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MOLECULAR MECHANISMS OF CANCER CHEMOPREVENTION MODULATED BY CURCUMA LONGA

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INTRODUCTION

Turmeric (*Curcuma longa*) has been used as a spice and a cosmetic in Indian culture traditionally and has been a component of Indian Ayurvedic medicine since 1900 BC. As a medicine, *Curcuma longa* is used mainly for various allergic and inflammatory respiratory conditions, as well as for liver disorders, anorexia, rheumatism and wound healing. Turmeric has nearly 20 molecules with antibiotic property, 14 molecules with cancer preventive potential, 12 with anti-tumor effect. Curcumin [diferuloylmethane ($C_{21}H_{20}O_6$)], a polyphenol, is an active principle of the perennial herb *Curcuma longa* and derived from the roots (rhizomes) of the plant. Curcumin, the principal curcuminoid of turmeric, has been intensely studied as a cancer protective agent. Its potential has been tapped in head and neck cancers, breast, lung, gastro-intestinal cancer, ovarian cancer, melanoma, neurological cancers, sarcoma, leukemias and lymphoma.

The term chemoprevention as coined by Michael Sporn and it means that the use of a chemical substance of either natural or synthetic origin to prevent, hamper, arrest, or reverse a disease. Cancer initiation may result from the assault to the cell by a carcinogen causing stable genotoxic damage by its metabolic activation or due to oxidase stress, chronic inflammation, and hormonal imbalance. Curcumin perform the chemoprevention by following pathways.

BY RESTRICTING THE FORMATION OF FREE RADICALS

Curcumin is a potent factor which binds singlet oxygen at physiological concentration. Singlet molecular oxygen is an electronically excited species of oxygen which is usually produced in mammalian cells under normal physiological and abnormal pathological conditions. The mutations which cause cancers in epithelial cells are started due to formation of reactive oxygen species and reactive nitrogen species. Both of theses are mainly formed by activated neutrophills and macrophages in the procedure of inflammation under influence of cyclooxigenase-2. Curcumin which is polyphenol in rhizome of plant curcuma longa potently inhibits the induction of nitric oxide synthetase which is by-production of activated macrophages. Anti tumor property of this Curcumin is more potentiated by inhibition of intracellular signaling cascades by significantly reducing NF- kappa B induced inducible nitric oxide synthetase. Curcumin, by blocking NF-kappa B activation, also reduces inducible nitric oxide synthetase gene transcription which results in the form of inhibition of cell proliferation, interleukin-2 production, nitric oxide generation reduction in cytokinin production.

BY REDUCING DNA DAMAGE

Experimental studies suggest that 12-O-detetradecanoylphorbol-13-acetate is reduced by Curcumin which is helpful for tumor promotion especially in mouse skin. It is a strong inhibitory action on DNA and RNA synthesis. Another experimental study (Bandyopadhyaya et al, 2008) suggested that supplementation of Curcumin, in those female rats whom significant DNA damage of liver tissues were done through nicotine, significantly antagonized the nicotine-induced genotoxic effect. Mutation by carcinogens is a procedure of irreparable damage in critical genes involved in growth. The regulative property on gene transcription and anti oxidant property of curcmin explains its protective role on DNA damage.

BY INDUCTION OF APOPTOSIS IN CANCER CELLS

Experiments suggest that survival molecules like phosphorylated protein kinase-like endoplasmic reticulum resident kinase, phosphorylated eukaryotic initiation factor-2α, glucose-regulated protein-78, and the apoptotic molecules such as capase-4 in HL-60 cells in Curcumin treated cancer cells, induction of apoptosis and endoplasmic reticulum stress in cancer cells is induced by Curcumin. Removing two double bonds in Curcumin resulted in a loss of the ability of Curcumin to induce apoptosis as well as endoplasmic stress in cancer

cells. Both mitochondrial DNA damage and nuclear DNA damage in cancer cells specially in liver carcinoma is initiated by curcumin. Curcumin causes the mitochondrial hyperpolarizatrion in the initial incidences of DNA damage and apoptosis of hepatocellular carcinoma.

Some experiments suggest that significant decrease in histone acetylation is induced by Curcumin and it causes arrest in cell cycle and loss of cell viability in cancer cells. Reactive oxygen is generated by high concentration of curcumin which inhibit histone acetylation by binding the histone acetyletransferase. Thus antitumor activity of Curcumin is conducted by growth arrest and apoptosis specially in T-cell leukemia.

BY UP-REGULATION OF PHASE II ENZYMES

Experiments on swiss mice showed that Curcumin regulates the expression of glutathione peroxidase and 4-hydroxynonenal metabolizing glutathione S-transferase agent in benzopyrene-induced forestomach tumors. Thus Curcumin protect against environmental carcinogen -induced carcinogenesis by up regulation of phase II conjugating enzymes and suppression of reactive oxygen species mediated NF-kappa B,, activator protein 1, mitogen-activated protein kinase activation. Daily dietary intake of Curcumin induced phase II detoxifying enzymes, suggesting that Curcumin has chemopreventive efficacy in inhibiting chemical carcinogenesis and other form of electrophilic toxicity.

CONCLUSION

Various natural products, particularly herbal drugs, seem to have the potency to prevent cancer. Analysis of mode of action of these substances is also very important since the fundamental data generated is useful when combination applications are considered for improved preventive potency. Curcumin has tumor suppressing properties with cellular process involved in tumor promotion and tumor progression. The chemopreventive potential of Curcumin has been studied extensively because of its non toxic nature. It is found to suppress NF-kappa B activation, providing a beneficial effect by killing and preventing tumor growth as well as inhibiting metastatic progression. Evidence from epidemiological studies and results of clinical trials will be needed to stimulate the development of Curcumin as a cancer preventive and therapeutic agent.

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