BIRM, AN ANDEAN PLANT EXTRACT, DOWN REGULATES ANDROGEN RECEPTOR AND SHOWS ANTI-TUMOR ACTIVITY IN PROSTATE CANCER

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INTRODUCTION: BIRM is a root extract of an Andean plant, Solanum dulcamara. We reported recently about the potent antiproliferative and anti-tumor activities of BIRM against prostate cancer (1). The glycosaminoglycan (GAG)-rich oligosaccharides make up the most active components of BIRM. It is orally bioavailable without systemic toxicity. The androgen receptor (AR) levels and activities are critical for prostate cancer (CaP) progression. Down-regulating AR may slow or halt CaP progression. We present evidence here to demonstrate potent-antiproliferative and anti-androgen receptor activity of BIRM in CaP cells that are androgen-sensitive or insensitive, synthesize normal or mutant AR.

METHOD Anti-proliferative activity or BIRM on AR-positive, and AR-negative cell lines (LAPC-4, LNCaP, C4-2 and PC-3ML) was investigated by DNA synthesis activity by [3H]-thymidine (3H-TdR) incorporation assay and flow cytometry. Activity of BIRM against AR was investigated by immunoblotting, co-immunoprecipitation and AR-promoter activity. BIRM activity against AR activity was probed by a PSA ELISA and PSA-promoter reporter assays.

RESULTS BIRM inhibited DNA synthesis activity in CaP cells (IC 50: ~1.0 µl/ml). BIRM induced cell-cycle arrest in CaP cells, increases in G2M (80-112% increase) with a concomitant decrease in S-Phase (23-38%). More significantly, BIRM caused a dose and time-dependent down regulation of normal and mutant- AR in androgen-sensitive LAPC-4 and LNCaP cells (Fig. 1) as well as androgen-insensitive C4-2 cells. AR degradation by BIRM preceded cell cycle arrest and inhibition.
of DNA synthesis. AR down regulation was due to increased proteosome-mediated AR degradation and was independent of PI-3 kinase/Akt pathway, a novel mechanism. BIRM also suppressed PSA promoter activity by 70.2±3.4% and PSA production by 86±2.7%. Decrease of phospho-AR level was seen by BIRM treatment and it was associated with degradation of total AR. Inhibition of PSA promoter by BIRM occurred concurrent with AR degradation. Accelerated AR degradation by BIRM was independent of androgens, suggesting its potential activity in androgen-insensitive CaP. BIRM decreased tumor growth in both LNCaP and PC-3ML tumor xenografts by 71% and 72.2%. Starting the treatment immediately following tumor implantation was more effective in preventing tumor incidence (25% in treated versus 90% in un-treated) than starting after tumors are palpable (100% incidence in either cases), thus implicating potential chemopreventive potential of BIRM against prostate cancer.

DISCUSSION: Total androgen deprivation is a common treatment option for patients with advanced prostate cancer (2). Although most patients initially respond to this therapy, the disease quickly progresses to an androgen-refractory state. Several studies have shown that androgen-ablation leads to the androgen refractory state which is attributed to AR overexpression, AR mutations or activation by its co-activators (2-3). Thus, ablation of AR would be a great therapeutic opportunity not only for localized androgen-dependent prostate cancer but also for the prostate cancer that is resistant to androgen ablation therapy. The plant extract BIRM, has significant anti-proliferative activity, contributed by its ability to induce cell-cycle arrest and AR down regulation. Studies with AR-positive LAPC-4, LNCaP, C4-2 as well as AR-negative PC-3 tumor models (reported earlier, 1) suggest a potential chemopreventive function of BIRM on all forms of prostate cancer.

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REFERENCES