Glycitein induces cellular differentiation in nontumorigenic prostate epithelial cells

Elizabeth A. Clubbs and Joshua A. Bomser
OSU Interdisciplinary PhD program in Nutrition, The Ohio State University, Columbus OH 43210, USA

ABSTRACT

We hypothesize that soy isoflavones may reduce prostate cancer risk by increasing prostate epithelial cell differentiation.

INTRODUCTION

- Prostate cancer (PCa) is the third leading cause of cancer related deaths among American males.
- Prostate carcinogenesis is characterized as a continuum of impairment of the homeostatic control governing differentiation, proliferation, and apoptosis of the prostate epithelium.
- The prostate epithelium consists of 2 primary differentiated cell types, luminal and basal, and are characterized primarily by their unique cytokeratin profiles.
- Loss of luminal cell differentiation and a concomitant increase in the proliferation is initially observed in low grade prostate intraepithelial neoplasia (PIN).
- Progression to high grade PIN involves disruption and partial loss of the basal cell population with a complete loss of this cell population observed in PCa.
- Asian populations have lower PCa incidence and mortality but similar rates of incidence of low grade PIN when compared to the United States. The reduced incidence of PIN in Asian populations is attributed to increased consumption of soy and soy-containing products.
- This suggests that soy consumption may reduce PCa incidence by maintaining the basal cell population in the prostate epithelium; however, this hypothesis is yet to be tested.

The objective of this study was to identify a potential mechanism of preserving the basal cell population during PCa progression via soy isoflavones-induced basal cell differentiation of an intermediate cell population.

MATERIALS & METHODS

To test our hypothesis, we examined the effects of soy isoflavones on prostate epithelial proliferation, cell cycle distribution, and different differentiation using the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, flow cytometric analysis, and western blot analysis, respectively.

Statistical significance between groups was determined by one-way analysis of variance with Tukey's post-hoc comparisons. Values of p<0.05 were considered significant.

RESULTS and DISCUSSION

Question 1: Do soy isoflavones reduce the proliferation of nontumorigenic prostate epithelial cells?

Table 1. Cell cycle analysis of RWPE-1 cells treated with soy isoflavones for 8 days as measured by flow cytometry. 4-HPR is a synthetic retinoid known to induce G0/G1 cell cycle arrest and used as a positive control.

Table 2. Comparative expression of cell cycle regulatory proteins in RWPE-1 cells treated with soy isoflavones for 8 days.

Conclusion 1: All isoflavones tested reduced RWPE-1 cell proliferation at concentrations of 50 μM. Of these, glycitein was the only isolate that reduced cell proliferation at 5 μM. Genistein, daidzein, and equol did not reduce cell proliferation.

Conclusion 2: 50 μM glycitein was required to reduce S phase and increase G2/M phase of the cell cycle as compared to the control whereas smaller concentrations of glycitein did not affect cell cycle distribution.

Question 3: Does glycitein induce expression of the basal cell marker, cytokeratin 5 and p63?

Conclusion 3: Unlike 4-HPR, a known inducer of cytokeratin 18 expression and luminal differentiation, 50 μM glycitein decreased cytokeratin 18 expression, showing that glycitein does not induce luminal differentiation.

Question 4: Does glycitein induce expression of the basal cell markers, cytokeratin 5 and p63?

Conclusion 4: Glycitein maintained cytokeratin 5 expression and increased expression of p63 suggesting glycitein induces basal cell differentiation in the RWPE-1 cell line.

CONCLUSIONS

Taken together, these data suggest that glycitein induces basal cell differentiation of prostate epithelial cells. Loss of the basal epithelium occurs during progression of precancerous lesions in the prostate to overt prostate cancer. Preserving the basal cell population may reduce the risk of prostate cancer incidence.