Connections between a Protein Synthesis Regulator, Cell Migration Pathways, and Ovarian Cancer

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Ovarian cancer has a high mortality rate and often goes undiagnosed until late stage tumor growth where treatment becomes difficult. Determining the role of TARS in cell angiogenesis could provide a new target for therapy in human ovarian cancer.

Recent studies have shown that the protein synthesis regulator threonyl–tRNA synthetase (TARS) secreted in response to cell stress promotes angiogenesis. In addition, expression of TARS within human ovarian tumor samples correlates with the aggressiveness of the cancer. The objectives of this study were to determine the intracellular signaling pathway activated by TARS and to further examine the relationship between TARS activity and ovarian cancer progression. The approach included an in vitro analysis of migration signals in cultured endothelial cells (HUVECs) and an in vivo analysis of tumor angiogenesis in a mouse model of ovarian cancer.

It was predicted that TARS would act through common cell migration pathways such as MAP kinase or nuclear factor kappaB. HUVECs were treated with TARS, and/or the specific TARS inhibitor BC194. Treatment with endothelial growth factor or tumor necrosis factor was used to determine the activation levels of ERK and NFkB, respectively. Overall, western blots showed an upregulation of P-ERK by a 1.5 fold increase in cells treated with TARS. Disrupting TARS signaling could provide a mechanism in which to prevent angiogenesis.

To test the hypothesis that TARS plays a role in tumor invasion and angiogenesis, mice harboring ID8 ovarian epithelial cancer cells were treated with the TARS inhibitor BC194. Immunohistochemistry was used to detect TARS, blood vessels, and inflammatory macrophages within tumor samples. Preliminary results suggest a decrease in tumor progression in animals treated with BC194. Overall, a quantitative decrease in blood vessels and inflammatory cells in animals treated with BC194 is expected. Success of this hypothesis would mean that TARS inhibition should be investigated as a treatment of ovarian cancer.