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Honokiol as a Radiosensitizing Agent for Colorectal cancers

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Abstract

Radioresistance is a frustrating obstacle for patients with colorectal cancers (CRCs) undergoing radiotherapy. There is an urgent need to find an effective agent to increase the sensitivity of CRCs to radiation. Honokiol, an active compound purified from Magnolia, was found to radiosensitize colorectal cancer cells both *in vitro* and *in vivo*. However, the mechanisms control important signaling that enhances radiosensitivity is currently unknown. In this study, we have reviewed important signaling pathways that are closely related to radiosensitization, such as cell cycle arrest, tumor angiogenesis, JAK/STAT3 signaling pathway and Mismatch repair. Studies show that honokiol can interfere with these pathways at different levels. With overall analysis, it may bring light on finding the possible mechanism by which honokiol acts as a radiosensitizing agent for CRCs.

Keywords

cell cycle; STAT3; angiogenesis; Notch

Introduction

Colorectal cancer (CRCs) is the third largest killer among all kinds of malignant tumors in United States [1]. The management of locally advanced CRCs requires a multidisciplinary effort, with surgical resection remaining the therapeutic cornerstone, and radiotherapy and neoadjuvant chemotherapy clearly improving long-term outcomes [2]. In Asian countries, most CRC patients are diagnosed or detected at a late stage with local invasion or metastasis. Moreover, some patients with tumor recurrence, lose the chance of surgical intervention, and hence radiotherapy will be the last straw for them. However, as a two-side

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Conflict of Interest

Zhiyun He declares that he has no conflict of interest.
Dharmalingam Subramaniam declares that he has no conflict of interest.
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Human and Animal Rights and Informed Consent

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sword, radiation treatment also leads to some serious side effects, which forces many cancer patients to stop receiving radiotherapy. Therefore, there is an urgent need to find an effective radiosensitizer to reduce the dose of radiotherapy without decreasing the tumor growth inhibiting effect.

Honokiol is an active compound purified from magnolia, and recent studies have demonstrated anti-inflammatory, anti-angiogenic, anti-oxidative and anticancer properties for the compound both *in vitro* and in preclinical models [3••]. It targets multiple signaling pathways including angiogenesis, nuclear factor kappa B (NF-κB) [4], signal transducers and activator of transcription 3 (STAT3), epidermal growth factor receptor (EGFR) and mammalian target of rapamycin (m-TOR) [5], all of which have great relevance during cancer initiation and progression. Furthermore, pharmacokinetic profile of honokiol has revealed a desirable spectrum of bioavailability after intravenous administration in animal models [3••].

From *in vitro* and *in vivo* studies, honokiol have demonstrated the ability to inhibit growth and induce apoptosis on a variety of cancer cell lines. Furthermore, our study showed that honokiol can also enhance the sensitivity of colon cancer cells to irradiation, which can safely reduce the dose of radiation without affecting the outcome [6••]. In addition, our studies found that honokiol in combination with irradiation can even enhance the sensitivity of colon cancer stem cells (CSCs) to ionizing radiation. It may target the stem cells by inhibiting the γ-secretase complex and the Notch signaling pathway [7••]. These findings throw light on the radiosensitizing effect of honokiol on CRCs.

It is well known that carcinogenesis is a multiple signal pathways procedure, which is still a complicate puzzle. There are gene mutations, apoptosis escape and aberrant angiogenesis, and other pathways. Here, we have reviewed previous studies on honokiol's anti-tumor effects and hope to identify some possible mechanism.

Honokiol and cell cycle arrest

Cell cycle is such an ordered procession that the initiation of every event must depend on the completion of the former event. Cells in different phases exhibit varying levels of radiosensitivity [8]. Many studies have demonstrated irradiation induced cell cycle delay [9, 10]. Furthermore, cells in different phase of cell cycle show diverse response to radiation. In general, cells are most radiosensitive in M and G2 phases and most radioresistant in S phase, while for cells with long cycle time, there is another peak of resistance in early G1 phase [11•].

Chemotherapeutic agents which can cause cell cycle arrest may increase the radiosensitivity of different cancer cells to radiation therapy. Our study showed that honokiol can lead to G0/G1 phase arrest of colon cancer cells. Moreover, when cells were treated with honokiol in combination with radiation, there was significant enhancement in their sensitivity to radiation. Hahm *et al* showed that honokiol induces cell cycle arrest of PC-3 and LNCaP human prostate cancer cells in a concentration and time-dependent manner [12]. The cells were mostly arrested in G0-G1 phase, with a decrease in protein levels of cyclin D1, cyclin-dependent kinase 4 (Cdk4), Cdk6, and/or cyclin E. In addition, there was suppression of complex formation between cyclin D1 and Cdk4 as revealed by immunoprecipitation using anti-cyclin D1 antibody followed by immunoblotting for Cdk4 protein [12].

According to the studies on honokiol's anti-tumor effect and the relation between cell cycle and tumor radiosensition, it puts forward that honokiol may perform radiosensitizing effect on malignant tumors, including colon cancer, by affecting cell cycle.

Honokiol and Angiogenesis

It is widely accepted that, for solid tumors, angiogenesis is necessary to grow over a diameter of 2 mm to obtain oxygen and nutrients [13]. Angiogenesis is a process of new vasculature formation. It can not only provide sufficient oxygen and nutrients, but also make sure that there is homeostasis inside and around tumors, which can support autonomous tumor proliferation [14•]. Angiogenesis also plays a vital role during the process of metastasis. New blood vessels are considered to be essential for the delivery of nutrients and oxygen to the tumor microenvironment. Moreover, new blood vessels seem critical by providing route for metastasis.

It is well known that radiation can lead to DNA damage; consequently, cells activate a phosphorylation-based signaling cascade known as the DNA damage response (DDR) [15]. DNA lesions are recognized by a network of sensor and mediator factors that result in the rapid recruitment of ataxia telangiectasia mutated (ATM) and ATM-Rad3 related (ATR) to the site of DNA damage [16]. These kinases activate Chk1 and Chk2 [17], which ultimately activate numerous cellular pathways including cell cycle arrest [18]. Truman and colleagues studied the relationship between radiation-induced apoptosis and the down-regulation of Ataxia telangiectasia mutated (ATM) protein [19]. They identified that downregulation of ATM protein can sensitize human prostate cancer cells to radiation-induced apoptosis [19].

Vascular endothelial growth factor (VEGF) is an important endothelial-stimulating factor of great importance to angiogenesis. In an *in vivo* study by Gupta and colleagues, they discovered that inhibition of VEGF could significantly reduce the sensitivity of ras-transformed murine fibrosarcoma cell lines to radiotherapy [20]. Furthermore, the mechanisms behind the relationship between angiogenesis and radiosensitization aroused a cascade of studies. As a result, hypoxia inducible factor1 (HIF-1) was identified as a key regulator [21]. Kang *et al* showed that HIF-1α over expression enhances tumor angiogenesis via up-regulation of vascular endothelial growth factor (VEGF) and other hypoxia-inducible angiogenic factors, which lead to a more aggressive tumor phenotype [22]. On the other hand, trichostatin A (TSA) was found to reduce both mRNA and protein levels of HIF-1α. In addition, VEGF expression was also reduced significantly. Together, these data suggest that TSA could be a promising drug targeting tumor angiogenesis via inhibition of HIF-1α and VEGF expression.

Radiation-induced hypoxia can trigger tumor radioresistance by activating angiogenesis through hypoxia-inducible factor 1-regulated (HIF-1-regulated) cytokines [23]. Study from Magnon *et al* indicated that the usage of angiogenic inhibitors, such as canstatin, combined with targeted radioiodide therapy enhances tumor cell apoptosis. This postulates that HIF-1 may display a radiosensitizing activity that is highly dependent on treatment modalities by regulating key apoptotic molecular pathways [23].

As we mentioned above, tumor angiogenesis is necessary for radioresistance. Conversely, radiation can also promote the process of angiogenesis. In the study of Sofia Vala *et al*, it was found that low-dose IR not only induced VEGF production in hypoxia mimicking conditions, but it also induced rapid phosphorylation of several endothelial cell proteins, including the VEGF Receptor-2. By activating the receptor, low-dose IR enhanced endothelial cell migration and prevented endothelial cell death that was promoted by an anti-angiogenic drug, bevacizumab [24•].

Hypoxia-inducible factor 1 (HIF-1) activity in turn induces the expression of angiogenic growth factors such as VEGF or bFGF. These cytokines promote endothelial survival pathways and counteract radiation-induced apoptosis in both tumor and endothelial cells. To circumvent this radiation-induced protective angiogenic response, one promising therapeutic

approach may be to combine angiogenesis inhibition with radiation [25]. During hypoxia, an intricate balance exists between factors that induce and those that counteract apoptosis or even stimulate cell proliferation [25]. Combined radiation and anti-angiogenesis treatment could thus be expected to inhibit HIF-1 induced angiogenic response.

Although modern technologies permit precise IR delivery to the tumor mass while minimizing exposure of surrounding healthy tissues, the efficacy of radiotherapy remains limited by the intrinsic or acquired radioresistance of many tumors. There is thus an ongoing search for agents that augment the sensitivity of tumor cells to radiation, with recent interest in targeting components of signaling pathways involved in tumor growth and radioresistance. In 1994, honokiol was first reported to have growth inhibiting effects on human leukemic HL-60 cells [26]. The mechanism was proposed to be a non-toxic one. Honokiol was also found to be more effective on inducing apoptosis in SVR angiosarcoma cells [27]. Honokiol also has direct antiangiogenic activity, in that honokiol blocks the phosphorylation and rac activation due to VEGF-VEGFR2 interactions. Honokiol has been shown to have both direct antiangiogenic and antitumor properties [27]. In a study of patients with chronic lymphocytic leukemia (CLL), honokiol had preferential activity against patient-derived CLL cells versus normal lymphocytes [28]. Honokiol causes apoptosis in CLL cells through activation of caspase-8, followed by caspase-9 and -3 activation [28]. Studies indicated that irradiation induces the production of VEGF or PDGF, which are closely related with angiogenesis [29]. It may promote tumor re-growth after irradiation and result in protection of vessels from radiation-induced cell damage.

Radiotherapy is commonly used to treat local tumors for directly killing tumor cells. However, growth factors such as VEGF and FGF-2 are induced by tumor cells subsequent to radiation exposure [30]. This clearly points out that at low-dose radiation, the cells can adapt by enhancing radioresistance in both tumor cells and vascular endothelial cells by inducing angiogenesis growth factors, thereby inhibiting cell death by apoptosis [30].

As we mentioned above, honokiol can effectively inhibit the angiogenesis of different kinds of malignant tumors. The other point is that irradiation can induce the production of angiogenesis growth factors such as VEGF and FGF-2. Our previous studies showed that honokiol can effectively radiosensitizing colon cancer cells. However, additional studies are required to determine whether honokiol increases the sensitivity of colon cancer cells to irradiation through the suppression of the angiogenesis signaling pathway.

Honokiol and STAT3 signaling

Signal transducer and activator of transcription (STAT3) mediates the expression of a variety of genes in response to cell stimuli, and thus plays a key role in many cellular processes such as cell growth and apoptosis. STAT3 can promote oncogenesis by being constitutively active through various pathways. STAT3 activation has been closely linked with proliferation, survival, invasion, and angiogenesis of hepatocellular carcinoma (HCC) and represents an attractive target for therapy [5]. Rahaman and colleagues have reported that inhibition of the STAT3 signaling pathway is associated with increased apoptosis and inhibition of proliferation in malignant glioma [31]. Indeed, development of Akt and STAT3 inhibitors has been a major goal of pharmaceutical companies since the discovery that these pathways are often activated in numerous human cancers such as melanoma, myeloma, brain cancer, breast cancers, and ovarian cancer.

Stat3 signaling pathway plays a pivotal role in mediating extracellular stimuli and activating different oncogene factors. Janus kinase (JAK)/STAT pathways serve to block the apoptosis process, keeping cells alive in very toxic environments such as chemotherapy or ionizing radiation (IR) [32, 33]. In Sun’s study, diindolylmethane (DIM) was used to study the effect

of STAT3 inhibition on human bladder cancer. It was found that different analogs of STAT3 were significantly inhibited by DIM, and that this obviously increased their radiosensitivity [34]. This suggests that STAT3 signaling plays an important role in the mechanism of radioresistance of human bladder cancer cell lines. Meanwhile, in Lee's reports on cucurbitacin's radiosensitivity enhancing effects on thyroid cancer-derived CD133+ cells, STAT3 signaling pathway was also highlighted [35]. In another study from Sun *et al*, TG101209, a small-molecule inhibitor of JAK2 (a STAT3- activating tyrosine kinase), was found to enhance the effects of radiation in lung cancer *in vitro* and *in vivo* [36••]. Claret reported that STAT3 inhibiter Stattic cancer significantly radiosensitizes nasopharyngeal carcinoma (NPC) cells by inhibiting STAT3. In fact, Stattic selectively inhibits activation, dimerization, and nuclear translocation of STAT3 and decreased STAT3-mediated cyclin D1 expression [37]. These data suggest that targeting STAT3 with chemotherapeutic agents may provide a new approach to increase the curative effect of radiation therapy.

As an effective chemotherapeutic agent, recent studies indicated honokiol could effectively perform anti-tumor function via inhibiting STAT3 signaling pathway. Ishikawa *et al* found honokiol can induces cell cycle arrest and apoptosis via inhibition of survival signals in adult T-cell leukemia [38]. It can suppress the phosphorylation and DNA binding of different oncogene factors such as NF-κB, AP-1, STAT3 and STAT5. Yu *et al* found that honokiol can cause necrosis and apoptosis in transformed Barrett's and esophageal adenocarcinoma cells through the inhibition of STAT-3 signaling pathway [39••]. Studies from Liu and his colleagues showed that honokiol can inhibit the growth and peritoneal metastasis of gastric cancer in nude mice, which was correlated with the inhibition of STAT3 signaling via the up-regulation of Src homology 2 (SH2)- containing tyrosine phosphatase-1 (SHP-1) [40, 41].

Taken together, these studies suggest that STAT3 signaling is closely related with radiosensitivity of many cancer cells. Honokiol can clearly inhibit the STAT3 signaling pathway in different cancer cell lines. On the basis of these findings, we proposed that honokiol may radiosensitize different cancer cell line through the inhibiting effects on STAT3 signaling pathway. Further studies are essential to determine whether inhibiting STAT3 signaling is essential for honokiol function.

Notch-1 and radiosensitization

Cancer stem cells (CSCs) or Cancer-Initiating cells are believed to be responsible for tumor initiation. More importantly, there is a growing body of evidence suggesting that CSCs contribute to radioresistance [42••–44]. The relatively higher radioresistance of CSCs has been attributed to different intrinsic and extrinsic factors. Although the exact molecular mechanisms that control these processes remain unclear, three major signaling pathways (Notch, Hedgehog and Wnt) have been identified to be highly active in CSCs, of which the Notch signaling pathway is probably the most important [44].

Notch signaling plays a pivotal role in the regulation of many fundamental cellular processes. Accumulating data indicate that abnormal activation of the Notch gene is also involved in the genesis of almost all kinds of human cancers [45]. In addition, Notch is a critical pathway in CSCs self-renewal and survival, while its inhibition was reported to deplete CSCs and inhibit tumor growth [46, 47]. Due to the abnormal activation of Notch signaling in variety of malignant tumors, this pathway comes to be an attractive target for effective treatment. In our previous studies, we demonstrated that the combination of honokiol with radiation resulted in downregulation of the Notch ligand Jagged1 as well as all 4 essential members of the γ-secretase complex, the critical enzyme that cleaves and releases the intracellular domain from the membrane [7••]. Therefore, honokiol couple

radiation–mediated inhibition of CRC cell growth is partly mediated via inactivation of Notch-1 activity. This is further supported by other studies with Notch inhibitors, which have significant anti-tumor effects [31, 48]. A number of agents including γ-secretase inhibitors (GSIs) [35], anti-Notch monoclonal antibodies and RNA interference have been demonstrate to effectively block the canonical Notch signaling pathway [49].

Recent studies demonstrate Notch inhibitors can provide radiosensitization to different human cancers. It may perform this pivotal role through multiple mechanisms. One could be through targeting cancer stem cells. Notch is a critical pathway in CSC self-renewal and survival, while its inhibition was reported to deplete CSCs and inhibit tumor growth. A second method could be by blocking other key signaling pathways thereby suppressing oncogene function such as PI3K/Akt, p53, Ras and MEK signaling [50•–52]. Further, Notch signaling can regulate expression of myc oncogene [53], survivin [54] and Bcl-2 and Bax [55].

As we reported previously, honokiol can inhibit Notch signaling pathway during the process of radiosensitizing colon cancer cells, and recent studies demonstrated Notch inhibitors can inhibit the proliferation and growth of many kind of cancer cells from different signaling pathway. These findings suggest that honokiol may perform as radiosensitizer.

Honokiol and Mismatch repair

DNA mismatch repair (MMR) is a highly conserved but complex system that ensures genomic stability on several levels including correcting mismatches generated during DNA replication, blocking genetic recombination events between divergent DNA sequences, and mediating cell death in response to certain DNA damaging agents. Importantly, MMR deficiency is associated with *in vitro* and *in vivo* "damage tolerance" (resistance) to multiple different classes of clinically active chemotherapy drugs as well as to other types of DNA damage (stress) agents including ionizing radiation and hypoxia.

Recent studies revealed that different states of MMR lead to diverse response to ionizing radiation. The research from Yan *et al* demonstrated that colon cancer cells have greater radiosensitivity with enhanced expression of apoptotic and autophagic markers, more pronounced cell cycle alterations (increased late-S population and a G(2)/M arrest) following LDR-IR compared to isogenic cell lines lacking MLH1 [56]. In addition, while examining the radiosensitizing effect of Gemcitabine [2',2'-difluoro-2'-deoxycytidine (dFdCyd)] on different colon cancer cell lines, Robinson and colleagues observed that only the MMR-deficient cell lines were radiosensitized. Furthermore, the data from this study showed radiosensitizing effect has no relationship with p53 pathway [57]. In our previous study, we also observed that honokiol radiosensitizes MMR-deficient colon cancer cell. Together, these studies demonstrate that mismatch repair system plays an important role in the process of mediating radiosensitization.

Conclusion

As a new developing chemotherapeutic agent, a number of studies indicate that honokiol can inhibit proliferation and induce apoptosis. Recent studies have demonstrated the ability of honokiol to radiosensitize various types of cancers including colon [6••], lung [58], ovarian and breast cancer [59]. These studies have also demonstrated that honokiol has the ability to radiosensitize by inhibiting different pathways. Moreover, the radiosensitizing effects involved affecting both extrinsic and intrinsic pathways that affect cell cycle progression, tumor angiogenesis, JAK/STAT3 signaling pathway, and cancer stem cell related Notch signaling pathway. Surely, carcinogenesis is a very complicated process and many oncogenic signaling pathways are involved into this process [60]. As a neoadjuvant

therapeutic approach, radiation plays a pivotal role in the treatment of colorectal cancers. We have determined that honokiol radiosensitizes colon cancer cells in a mismatch repain dependent mechanism. However, how this pathway affects stemness is yet to be determined. As we continue to dissect the mechanism of honokiol, we hope to not only provide additional pathways affected by the compound but also develop novel derivatives of the compound to further enhance the activity while reducing side effects, if any from increasing dosing to pharmacological levels.

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•• Of major importance

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