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Analyzing Novel Mechanisms Involved In Tumor-Adipose Tissue Crosstalk During Metastasis: Role Of Secreted Exosomes And Soluble Factors.

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BACKGROUND

Obesity has severely increased over the past decades, becoming a major health problem nowadays. During obesity, the physiological function of the adipose tissue is altered, disturbing remote and local tissue function. Increasing evidences revealed a link between obesity and the development and progression of certain types of cancer. However, the role of obesity in tumor metastasis in melanoma is not well known. Recent data support a role for secreted factors [e.g. soluble factors and extracellular vesicles (EVs)] in the communication between tumor cells and adipose tissue during tumor metastasis. Still, the specific factors reinforcing the metastatic behavior have not been defined yet.

OBJECTIVES

Here, we focus on determining the influence of obesity in melanoma metastasis and the characterization of the mechanisms involved in tumor-adipose tissue communication during tumor progression/metastasis. We postulate that the crosstalk between cancer cells and adipocytes within the tumor microenvironment by secreted factors induce the formation of a tolerant niche for cancer cell growth and metastasis.

METHODS

Mice under regular and high fat diet (HFD) were intravenously injected with mouse melanoma cell lines to analyze their metastatic behavior in both conditions. In addition, we have isolated adipose tissue from control and HFD mice to analyze the secretome of different fat depots by cytokine array and mass spectrometry. We have also performed *in vitro* and *in vivo* approaches to determine the uptake of exosomes by adipose tissue. Flow cytometry analysis was done after the *in vivo* injection of tumor-derived exosomes in control and HFD mice to characterize exosome uptake. The *in vitro* analysis was performed using the Opera High Content Screening System. We analyzed the phenotypic changes promoted by tumor-derived exosomes in adipose tissue-derived mesenchymal stem cells (AD-MSCs).

RESULTS

We found that HFD-fed mice had increased metastatic burden in specific anatomical locations of adipose tissue (e.g. mammary, retroperitoneal, pericardial and mesenteric fat) as compared with mice under regular diet. To decipher the factors involved in this process, we are currently characterizing the chemokine and lipidomic profile of the secretome of different fat depots isolated from HFD and control mice. Our preliminary result showed that chemokines secreted by adipose tissue could be involved in metastatic cell homing. In addition, we started the characterization of the mechanisms involved in tumor-adipose tissue crosstalk. We found that tumor-secreted exosomes home to specific adipose tissue depots and are uptaken by specific subpopulations within the adipose tissue resembling AD-MSCs. The *in vitro* treatment of AD-MSCs isolated from mouse adipose tissue with tumor-derived exosomes suggests that tumor exosomes impair lipid accumulation. We are currently analyzing the relevance and the mechanisms involved in these findings.

CONCLUSIONS

Overall, our data show that chemokines secreted by adipose tissue from specific anatomical locations favor metastatic seeding and progression. Morevover, we propose that tumor-secreted exosomes are a novel mechanism of communication between tumor and AD-MSCs impairing their normal function, lipid accumulation and reinforcing metastatic behavior.

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