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Breast cancer is the most common malignancy among women in the Western world. Between 5 to 10% of breast cancer cases are hereditary, the majority of which are caused by germline mutations in the breast cancer susceptibility gene BRCA1 or BRCA2. In addition, germline mutations in these two genes also lead to increased risk of hereditary ovarian cancer. The long-term objective of my research is to elucidate the underlying mechanism by which BRCA1 suppresses development of breast and ovarian cancers in women. The ongoing research in my laboratory has been focused on addressing two conundrums regarding BRCA1 functions: 1) Why do mutations in BRCA1 specifically lead to breast and ovarian cancer in women (gender- and tissue-specificity)? 2) Why are somatic mutations of BRCA1 rarely found in sporadic breast cancers?

Our earlier work on BRCA1's potential in remodeling chromatin and transcriptional regulation led us to the hypothesis that BRCA1 may modulate tissue-specific gene expression critical to cancer development in breast and ovary. We have shown that BRCA1 down-regulates the expression of aromatase, the rate-limiting enzyme in estrogen biosynthesis. To more rigorously test the hypothesis, we have launched additional studies in both tissue culture and animal models in the following three directions:

1. In-depth mechanistic studies at the molecular and cellular levels.
2. Genetic studies in mouse models.
3. Cancer biology studies with clinical samples.

In addition to the function of BRCA1 in aromatase expression, we also study the role of BRCA1 in DNA double strand break (DSB) repair. Our mouse model reveals a Brca1 point mutation that likely impairs DNA repair, but has no effect on hormone pathway. Mice carrying this mutation develop spontaneous tumors without tissue specificity. We are currently dissecting its potential function in DSB repair.

The aromatase also plays an important role in sporadic breast cancer development. One of the projects in the lab is to characterize its regulation by transcription factors as well as by epigenetic changes around the promoter.