Commentary

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Soy Phytoestrogens on DNA Methylation in Prostate Cancer

Marine Daures[1,2], Marjolaine Ngollo[1,2], Mouhamed Idrissou[1,2], Gaëlle Judes[1,2], Khaldoun Rifaï[1,2], Frédérique Penault-Llorca[2,3], Yves Jean Bignon[1,2], Laurent Guy[2,4] and Dominique Bernard-Gallon[1,2*]

1 Department of Oncogenetics, Centre Jean Perrin, 63001 Clermont-Ferrand, France
2 University Clermont Auvergne, INSERM U1240, IMoST, 63000 Clermont-Ferrand, France
3 Department of Biopathology, Centre Jean Perrin, 63000 Clermont-Ferrand, France
4 Department of Urology, CHU Gabriel Montpied, 63000 Clermont-Ferrand, France

Corresponding author:
Dominique Bernard-Gallon

dominique.gallon-bernard@clermont.unicancer.fr

Department of Oncogenetics, Centre Jean Perrin, INSERM U1240, Clermont-Ferrand, France.

Tel: 0473178358

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Soy phytoestrogens are dietary components with considerable effects on reducing the incidence of prostate cancer. Furthermore, the epigenetic regulation of gene expression can be modified by soy phytoestrogens [1]. Qualitative and quantitative studies show a decrease of promoter methylation on tumour suppressor gene such as *BRCA1, BRCA2, EPHB2, GSTP1* and *RASSF1A* on prostate cancer cell lines treated with genistein and daidzein. Effects of both molecules were compared to the demethylating agent of DNA, the 5-azacytidin [2,3]. Indeed, these genes are known to be hypermethylated in prostate cancer. This hypermethylation leads to the loss of their expressions and to chemotherapy-resistance of tumor cells [4,5].

In order to understand the molecular mechanisms involved in the methylation reversion of DNA by phytoestrogens, a comparative study of the effect of phytoestrogens and 17β-estradiol was carried out on prostate cancer cell lines PC-3, LNCaP and DU 145 which differ in their Androgen Receptor (AR) status but share Estrogen Receptor Beta (ERβ). For this purpose, 24 genes were selected for their direct involvement in prostate cancer. This gene panel compared the effects of genistein, daidzein, 17β-estradiol and 5-azacytidine. A demethylating effect of genistein and daidzein on most genes was observed except for the *DLC1* and *hsa-miR-34a* genes in the PC-3; *DLC1*, *hsa-miR-34a* and *MSX1* in DU 145 and *OPCML* in LNCaP [6].

Furthermore, 17β-estradiol effect on gene demethylation was similar to 5-azacytidine and soy phytoestrogens, it reduces the methylation of oncosuppressors in prostate cancer. This result suggests that demethylating action of phytoestrogens, which have a similar molecular structure to estrogens, would pass through ERβ. However, it is possible that some of phytoestrogen effects on DNA methylation operate by other pathways because all genes don't have Estrogen Response Elements (EREs) in their regulatory regions. Indeed, phytoestrogens-ERβ complex is translocated in nucleus where it binds to the EREs on target genes promoters in order to moduce their demethylating effect in cells. In addition, methylome study by MeDIP-on-chip technique on DU 145 and LNCaP cells after treatment with genistein, daidzein and 5-azacytidine showed 88 genes modulated by soy phytoestrogens in DU 145 against 478 genes in LNCaP. *MAD1L1, TRAF7, KDM4B* and *hTERT* genes were commonly differentially methylated in both cell lines after treatment and demethylating effect of genistein and daidzein was more marked than 5-azacytidine [7]. These demethylating effects imply a transcription regulation of these genes by DNA methylation. Signaling pathways analysis of these 4 genes reveals an association with the NF-kB and p53 pathways. These two pathways are deregulated in prostate cancers and play a major role in proliferation and apoptosis. Previous studies have shown a decrease in NF-kB activity by genistein in prostate cancer cell lines suggesting an indirect effect of genistein on tumor proliferation [8].

Mitotic arrest deficient-like 1 (*MAD1L1*) is involved in the cell cycle by controlling the mitotic spindle-assembly and chromosome alignment. The expression loss of this gene contributes to tumor development. This result suggests a reactivation of *MAD1L1* gene expression by promoter demethylation by phytoestrogens.

Interplay between *TNF Receptor-associated factor 7* (*TRAF7*) and p53 was demonstrated in breast cancer and it shows a decrease in *TRAF7* expression [9]. TRAF7 impair p53 via its E3 ubiquinine ligase activity. Decrease of *TRAF7* expression leads to an accumulation of p53 protein in tumor cells causing a proliferation increase. Decrease of *TRAF7* methylation with genistein and daidzein would increase transcription of this gene in prostate cancer cells, reflecting the anti-proliferative role of soy phytoestrogens in cancer.

Lysine (K)-specific demethylase 4B (*KDM4B*) and *telomerase reverse transcriptase* (*hTERT*) possess oncogenic activity in cancers [10-12]. KDM4B overexpression in prostate cancer and its association with the Androgen Receptor (AR) suggest that KDM4B is a potential factor in tumor progression [13]. KDM4B acts as a co-activator of AR, increasing its transcriptional activity and stability by inhibiting its proteasome degradation [14]. Thus, *KDM4B* promoter does not show methylation, which leads to suppose that gene regulation is not dependent on DNA methylation. These observations may explain the work of Coffey et al. which shows a KDM4B increase in prostate cancers. However, genistein and daidzein treatments show an increase on *KDM4B* and *hTERT* methylation. These results suggest a methylation effect of soy phytoestrogens on genes with an oncogenic effect. Genistein effect on repression of *hTERT* transcription has been previously demonstrated. Indeed, genistein would indirectly inhibit *hTERT* repression by negatively regulating *C-MYC* transcription factor which activate *hTERT* transcription [15].

These results confirm the major role of epigenetic mechanisms in tumor development and suggest that soy phytoestrogens behave like epidrugs in prostate cancers.

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