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ROLE OF CURCUMIN IN CERVICAL CANCER PREVENTION AND TREATMENT

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ABSTRACT

Cervical cancer is one of the most common cancers among women worldwide. Current standards of care for cervical cancer includes surgery, radiation, and chemotherapy. Conventional chemotherapy fails to elicit therapeutic responses and causes severe systemic toxicity. Thus, developing a natural product based, safe treatment modality would be a highly viable option. Curcumin (CUR) is a well-known natural compound, which exhibits excellent anti-cancer potential by regulating many proliferative, oncogenic, and chemo-resistance associated genes/proteins.

KEYWORDS: Curcumin, cervical cancer, prevention and treatment.

INTRODUCTION

Cervical cancer is one of the most common and deadly cancers among women worldwide and is associated with persistent Human Papillomavirus (HPV) infection.[1] Only a small subset of women with chronic HPV infection progresses to develop the disease.[2] Additional factors are needed to acquire an immortal phenotype and to further advance towards malignant and invasive phenotypes.[3,4] In addition to HPV infection, cigarette smoking and smoke carcinogen (benzo[a]pyrene, BaP), are known risk factors associated with cervical cancer.[2,5] Viral morphogenesis is increased subsequent to BaP treatment of cells infected with the high-risk HPVs, 31, 16 and 18 in organotypic raft cultures derived from a cervical intraepithelial neoplasia type I cell line.[6] Moreover, micro RNAs (miRNAs), small noncoding RNAs that regulate the expression of protein-coding genes, also play an important role in the development of carcinogenesis. Resistance to chemo/radio-therapies with prolonged treatment, resulting in an invasive form of cancer, requires the development of novel therapeutic modalities to conquer chemo-resistance and improve the overall life expectancy of patients. Curcumin (CUR) is a natural polyphenol compound that is derived from the rhizome of the medicinal plant Curcuma longa Linn. It has been widely used in traditional Indian medicine for its efficacy against inflammation, respiratory diseases and other disorders.[7,8] Due to its anti-inflammatory and anti-carcinogenic qualities, it has also been extensively studied in the field of cancer therapeutics. CUR has shown dose-dependent chemopreventive and chemotherapeutic effects in a number of studies and pre-clinical trials.[9,10] Curcumin exhibits cytotoxic effects in cervical cancer cells in a concentration-dependent and time-dependent manner and its activity was found to be higher in HPV infected cells.[11] Curcumin has been proven to downregulate HPV18 transcription by selectively inhibiting AP-1 activity, which reverses the expression dynamics of c-fos and fra-1 in cervical cancer cells.[11] Superior inhibitory action of curcumin against cervical cancer cells[12–14] was due to the inhibition of telomerase activity, Ras, and ERK signaling pathways, cyclin D1, COX-2 and iNOS activity, and the mitochondrial pathway.

Curcumin in Chemoprevention

Since 1987, the National Cancer Institute (NCI) has tested over 1,000 different potential agents for chemoprevention activity, of which only about 40 promising agents were moved to clinical trials.[12] Curcumin, present in the Indian spice "haldi", is one such agent that is currently under clinical investigation for cancer chemoprevention. Three polyphenols were isolated from Curcuma longa, of which curcumin (bis-α,β-unsaturated βdiketone) is the most abundant, potent and extensively investigated.[13] Curcumin has been used empirically as a remedy for many illnesses in different cultures. It is only in the last few decades that curcumin's effects against cancer and cancer therapy-related complications have emerged, through much investigation. The first clinical report of the anticancer properties of curcumin was from Kuttan and coworkers,

who used 1% curcumin ointment on skin cancerous lesions with a reduction in smell in 90% of patients.[14] 10% patientsexperienced a reduction in pain and lesion size. In an experimental model of mammary cancer induced by 7,12-dimethylbenz-[a]-anthracene (DMBA) in female rats, the initiation of DMBA-induced mammary adenocarcinoma was significantly decreased by intraperitoneal infusion of curcumin 4 days before DMBA administration.[15] In a study of esophageal cancer prevention in curcumin-fed F344 rats, the chemopreventive activity of curcumin was observed not only in the initiation phase but also in post-initiation phases.[16] Also, in a familial adenomatous polyposis (FAP)-simulated study in which the APC gene of C57Bl/6J Min/+ mice was mutated to result in the development of numerous adenomas by 15 weeks of age, an oral curcumin diet prevented adenoma development in the intestinal tract, suggesting the chemopreventive effect of curcumin in colorectal cancer with APC mutation.[17] Moreover, in a rat model of N-nitrosodiethylamine and phenobarbitalinduced hepatic cancer, curcumin reduced lipid peroxidation and salvaged hepatic glutathione antioxidant defense, which eventually may have contributed to hepatic cancer prevention.[18] Several studies of cancer prevention at different stages have demonstrated the multi-targeted anticancer and chemopreventive effects of curcumin and have suggested it as a very favorable agent for chemoprevention.

Mechanisms of Anticancer Effects

According to their mode of action, chemopreventive agents are classified into different subgroups: antiproliferatives, antioxidants, or carcinogen blocking agents. Curcumin belongs to all three subgroups, given its multiple mechanisms of action. The anticancer effects of curcumin mainly result from multiple biochemical mechanisms that are involved in the regulation of programmed cell death and survival signals. The curcumin targets that are involved in signaling pathways include transcription factors, growth factors, inflammatory cytokines, receptors, and enzymes (Figure 2). In different types of cancers, curcumin exhibits anticancer actions through a combination of different mechanisms including; survival signal reduction, proapoptotic promotion, anti-inflammatory actions, and reactive oxygen stress (ROS) scavenging to different degrees. The effects of curcumin on these signaling pathways are expected to be more complicated in the real setting, and the mechanisms of curcumin's chemopreventive, chemosensitizing, and radiosensitizing effects are more vigorously being studied now.[19-27]

How it works incervical cancer

Interestingly, curcumin acted upon multiple targets and due to pretreatment was in turn able to revert the proliferative effects of cervical cancer cells. A recent proteomic study suggests that curcumin induces significant changes in tumor-related proteins that are associated with cell metabolism, cell cycle, and carcinogenicity in HeLa cells.[28] Additionally, curcumin acts as a sensitizer for chemotherapy and radiation in cervical cancer therapy. We reported a detailed cellular suppressive mechanistic role of curcumin in a three-dimensional cervical cancer raft culture system.[29] A study demonstrated that curcumin inhibited cell motility, induced apoptosis, decreased the expression of HPV oncoproteins, and restored tumor suppressor proteins. At present, about[30] 55 clinical trials are listed on clinicaltrial.gov related to curcumin and cancer therapy (as of December 2, 2015), which suggest its translational and clinical potential. Furthermore, it has demonstrated no toxicity to healthy organs at higher doses such as 8 g/day in clinical trial.[31] However, it suffers from very low systemic bioavailability, poor pharmacokinetics, poor absorption ability, high metabolic rate, inactivity of metabolic products, together with rapid elimination and clearance from the body.[32] Some studies have shown that a trace amount of CUR was detected in the serum of humans when 4–12 g/day of CUR was administered.[32] Although curcumin has inspired considerable interest for its extensive physiological activities, its poor bioavailability restricts its clinical translation. Nanoparticle technology provides an effective way to deliver anti-cancer drug(s) into tumors.[21] To circumvent curcumin's inherent issues, a study has developed a curcumin nanoparticle formulation (Nano-CUR), based on poly(lactic-co-glycolic acid) (PLGA), an FDA approved polymer.[30] This formulation has shown to be effective for improved therapeutic effects in metastatic ovarian and breast cancer cells.[33]

Hurdles: Pharmacokinetics and Pharmacodynamics

Phase I/II clinical trials have clearly shown that curcumin exhibits poor bioavailability in humans, ~1% after oral administration, a major barrier for its use in the clinic. The major factors contributing to the low plasma and tissue levels of curcumin appear to be its poor absorption due to insolubility in water, rapid systemic elimination in the bile and urine due to extensive enterohepatic recirculation and fast metabolism.[34]

Curcumin analogs

Studies suggest that the β-diketone moiety is responsible for the instability and weak pharmacokinetic profile of curcumin. Modifications of the structure of natural curcumin significantly improved solubility, stability and bioavailability. James Snyder's group at Emory University has synthesized a series of curcumin analogs by modifying the diketone moiety and the side chains of the benzene rings. Many of these compounds showed increased water solubility and improved pharmacokinetic properties including tissue distribution and terminal elimination half life.[35]

Curcumin nanoparticles

Delivery of drugs via their formulation as nanoparticles is an emerging platform for an efficient approach to improve pharmacokinetic properties such as solubility and stability, and thus bioavailability of poorly

bioavailable drugs. This approach has been extensively used for curcumin with success in preclinical studies. Formulation of curcumin by encapsulation in polymeric micelles, liposomes, polymeric nanoparticles, lipid-based nanoparticles and hydrogels makes the formulation aqueous soluble.[36]

Curcumin conjugates

Conjugation of curcumin with polymers or other lipophilic compounds is another widely used approach to improve the water solubility and stability of curcumin. Conjugation of curcumin with hyaluronic acid or polyvinylpyrrolidone forms water soluble micelles with improved stability at physiological pH and cytotoxic activities.[37]

Adding adjuvant

One of the major reasons for the poor bioavailability of curcumin is its rapid glucuronidation. Protection of curcumin from such metabolic conversion using an adjuvant was found to be successful in improving its bioavailability. Piperine is an inhibitor of intestinal and hepatic glucuronidation. Concomitant administration of curcumin with piperine increased the bioavailability of curcumin by 1100% in human volunteers and 154% in rats.[38]

Future Possibilities

High risk individuals and cancer survivors alike may benefit from chemoprevention, not only because primary cancer chemoprevention is beneficial for high risk groups but also because of the devastating nature of the disease course when patients experience SPT or recurrence. As curcumin is a non-prescription dietary derivative that has multiple targets at different levels in multiple pathways, it has great potential in the prevention of cancer and SPT. When its systemic bioavailability is increased through the development of different analogs and formulations, the promise of curcumin in chemoprevention may be feasible in many cancer types.

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