White Button Mushroom Disrupts AR Signaling in Prostate Cancer: the Scientific Basis for a Diet-based Chemoprevention

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Abstract: White button mushroom (WBM) (Agaricus bisporus) is a potential prostate cancer (PCa) chemo-preventive and therapeutic agent. Our clinical phase trial of WBM powder in patients with biochemically recurrent PCa indicated that WBM intake reduced the circulating levels of prostate-specific antigen (PSA), with minimal side effects [1]. We hypothesized that WBM exerts its effects on PCa through the androgen receptor (AR) signaling axis. We thus conducted the reverse translational study. Androgen-sensitive PCa cell lines (LNCaP and VCaP) and patient-derived-xenografts (PDX), of a prostate tumor (TM00298) were used. In both LNCaP and VCaP cells, western blots and qRT-PCR assays indicated that WBM extract (6~30 mg/mL) suppressed DHT-induced PSA expression and cell proliferation in a dose-dependent manner. Immunofluorescence on AR revealed that the nuclear localization of AR was reduced upon WBM extract treatment, which agreed with the results of a PSA promotor-luciferase assay, suggesting that WBM extract inhibited DHT-induced luciferase activity. RNA-Seq on WBM-treated LNCaP cells confirmed that WBM treatment suppressed androgen response pathways and cell-cycle control pathways. Our prostate cancer PDX showed that oral intake of WBM extract (200 mg/kg/day) significantly suppressed tumor growth, as well as decreased PSA levels in both tumors and serum. Both in vitro and in vivo studies suggested that chemical(s) in WBM extract behave as AR antagonist(s). We previously identified a conjugated linoleic acid isomer (CLA-9Z11E) as an active component in WBM extract. In the present study, we extended these findings by performing LanthaScreen™ TR-FRET AR Coactivator Interaction Assays for a direct interaction of CLA-9Z11E with AR. We report here that CLA-9Z11E exerts a strong antagonist potency against the recruitment of an AR coactivator peptide towards AR. The inhibitory effect of CLA-9Z11E (IC50: 350 nM) was nearly two times stronger than the known AR antagonist, cyproterone acetate (IC50: 672 nM). The information gained from this study improves the overall understanding of how WBM may contribute to the prevention and treatment of PCa. It also serves as an important, scientific basis for developing diet-based chemoprevention and integrative therapeutic strategies for prostate cancer (supported by NIH R01 CA227230).

Reference [1] Twardowski P, et al. A phase I trial of mushroom powder in patients with biochemically recurrent prostate cancer: Roles of cytokines and myeloid-derived suppressor cells for Agaricus bisporus-induced prostate-specific antigen responses. Cancer. 2015.121(17):2942-50.