



# Suppression of MMP Expression and Invasion of Human Cervical Cancer Cell lines HeLa and DoTc2 4510 by Nutrients

M.W. Roomi, V. Ivanov, A. Niedzwiecki, M. Rath

**Presented at:** 44th Annual Meeting of the Society of Toxicology, New Orleans, March 6-10, 2005.

**Published in:** Proceedings of the 44th Annual Meeting of the Society of Toxicology, Abstract #1494

## Abstract

### **Background:**

Cervical cancer is the seventh most common cancer worldwide and the second most common cancer in women. Early detection by screening followed by appropriate treatment is associated with a high cure and survival rate. Untreated dysplasia and carcinoma in situ leads to 30% to 40% invasion within ten years.

### **Objective:**

We investigated the synergistic effect of a unique nutrient formulation (NM) containing lysine, proline, arginine, ascorbic acid, and epigallocatechin gallate on human cervical cancer cells HeLa (adenocarcinoma of cervix - CCL2) and DoTc2 4510 (carcinoma of cervix - CRL7920) by measuring: cell proliferation, modulation of MMP-2 and -9 expression, and cancer cell invasive potential.

### **Materials and Methods:**

Human cervical HeLa (CCL-2) and carcinoma DoTc2 4510 (CRL 7920), obtained from ATCC, were grown in DME medium supplemented with 10% FBS, penicillin (100 U/ml) and streptomycin (100 mg/ml) in 24-well tissue culture plates. At near confluence, the cells were treated with the nutrient mixture (NM) dissolved in media and tested at 0, 10, 100, 500, and 1000 µg/ml in triplicate at each dose. Cells were also treated with phorbol myristate (PMA) 200 ng/ml to study enhanced expression of MMP-9. Cell proliferation was evaluated by MTT assay, MMP expression by gelatinase zymography, and invasion through Matrigel.

### **Results:**

NM with and without PMA 200 ng/ml showed significant antiproliferative effect on human cervical CCL-2 cancer cell growth (untreated 37% treated 57% at 1000 µg/ml) ( $p < 0.0002$ ). NM significantly inhibited cervical DoTc2 4510 cancer cell growth (untreated 45% treated 49%) ( $p < 0.0004$ ). Zymography demonstrated expression of MMP-2 by untreated cervical CCL-2 and enhanced MMP-2 and induced MMP-9 by PMA (200 ng/ml) treated CCL-2 cells. NM inhibited the CCL-2 expression of MMP-2 and -9 in a dose-dependent fashion, with virtual total inhibition of MMP-2 at 1000 µg/ml and MMP-9 at 500 µg/ml concentration.

Untreated DoTc2 4510 cells demonstrated MMP-9 expression, which was enhanced with PMA treatment. NM inhibited MMP-9 expression in a dose-dependent fashion with virtual inhibition at 500 µg/ml. The synergistically acting nutrient mixture significantly reduced the invasion of human cervical cancer cells CCL-2 through Matrigel in a dose-dependent fashion, with 76% inhibition at 100 µg/ml and 100% at 500 µg/ml NM (p<0.0001). Invasion inhibition of cervical cancer cells DoTc2 4510 97% at 500 µg/ml and 100% at 1000 µg/ml (p<0.0001).

**Conclusion:**

Our results suggest that NM is an excellent candidate for therapeutic use in the treatment of cervical cancer, by inhibiting critical steps in cancer development and spread, such as cell growth, MMP expression and invasion.

**Comment:**  
 Cervical cancer is the seventh most common cancer worldwide and the second most common cancer in women. Untreated dysplasia and carcinoma in situ leads to 30% to 40% invasion within ten years. We studied the synergistic effect of a unique nutrient formulation containing lysine, proline, arginine, ascorbic acid, and epigallocatechin gallate on metastatic parameters on human cervical cancer cells such as effect on MMP-2 and -9 expression and cancer cell invasive potential. Our results demonstrated complete inhibition of Hela MMP-2 expression at 1000 µg/ml and MMP-9 at 500 µg/ml, and of Matrigel invasion at 500 µg/ml. NM demonstrated complete inhibition of cervical DoTc2 4510 cell expression of MMP-9 at 500 µg/ml and of invasion at 1000 µg/ml. These findings are significant as they suggest that the nutrient mixture would be an effective and safe therapeutic regimen for treatment of cervical cancer.



