenesis.

Kathuria and Singla[17] posited that the study of Huang *et al*[5] includes areas that require further investigations, such as *C. bovis*'s potential effect on angiogenesis[17]. Kathuria and Singla[17] stated that future studies are needed to understand the effect of *C. bovis* on angiogenesis and to gain deeper insights into the mechanism by which *C. bovis* potentially exerts its anti-angiogenic effect[17]. For instance, TME harbors a myriad of cells, such as HSC. TME is also an environment of constant ECM remodeling and altered vasculature. It has been well-documented that TGF-β promotes angiogenesis. By virtue of paracrine signaling from endothelial cells to mesenchymal cells, TGF-β drives vascular smooth muscle cell and pericyte differentiation during blood vessel coverage by smooth muscle cells[18]. Therefore, TGF-β regulates angiogenic process. *C. bovis* downregulates TGF-β and thus vasculature is altered and angiogenesis ceases. Hence, *C. bovis* indirectly halts angiogenesis by suppressing the Wnt signaling pathway, which in turn downregulates TGF-β and its pro-angiogenic effects. It becomes clear that *C. bovis* mitigates TME in a multifaceted pattern. *C. bovis* suppresses the polarization of M2-TAM *via* the Wnt signaling pathway which downregulates TFG-β. Lower expression of TGF-β hinders angiogenesis and engenders TME regression. In other words, the "cross-talk" between TGF-β signaling pathways brings about the "Domino effect" whereby one event, in this case *C. bovis*'s suppression of M2-TAM polarization *via* regulation of the Wnt pathway, sets off a series of related events, in this case downregulation of TGF-β and halting its resultant pro-fibrotic and pro-angiogenic potentials. This falling row of "dominoes" culminates into TEM regression.

CONCLUSION

This study uncovered the molecular pathway behind *C. bovis*'s anti-tumor effects in liver cancer cells. *C. bovis* suppresses the polarization of M2-TAM by halting the Wnt/β-catenin signaling pathway. The Wnt pathway upregulates TGF-β, a growth factor involved in liver fibrosis, angiogenesis and oncogenesis. A suppressed Wnt signaling pathway engenders the downregulation of TGF-β. This process counteracts the pro-tumorigenic, pro-angiogenic and pro-fibrotic effects of TGF-β. Thus, *C. bovis* deems not only anti-tumorigenic, but also anti-fibrotic and anti-angiogenic. This lays a new foundation regarding the potential therapeutic effects of *C. bovis* in patients with liver fibrosis. Owing to the "cross-talk" between the Wnt signaling pathway and TGF-β signaling pathway, future studies should be generated to further elucidate the anti-tumor effects of *C. bovis* at the molecular level and evaluating its potential therapeutic benefits in liver fibrosis.

FOOTNOTES

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