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Chitinase-3-like-1 protein (CHI3L1) expressed during allergic pulmonary inflammation alters lung microenvironment accelerating breast cancer metastasis

Metastasis is the primary cause of death in women with breast cancer. Elevated serum levels of a glycoprotein known as chitinase-3 like-1 protein (CHI3L1) has been correlated with poor prognosis and shorter survival of patients with cancer and inflammatory diseases (Jensen, Johansen, and Price 2003b). CHI3L1 is known to be expressed in solid tumors such as breast (Johansen et al. 2003). Inflammation plays a pivotal role during tumor progression and metastasis. Since previous studies showed that CHI3L1 modulates inflammation, we determined the role of CHI3L1 in the context of pre-existing inflammation and metastasis. Using triple negative model of breast cancer, we demonstrated that CHI3L1 alters the cellular composition and inflammatory mediators in the lungs of mice with pre-existing pulmonary inflammation leading to the establishment of a metastatic niche. We found that CHI3L1 deficient mice with pre-existing inflammation had decreased pro-inflammatory mediators, and significant reduction in tumor volume and metastasis compared to wild type controls. Pre-existing inflammation and CHI3L1 may be driving the establishment of a pre-metastatic milieu in the lungs and aiding in the establishment of metastasis. We show that CHI3L1 levels are increased at both the "pre-metastatic" and "metastatic stage" and that tumor cells, splenic, alveolar and interstitial macrophages, and myeloid derived population produce CHI3L1. Thus, CHI3L1 may be one of the more promising prognostic markers for recurrent breast cancer (Johansen et al. 1995), metastatic breast cancer (Jensen, Johansen, and Price 2003b) and advanced breast cancer (Coskun et al. 2007). Therefore, understanding the role of CHI3L1 in inflammation during tumor progression could result in targeted therapies for breast cancer patients.

Methods: 8-12 week-old female BALB/c mice and CHI3L1 knockout mice were used in all studies. Allergic pulmonary inflammation was induced in mice using an established ragweed sensitization aerosol challenge model (Shibata et al. 2000). Mice with established pulmonary inflammation were implanted with luciferase transfected 4T1 mammary tumor cells and monitored for tumor progression by *in vivo* imaging. Excised pulmonary tissue was formalin-fixed and H & E histological analysis was done to assess metastasis, inflammatory cellular infiltrates and pulmonary architecture. Flow cytometric analysis of alveolar and interstitial fluid was performed using antibodies specific.

Results & Discussion: It is well established that inflammation within the tumor microenvironment fosters tumor growth and metastasis. Growth of tumors in 4T1 ragweed mice was higher compared to the 4T1 saline control mice. Furthermore, survival in 4T1 ragweed mammary tumor mice was decreased compared to the 4T1 saline controls.

Speaker Biography

Vijaya Iragavarapu-Charyulu obtained her Ph.D. in Microbiology and Immunology from University of Miami, Miami, Florida. She is an Associate Professor in Biomedical Sciences Department where she has been conducting breast cancer research. She is also invested in the educational mission of College of Medicine. She is a Co-director of the Fundamentals of Biomedical Sciences course at FAU.

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