CANCER PREVENTION & RESEARCH INSTITUTE OF TEXAS

Award ID:
RP140412

Project Title:
Endotrophin and the Obesity/Cancer Nexus: Role in Growth and Chemoresistance

Award Mechanism:
Individual Investigator

Principal Investigator:
Scherer, Philipp

Entity:
The University of Texas Southwestern Medical Center

Lay Summary:

We have identified a novel molecule derived through a cleavage event from an abundant extracellular scaffold protein in fat tissue. The generation of this fragment termed ENDOTROPHIN is enhanced in the context of obesity and further stimulated by infiltrating tumor cells into the fatty tissue of the breast. With obesity and all of its negative health consequences on the rise, the fat cell
is increasingly moving center stage in the context of studies of local effects on tumor growth. ENDOTROPHIN is a fat cell-derived molecule that is a novel growth factor exerting potent effects in the tumor microenvironment, conveying chemo-resistance to tumor cells. Since it is upregulated in obese adipose tissue, it is a link between obesity-associated adipose tissue dysfunction and the potent growth-stimulatory effects of fat tissue on tumor growth. We find very high levels of this protein in human breast cancer samples as well. Mice that have an excess of the protein develop bigger tumors and more metastatic lesions. Neutralizing antibodies against endotrophin in the mouse slow down tumor growth and enhance chemo-sensitivity against cisplatin. Endotrophin also enhances the pro-fibrotic environment and attracts inflammatory immune cells to the tumor. Here, we propose to identify the receptor that binds endotrophin and exerts its downstream signaling events. We aim to identify the molecules that are responsible for the cleavage of endotrophin from its parent molecule. Finally, we want to test how broad the effects of endotrophin are on chemoresistance. Since we have observed endotrophin upregulation in a wide spectrum of human breast cancer specimens, we expect that the therapeutic applications will be very broad. This will include a reduced growth rate of tumors upon endotrophin neutralization. Neutralization of endotrophin may enhance the efficacy of chemotherapeutics and may even allow the use of lower doses, reducing the side effects on healthy cell types.