

# Estrogen induced metastatic modulators MMP-2 and MMP-9 are targets of 3,3'-diindolylmethane in thyroid cancer.

[Rajoria S<sup>1</sup>](#), [Suriano R](#), [George A](#), [Shanmugam A](#), [Schantz SP](#), [Geliebter J](#), [Tiwari RK](#).

## Author information

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Department of Microbiology and Immunology, New York Medical College, Valhalla, New York, United States of America.

## **Abstract**

### **BACKGROUND:**

Thyroid cancer is the most common endocrine related cancer with increasing incidences during the past five years. Current treatments for thyroid cancer, such as surgery or radioactive iodine therapy, often require patients to be on lifelong thyroid hormone replacement therapy and given the significant recurrence rates of thyroid cancer, new preventive modalities are needed. The present study investigates the property of a natural dietary compound found in cruciferous vegetables, 3,3'-diindolylmethane (DIM), to target the metastatic phenotype of thyroid cancer cells through a functional estrogen receptor.

### **METHODOLOGY/PRINCIPAL FINDINGS:**

Thyroid cancer cell lines were treated with estrogen and/or DIM and subjected to in vitro adhesion, migration and invasion assays to investigate the anti-metastatic and anti-estrogenic effects of DIM. We observed that DIM inhibits estrogen mediated increase in thyroid cell migration, adhesion and invasion, which is also supported by ER- $\alpha$  downregulation (siRNA) studies. Western blot and zymography analyses provided direct evidence for this DIM mediated inhibition of E(2) enhanced metastasis associated events by virtue of targeting essential proteolytic enzymes, namely MMP-2 and MMP-9.

### **CONCLUSION/SIGNIFICANCE:**

Our data reports for the first time that DIM displays anti-estrogenic like activity by inhibiting estradiol enhanced thyroid cancer cell proliferation and in vitro metastasis associated events, namely adhesion, migration and invasion. Most significantly, MMP-2 and MMP-9, which are known to promote and enhance metastasis, were determined to be targets of DIM. This anti-estrogen like property of DIM may lead to the development of a novel preventive and/or therapeutic dietary supplement for thyroid cancer patients by targeting progression of the disease.