

Susan G. Komen

Research Grants – Fiscal Year 2015

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Loss of the lncRNA Malat1 impacts breast tumor progression and metastasis

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Lead Organization: Cold Spring Harbor Laboratory

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Public Abstract:

We have identified a long nuclear retained non-coding RNA, Malat1, whose knockdown with a highly specific therapeutic leads to differentiation of primary luminal B breast tumors to a less aggressive state and significantly impacts metastasis. Malat1 is one of the most abundant long non-coding RNAs whose expression is altered in many different cancers including breast cancer. Malat1 was originally identified as an RNA whose expression was increased in primary tumor that subsequently metastasized in non-small cell lung cancer patients. In collaboration with other groups we have shown that Malat1 loss using antisense oligonucleotides (ASOs) results in reduced metastasis in mice where lung cancer cell lines of human origin was transplanted. Studies have also shown that, Malat1 gene mutation occurs frequently in luminal breast tumor patients. Our preliminary data on matched primary and metastatic tumors from patients show that MALAT1 is highly abundant in metastatic lesions compared to the primary tumor. Thus Malat1 is an exciting target for understanding metastatic breast cancer and understanding its role in disease progression and metastasis is highly relevant for therapeutic and clinical implications.

Here, I propose to address the role of Malat1 in mammary breast tumor using antisense (ASOs) mediated knock down of Malat1 RNA in mouse models of breast tumors, such as MMTV- PyMT model that recapitulates human luminal B tumors and luminal PDX model. Additionally we will also employ a complimentary approach wherein, organoids, obtained from tumor mammary gland of the mouse models described above will be treated with the ASOs to study their property. We will also analyze the down stream effect of the loss of Malat1 in breast tumor tissue and the tumor organoid to understand the impact of the ASO medicated knock down and to study the mechanism of action. Anti-sense oligonucleotides are a short stretch of DNA that work by blocking the target RNA in the cell and direct them to degradation. Currently these are in clinical trials for

many diseases such as spinal muscular atrophy and Duchenne Muscular Dystrophy. Malat1 knock out mice developed in our lab has no obvious phenotype and no changes in the physiology of the animal were observed. Thus it is believed that Malat1 has more specific role to play in tumors and thus its loss in tumors using the Malat1 specific ASOs will specifically impact tumors.

These studies proposed above will be the basis to extend our findings to subsequent clinical trials. The optimization of the use of Malat1 ASO in the organoids will also be useful in the future to evaluate the effect of Malat1 loss in tumor organoid derived from patients which requires very less biological material and study the patient tumor response to ASO which can be subsequently translated to a clinical treatment protocol. Overall this study has a very high impact in understanding the role of Malat1 in treatment against metastatic breast cancer.