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Short Communication

Mycotoxin- A Target for Anticancer Drug Development

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Abstract

The aim of this present article is to underscore the recent evidence linking anticancer activity and free radical scavenging activity of mycotoxins and its significance in the development of newer anticancer drugs. Although acute exposure to a massive amount of mycotoxin is rare but long-term exposure/consumption of food with low levels of lipophilic mycotoxin remains problematic. The aneuploidogenic and clastogenic potentials of the mycotoxins citrinin and patulin were studied in human cells is especially relevant for calculating the risk of carcinogenicity. The literature reviewed suggests that mycotoxins not all mycotoxins are toxic and some mycotoxins or mycotoxin derivatives have found use as anticancer drugs. The development of cancer in humans is a complex process including cellular and molecular changes mediated by diverse endogenous and exogenous stimuli and oxidative DNA damage. Reactive oxygen species (ROS), the key mediators of cellular oxidative stress and redox dysregulation involved in cancer initiation and progression, have recently emerged as promising targets for anticancer drug discovery. Some of the mycotoxins are also effective against multidrug resistant cancer. The present review enlightens the development of potential anticancer agent from mycotoxins.

ABBREVIATIONS

ROS: Reactive Oxygen Species; RNS: Reactive Nitrogen Species; NOX: Mono-Nitrogen Oxides NO and NO_2; BCR: Breakpoint Cluster Region Protein; ABL: Abelson Murine Leukemia Viral Oncogene; CML: Chronic Myelogenous Leukemia; TP53INP1: Tumor Protein 53-Induced Nuclear Protein 1; MAP Kinases: Mitosin Activated Protein Kinases; AP 1: Activator Protein 1

INTRODUCTION

Fungi are ubiquitous to the environment and primarily saprophytic, using nonliving organic material as a nutrient source for growth and reproduction. There are over 200 recognized mycotoxins, however, the study of mycotoxins and their health effects on humans is in its infancy and many more are waiting to be discovered. Many mycotoxins are harmful to humans and animals when inhaled, ingested or brought into contact with human skin. Mycotoxins can cause a variety of short term as well as long-term health effects, ranging from immediate toxic response to potential long-term carcinogenic and teratogenic effects. Mycotoxicoses are the animal diseases caused by mycotoxins; mycotoxicology is the study of mycotoxins [1]. Mycotoxins are small and low-molecular-weight natural products generally exotoxins produced as secondary metabolites by filamentous fungi. These metabolites constitute toxigenically and chemically heterogeneous assemblages that are grouped together only because the members can cause disease and death in human beings and others [2]. The term mycotoxin was coined in 1962 in the aftermath of an unusual veterinary crisis near London, England, during which approximately 100,000 turkey poults died [3,4]. The majority of human mycoses are caused by opportunistic fungi [5-8]. While all mycotoxins are of fungal origin, not all toxic compounds produced by fungi are called mycotoxins.

From literature it is revealed that many natural products are available as chemo-preventive agents against commonly occurring cancer types. However, there is continuing need for identification, characterization, and development of new chemo-preventive agents from enormous pool of synthetic, biological and natural products. About 60% of currently used anticancer agents are obtained from natural sources, including plants, marine organisms, and microorganisms. Fungal toxins (mycotoxins) though known to be toxic to the animal and human systems still find their use in therapeutic application. Mycophenolic acid, penicillic acid, 5-methoxy-sterigmatocystin [9], a series of analogues of anguidine [10,11], including triacetoxyscirpenol , three diacetoxyscirpenols, three monoacetoxyscirpenol and scirrpenol , T-2 toxin and related tricocethecenes [12] , cytochalasin B [13], patulin [14], aflastatin A [15], 14'-Hydromytoxin B and 16-Hydroxyroridin E [16], tenuazonic acid [17], 4- beta-acetoxyscirpendiol [18], gliotoxin [19], fluorinated pseurotin A, synerazol [20], rubratoxin B, beauvericin showed antitumour activities in different types of cancer cell line and *in vivo*. Harri

et al. reported that the trichothecenes verrucarins A and B and roridin A inhibited the growth of Ehrlich ascites tumour, in mice and Walker carcinoma in rats. Myrocin C, a new diterpene from soil fungus Myrothecium verrucaria increases the life span of EAC–bearing mice. Leuteoskyrin, a hydroxyanthraquinone is proved to inhibit mRNA synthesis in Ehrlich ascites tumour cells [21].

Redox dysregulation as anticancer drug target

Molecular mechanisms by which redox alterations contribute to cancer cell proliferative control, survival, invasion, and metastasis are the area of equal interest to researchers focusing on fundamental cancer biology or translational anticancer drug discovery, as expertly reviewed recently [22-26]. The involvement of ROS in cancer initiation and progression is now strongly established. Apart from its role as a causative factor in carcinogenesis through ROS-induced carcinogenesis, redox dysregulation contributes to malignant transformation and progression through ROS-mediated carcinogenic signaling and redox modulation of apoptotic and survival pathways [27,28]. Following early studies that described increased production of ROS including superoxide free radical anions and hydrogen peroxide (H_2O_2) by human tumor cells [29], recent research supports a causative role of altered redox regulation in the genesis of tumor and has identified numerous cellular sources of ROS production in cancer cells, including over expression of ROS-generating NOX family members and enhanced electron leakage from the mitochondrial respiratory chain [30-35]. Furthermore, NOX-dependent ROS generation driving angiogenesis has recently emerged as a promising target for pharmacological anticancer redox intervention as suggested by prototype studies performed in murine hemangioma [36].

Early studies established a correlation between expression of oncogenes and cellular ROS levels, *e.g.*, increased ROS production in response to Ras oncogenic activity has been described in H-RAS^{v12}-transformed NIH3T3 fibroblasts [37]. It is now established that constitutive upregulation of Ras protein signaling through overexpression or mutational activation, one of the most common genetic events observed in carcinogenesis, is associated with increased ROS production, cellular oxidative stress, and mutagenesis observed in many tumors [38,39]. RAS-transformed cells are more sensitive to pharmacological depletion of glutathione, suggesting that an elevated rate of constitutive ROS production in Ras-transformed cells may represent a functional target for pharmacological intervention that undermines the cellular antioxidant capacity.

The chimeric BCR / ABL tyrosine kinase responsible for chronic myelogenous leukemia (CML), increases intracellular oxidative stress and causes inactivation of protein phosphatases and genomic instability in ROS-dependent manner, providing another example of oncogene-controlled redox dysregulation in cancer cells [40]. ROS-producing signaling pathways are activated by BCR / ABL leading to oxidative DNA damage and transitional mutations that encode clinically relevant amino acid substitutions in the BCR/ABL kinase domain causing imatinib resistance [41].

On the other hand, inactivation of tumor suppressor genes may cause deviations from redox homeostasis that increases mutagenesis and tumorigenesis. For example, recent mouse studies suggest that p53 mutational inactivation impairs p53 antioxidant function through transcriptional downregulation of key mediators including TP53INP1 (tumor protein 53-induced nuclear protein 1) resulting in increased oxidative stress, accelerated mutational rate, and increased tumor growth, all of which can be suppressed by antioxidant supplementation [42]. These exemplary studies suggest that a number of oncogenes and tumor suppressor genes exert their functions in part through redox mechanisms that may be amenable to pharmacological intervention by redox chemotherapeutics.

Redox dysregulation in cancer cells is a complex integration of many aspects of the cancerous phenotype, including alterations in metabolism, proliferative control, and anti-apoptotic survival signaling, as reviewed extensively elsewhere. In many human cancer cell lines and tumors, alterations of proliferative and apoptotic control have been shown to depend partly on constitutive activation of multiple redox sensitive targets through autocrine production of ROS, including components of signaling cascades (*e.g.*, Akt/protein kinase B and MAP kinases) as well as transcription factors [*e.g.*, nuclear factor κB (NFκB) and activator protein 1 (AP-1) [43,44]. Recently, the role of ROS-dependent redox dysregulation in tumor progression has been studied in detail in human melanoma where over expression of Akt converts noninvasive to invasive growth phase tumors with increased generation of superoxide originating from NOX4 upregulation, preferential glycolytic energy metabolism, and VEGF-dependent angiogenesis. It is obvious to mention that the antagonist of phosphoinositide-dependent Akt activation and tumor suppressor PTEN and other members of the protein tyrosine phosphatase super family are established molecular targets of ROS signaling, chemically inactivated by ROS-dependent oxidation of essential cysteine residues facilitating tumorigenic tyrosine kinase receptor signaling [45-49].

Other than the proliferative, anti-apoptotic, metastatic, and angiogenic signaling, ROS may also exert cytotoxic and proapoptotic functions that would limit tumorigenicity and malignant progression. Any changes in cellular redox homeostasis and ROS levels will affect viability through redox modulation of the mitochondrial permeability transition pore opening leading to cytochrome C release, apoptosome assembly, and activation of executioner caspases, if cellular ROS levels reach a certain threshold incompatible with cellular survival. Consequently, redox homeostasis in cancer cells that produce ROS at elevated levels due to glycolytic metabolic adaptations, mitochondrial insufficiencies, and ROS-dependent survival signaling depends on a concerted upregulation of antioxidant defense mechanisms, most notably the glutathione- and thioredoxin-dependent redox systems [50,51], but also involves upregulation of fundamental stress response signaling including the heat shock response and the electrophilic stress response.

Taken together, evidence suggests feasibility of chemotherapeutic redox intervention by modulation of constitutively elevated levels of cellular oxidative stress using novel pro- and antioxidant redox chemotherapeutics that target mitogenic and anti-apoptotic ROS-signaling. It has been

suggested that differential redox set points in cancer cells versus non transformed normal cells represent a therapeutic window of sufficient width permitting redox intervention that selectively targets cancer cells with constitutively upregulated levels of ROS. Therefore, attention has therefore focused on the identification and development of experimental chemotherapeutics that induce positive deviations from redox homeostasis through prooxidant action, either by direct production of oxidizing species or by modulation of specific cellular targets involved in redox homeostasis. Theoretically, prooxidant deviation induces a redox shift that leads to cell cycle arrest and cell death without compromising viability of untransformed cells based on the redox differential between normal and tumor cells. Notably, the requirements for prooxidant proliferative and survival signaling encountered in rapidly dividing cancer cells also suggest feasibility of antioxidant intervention by pharmacological induction of negative deviations from redox homeostasis expected to attenuate the cancer cell proliferative engine.

ROS in cancer chemotherapy: From toxicological liability to therapeutic asset

It is well established that dose-limiting off-target toxicity of anthracycline tumor antibiotics can result in cardiomyopathy, attributed to the generation of free radical-mediated damage originating from anthraquinone-derived redox active drugs in cardiac sarcoplasmic reticulum and mitochondria [52]. Indeed, considerable effort has pursued the identification of cytoprotective metal chelators (*e.g.*, dexrazoxane hydrochloride) and antioxidant cytoprotective adjuvants (*e.g.*, amifostine) that can serve as combinatorial agents for prevention of chemotherapy-associated organ toxicity without compromising chemotherapeutic efficacy of these agents [52,53]. Recently, improvement of the therapeutic index of anticancer drugs by the superoxide dismutase mimetic mangafodipir has been established, and mangafodipir protective activity against oxaliplatin neurotoxicity is currently evaluated in a Phase II clinical trial.

DISCUSSION

The development of cancer in humans is a complex process including cellular and molecular changes mediated by diverse endogenous and exogenous stimuli. It is well established that oxidative DNA damage is responsible for cancer development [54-55]. Cancer initiation and promotion are associated with chromosomal defects and oncogene activation induced by free radicals. A common form of damage is the formation of hydroxyled bases of DNA, which are considered an important event in chemical carcinogenesis [56,57]. This adduct formation interferes with normal cell growth by causing genetic mutations and altering normal gene transcription. Oxidative DNA damage also produces a multiplicity of modifications in the DNA structure including base and sugar lesions, strand breaks, DNA-protein cross-links and base-free sites. For example, tobacco smoking and chronic inflammation resulting from noninfectious diseases like asbestos are sources of oxidative DNA damage that can contribute to the development of lung cancer and other tumors [58,59]. In a study, the effects of mycotoxin on cell cycle arrest and microtubule formation were investigated by applying human embryonic kidney (HEK293) cells as a model. With the assistance of immunocytostaining of α-tubulin and citrinin was found to disrupt the stable microtubule skeleton during the interphase of cell cycle during mitosis which contributes to the induction of numerical chromosome aberration in human cells. Although acute exposure to a massive amount of mycotoxin is rare but long-term consumption of food with low levels of lipophilic mycotoxin such as citrinin remains problematic. This study clearly demonstrates the molecular mechanism and aneuploid potential of mycotoxin. The induction of chromosome loss and/or non disjunction by citrinin in human cells is especially relevant for calculating the risk of carcinogenicity [60]. Among the many mycotoxins, T-2 toxin, citrinin, patulin, aflatoxin B1 and ochratoxin A are potential to induce dermal toxicity and/or tumorigenesis in rodent models [61]. Cancer is considered as a multifactor disease, where oxidative stress may be involved in both initiation and promotion of multi-step carcinogenesis. ROS can accelerate DNA damage, stimulate pro-carcinogenesis, initiate lipid per oxidation, inactivate antioxidant enzyme systems and thus can modulate the expression of genes related to tumor promotion [62,63]. A significant number of attractive molecular cancer targets, many of which are amenable to redox intervention by small molecule therapeutics, have now been identified and validated [64-67]. Further translational research will be necessary to enhance the therapeutic benefit provided by early developmental candidates, but it is now evident that redox drugs represent a significant expansion of the chemotherapeutic armamentarium providing novel weapons that promise to impact the ongoing war on cancer.

CONCLUSION

ROS, the key mediators of cellular oxidative stress and redox dysregulation involved in cancer initiation and progression, have recently emerged as promising targets for anticancer drug discovery. The exploration of these fungal toxins may develop better treatment options for the deadly diseases like cancer. Mycotoxin could be the next big thing for the development of anticancer drugs especially for the treatment of multidrug resistant cancer. The derivatives or analogues of the natural mycotoxin are sometimes better in activity as well as less harmful as far as side effects are concerned. Although more studies should be undertaken to unravel the molecular mechanisms and safety is a great concern to use mycotoxin as anticancer agents but it may contribute for the development of a new group of anti-cancer agents.

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