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THE CHEMOKINES GRO-A AND IL-8 SECRETED FORM OMENTUM PROMOTE AGGRESSIVENESS OF OVARIAN CANCER CELLS

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INTRODUCTION: Metastatic cancer progression is the major cause of the high mortality of ovarian cancer. Omental metastasis is the most common route in ovarian cancer metastatic progression. Our previous studies have found that TAK1/NFκB signaling cascade is required for ovarian cancer cell aggressiveness in omental metastasis. Here, we further reported that the chemokines secreted from omentum promote the aggressiveness of ovarian cancer by activating TAK1/NFκB signaling cascade.

MATERIAL AND METHOD: Omentum condition media (OCMs) were prepared by incubating fresh human normal or cancerous omentum tissues in culture medium. Chemokine array profiling was conducted to identify chemokines secreted from omental tissues. Effects of OCMs and chemokines found in OCMs on ovarian cancer cell lines were studied by functional assays, western blots and NF-κB luciferase reporter assays. A pair of ovarian cancer cells isolated from a patient's ovaries and omentum was included to investigate the differential effects of OCMs and chemokines towards primary and metastatic ovarian cancer cells. TAK1 inhibitor, (5Z)- 7-oxozeaenol, was used to study the effects of OCMs and chemokines in activation of TAK1.

RESULTS AND DISCUSSION: We found that OCMs could significantly promote ovarian cancer cell migration, invasion and soft-agar colony formation. The oncogenic effect was stronger in metastatic ovarian cancer cells than primary ovarian cancer cells,

indicating that OCMs contain oncogenic factors enhancing the aggressiveness of metastatic ovarian cancer cells. Chemokine array profiling revealed that chemerin, growth-regulated oncogene α (GRO-α) and interleukin 8 (IL-8) were remarkably upregulated in OCMs. Functionally, GRO-α and IL-8 but not chemerin promoted the similar oncogenic effects as OCMs on ovarian cancer cells, while such effects were stronger in metastatic ovarian cancer cells. Moreover, OCMs and the two chemokines remarkably elevated NF-κB reporter luciferase activity, as well as the expression levels of p-TAK1S412, p-IKK and p-IκBα. However, co-treatment of TAK1 inhibitor (5Z)-7-oxozeaenol abrogated the oncogenic effects of OCMs and both chemokines in ovarian cancer cells, suggesting GRO-α and IL-8 secreted from omentum play as activators of TAK1/NFκB pathway in ovarian cancer cells. **Conclusion.** GRO-α and IL-8 are the dominant chemokines secreted from omentum tissues for promoting ovarian cancer cell aggressiveness by activating TAK1/NFκB pathway.