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PROJECT TITLE (200 Characters max):
“Role of the Fibroblast Growth Factor 21 (FGF21) in Tumor Microenvironment”

HYPOTHESIS:
“FGF21 plays a role in the crosstalk between adipocytes and breast tumor cells”.

PROJECT DESCRIPTION (Include design, methodology, data collection, techniques, data analysis to be employed and evaluation and interpretation methodology)

Epidemiological studies have suggested a close link between obesity and breast cancer. There is an urgent need to investigate the potential pathways linking obesity and breast cancer to have an early diagnosis in patients and optimize the chance of cure. Obesity is an established risk factor for the development of postmenopausal breast cancer and is an independent prognostic factor for the development of distant metastases and death after the diagnosis of breast cancer. Triple Negative Breast Cancer (TNBC) is an aggressive disease subtype that has a poor prognosis and there are inadequate therapies to prevent recurrence in those patients.

Fibroblast Growth Factor 21 (FGF21) belongs to the FGF sub family of endocrine factors, acts as an endocrine factor with important roles in regulating local and systemic metabolic homeostasis of lipid, glucose and energy metabolism. High serum levels of FGF21 were found in obese individuals, subjects with metabolic syndrome, type 2 diabetes mellitus and coronary heart disease. Up to date, the clinical implication of FGF21 in cancer was not elucidated.

We have recently reported that FGF21 levels were significantly increased in clear cell renal cell carcinoma (ccRCC) patients compared with healthy controls. Moreover, there was an association between the increased serum FGF21 levels and the shorter disease free survival in a cohort of 98 ccRCC patients, after adjustment for other predictors of outcome. Our results suggest that higher FGF21 serum level is an independent prognostic biomarker, associated with worse free-disease survival.

There is no information available on the role of FGF21 in mammary tumor initiation and progression; further studies are needed to elucidate the mechanisms behind the increased serum FGF21 levels in cancer patients. The elevated FGF21 levels observed in these patients could be
due to a high FGF21 synthesis by the tumor cells or the stress caused microenvironment metabolic disorders. Our preliminary studies have shown that the level of circulating FGF21 is also potentially useful as a high sensitive biomarker for early diagnosis of breast patients. We have found increased serum FGF21 levels since the early stages of breast cancer but no differences were observed among stages. These findings suggest that the initiation of the tumor itself could be considered as a stressful condition that induces an increased FGF21 secretion by hepatocytes or/adipocytes.

In order to elucidate the role of FGF21 in tumor growth and microenvironment; in our studies, we will use the E0771 mammary cancer cells and the 4T1 mammary aggressive “triple negative” tumor model which resembles breast cancer in patients. In addition, we will use the 3T3-L1 cells to elucidate the involvement of the FGF21 secreted by the adipocytes. We believe that our studies will serve as a preliminary groundwork for a novel target in the treatment of metastatic ER negative cancer.

Our overall hypothesis is that “**FGF21 plays a role in the crosstalk between adipocytes and breast tumor cells**”. Based on our clinical results in cancer patients, we are proposing to elucidate the molecular mechanism by which FGF21 is produced and affects the mammary tumor microenvironment. To this end, the student will have to implement the following plan:

1. **To culture E0771 and 4T1 mammary tumor cells and collect conditioned medium (CM).**
2. **To differentiate of 3T3-L1 adipocytes.**
3. **To characterize CRISPR/Cas9 modified FGF-21KO- tumor cells vs. parental cells.**
4. **To evaluate by western blot, ELISA and PCR some critical molecules in tumor microenvironment. For example: Adipokines: leptin, adiponectin, TGF-beta, IL-8, FGF21, VEGF. TAMs receptors: Prostaglandins and Inflammatory: COX-2, mPGES, 15-PGDE, NFkβ, PGE2 levels, TNF-α, IL-6, IL-8, IL1β. ECM: MMP-9, MMP-2, Collagens I, IV and VI, Fibronectin, E-Cadherin.**
5. **To co-culture 3T3-L1 murine adipocytes with mammary tumor cells (4T1 or E0771) or treated the tumor cells with the CM from 3T3-L1 adipocytes to evaluate cell proliferation, adhesion, migration and invasion properties.**

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Project Description


Project Description


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Project Description


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IS THIS PROJECT SUPPORTED BY EXTRAMURAL FUNDS?
Yes ☑ or No ☐
(If Yes, please supply the granting agency's name)

THIS PROJECT IS: ☐Clinical   ☑Laboratory   ☐Behavioral   ☐Other

THIS PROJECT IS CANCER-RELATED ☑
Please explain Cancer relevance

In our studies, we will use the 4T1 mammary aggressive “triple negative” tumor mouse model which resembles breast cancer in patients. We believe that our studies will serve as a preliminary groundwork for the potential application in the prevention of recurrence of local and metastatic ER negative tumors after the initial adjuvant therapy.
WHAT WILL THE STUDENT LEARN FROM THIS EXPERIENCE?

The student will establish the differentiation of pre-adipocytes into adipocytes and perform cell co-culture experiments with 4T1 and E0771 mammary tumor cells to analyze different molecules in the CM and cell lysates. The student will analyze these molecules using ELISA kits, western blot, enzyme activity kits or q-PCR. The student will acquire laboratory experience and learn several basic molecular and biochemical techniques. Look relevant bibliography and prepare analytic tables comparing different research made on this subject. To be able to think and develop the own ideas related to the project. The student will also learn the importance of discovering new molecular targets to translate basic research findings into potential pharmacological approaches to combat cancer disease.