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Mini Review

A Rapidly Developing Biotechnology Field for Cancer Therapy and other Bioactivities: Medicinal Mushrooms When Androgen and Glucocorticoid Receptors are Targeted Differently; Prostate Cancer Cells Experience ER Stress and Apoptosis

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Abstract

When it comes to prostate cancer, androgen (AR) and glucocorticoid (GR) receptor signalling play opposing roles: in the prostate, AR functions as an oncogene and GR as a tumour suppressor. Recently, we discovered that the non-steroidal phytochemical compound A (CpdA) is an anti-inflammatory anti-androgen that modulates AR/GR. CpdA suppresses GR transrepression while suppressing AR and preventing GR transactivation. Degradation by proteasomes regulates GR and AR. We discovered that prolonged treatment with the proteasome inhibitor Bortezomib (BZ) resulted in the accumulation of GR and the degradation of AR in prostate cancer (PCa) cells LNCaP, LNCaP-GR, DU145, and PC3. BZ improved CpdA's capacity to suppress AR and increase GR transrepression. Additionally, we discovered that CpdA+BZ differently regulated GR/AR to inhibit PCa cell growth and survival while simultaneously inducing endoplasmic reticulum stress (ERS). The differential regulation of GR-responsive genes by CpdA+BZ is significant (Ikekawa T 2001).

Glucocorticoid-responsive pro-survival genes, such as SGK1, were inhibited by CpdA+BZ, but BZ-induced ERS-related genes BIP/HSPA5 and CHOP/GADD153 were activated. We demonstrated using ChIP that the effects of CpdA and CpdA+BZ on GR loading on the promoters of SGK1, BIP/HSPA5, and CHOP were responsible for their regulation. In addition, we discovered that AR and GR were widely expressed in advanced PCa from patients who underwent androgen ablation and/or chemotherapy: 56% of these patients' carcinomas exhibited both receptors, whereas the remaining 27% expressed either GR or AR. Overall, our findings support the idea that prostate cancer (PC) may be treated with dual AR/GR targeting, and they point to the great therapeutic potential of the BZ and dual-target steroid receptor modulator CpdA combinations (Kidd PH 2000).

In the past, it has been demonstrated that medicinal mushrooms (basidiomycetes) have significant health-promoting effects, and current research—which is presented here—is now verifying this and identifying many of the bioactive chemicals in these mushrooms. Large-scale solid substrate and liquid culture fermentation cultivation techniques are also briefly covered (Tsumoo H et al., 1994).

Keywords: Prostate cancer, Proteasome inhibitor, Non-steroidal modulator, Apoptosis, ER stress, Cancer, Immunology, Medicinal mushrooms, Solid and liquid fermentations

INTRODUCTION

The development of prostate cancer depends in large part on steroid hormone receptors (PC). Androgen ablation has been the main therapy for both local and metastatic PC as the androgen receptor (AR) promotes carcinogenesis. 1-4 in contrast, the glucocorticoid receptor (GR) in the prostate suppresses tumour growth. 5-9. Here, we suggest a unique approach to treating PC that involves simultaneously inhibiting AR and activating GR signalling. From a superfamily of nuclear hormone receptors, GR and AR are related transcription factors. AR and GR bind to their specific steroid ligands, separate from the cytoplasmic chaperone proteins, go to the nucleus, form homodimers with palindromic hormone response elements (HRE), and bind these to stimulate gene expression (transactivation). DNA binding is often not necessary for the negative control of gene expression (transrepression) by steroid hormone receptors. NF-B, AP-1, and p53 are just a few of the transcription factors (TFs) that GR directly interacts with. It is commonly acknowledged that GR transrepression drives glucocorticoids' anti-inflammatory effects. We recently demonstrated that the GR transrepression's tumor-suppressing actions depend on it. Additionally, NF-B and AP-1 are two TFs with which AR interacts and modifies activity (Shen L et al., 2004). Dual steroid receptor modulators that operate as anti-androgens and concurrently encourage transrepression by GR would provide the best treatment for PC given the competing roles that AR and GR play in the development of prostate tumours. Compound A (CpdA), a new nonsteroidal AR/GR ligand with the required qualities that is a synthetic analogue of the substance from the Namibian shrub Salsola tuberculatiformis Botschantzev, has recently been described by us and others. CpdA inhibits GR homodimerization and transactivation and hinders AR function, while it promotes GR-mediated transrepression. We discovered that CpdA significantly alters the activity of both AR and GR to severely restrict the proliferation and viability of prostate cancer (PCa) cells. Importantly, in vivo CpdA exhibits less adverse effects while maintaining the therapeutic effectiveness of glucocorticoids. The 26S proteasome is a crucial part of the ubiquitinproteasome system, which is in charge of degrading cellular proteins that have been damaged or misfolded. Additionally, the proteasome has a role in regulating the expression of several proteins with a high turnover rate, such as the steroid hormone receptors GR and AR. We anticipated that since proteasome inhibitors were known to suppress AR and activate GR, they may increase CpdA's actions as a dual AR/GR modulator and increase its toxicity for PCa cells (Dong H et al., 2009).

In this study, we evaluated the effects of the FDA-approved first-in-class proteasome inhibitor Bortezomib (BZ) on (1) the stability and function of the AR and GR in the presence of CpdA and AR/GR steroid ligands, (2) the dual AR/GR modulator properties of CpdA, and (3) the effect of CpdA against PC. The association between nutrition and disease has led to the development of the idea of "functional foods," which may be used to treat a variety of chronic diseases including cancer and cardiovascular dysfunction. Functional foods are ones that "encompass potentially health items," including "any changed food or food ingredient that may give a health advantage beyond the typical nutrients it provides," according to the US Academy of Science. The concept of "foods as medicine" is the cornerstone of functional foods (Schwarze SR et al., 2008). Although functional foods cannot make any health claims, more data is pointing to their potential significance in disease prevention. The idea of using food as medicine does not easily fit within the present knowledge of either pharmaceutical or food corporations, and the complete development of functional foods may possibly require new partnerships between these companies with regard to regulatory difficulties. Many communities across the world have long recognised fleshy mushrooms (members of the class Basidiomycetes) as delicious and healthy meals. They were referred to as "the meals of the Gods" by the ancient Romans, "a gift from the God Osiris" by the early Egyptians, and, more properly, "the elixir of life" by the Chinese. Amanita muscaria and Psilocybe spp. in particular have psychoactive and hallucinogenic characteristics, and some ancient tribes dating back to the Palaeolithic period used them in their religious beliefs and activities. Extracts from certain mushrooms were discovered to offer substantial health-promoting advantages by various civilizations across the world, but mainly in the Orient. As a result, they became vital components in many traditional Chinese medicines. The phrase "medicinal mushroom" is currently acquiring more and more traction on a global scale. At least 270 species of mushrooms are known to have a variety of therapeutic characteristics. Species of Lentinula, Hericium, Grifola, Flammulina, Pleurotus, and Tremella are edible mushrooms that exhibit medicinal or functional properties; however, Ganoderma lucidum and Trametes (Coriolus) versicolor, which are only known for their medicinal properties, are categorically inedible due to their bitter taste and coarse texture (Yang H et al., 2008). In the past, the majority of the species of medicinal mushrooms were rather rare and were harvested from the forests where they grew on dead or live trees as well as on forest debris. They mostly break down lignocellulose. They were nearly invariably produced for therapeutic use as hot water extracts, concentrates, or powders. Today, virtually all of the significant therapeutic mushrooms have undergone extensive artificial culture on a massive scale using solid substrate or low moisture fermentation, eliminating the historical scarcity problem and enabling for the development of major commercial enterprises. The only significant biotechnological process that inventively makes use of lignocellulosics is mushroom farming (Wang Q et al., 2007).

CONCLUSION

A straight chain saturated aliphatic alcohol with a carbon

number within a particular range of 26 and 36 carbon atoms has been added to the culture media, which has been shown to further promote the development of Basidiomycetes in both liquid culture and solid substrate culture.

Although most Basidiomycete fermentations are dominated by mycelial cultures, yeast-like cultures have also been applied commercially. Glucuronoxylomannan, a polysaccharide found in Tremella mesenterica fruitbodies, is said to have hypocholesterolemic properties. For the neutriceutical business, new techniques have been developed to standardise production through liquid fermentation methods because such production from fruit-bodies can be very unpredictable. In contrast to other Basidiomycetes, this fungus has an extremely complicated life cycle. On nutritive media, a single basidiospore can germinate to produce hyphal growth or yeast-like budding. It has been established that the haploid yeast budding culture is the optimal method of growth for submerged liquid culture and for yielding significant quantities of the required polysaccharide (Haselkorn R et al., 1973).This buried culture's dynamics may be split into two phases. When nutrient uptake is balanced, the first phase, known as the trophophase, favours the accumulation of unicell biomass. The second phase happens when a carbon supply is overly abundant, but characterised by poor nitrogen assimilation and buildup of glucuronoxylomannan.

While solid substrate fermentations will remain the chosen method of production for whole mushrooms for food and nutriceutical purposes, there will be a continued increase in the development of submerged liquid culture to produce a more uniform and reproducible biomass for dietary supplements and pharmaceutical products. Western biotechnology companies have yet to recognise the potential of this area of medical bioscience.

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