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Targeting the APOBEC3B-induced mutator phenotype in breast cancer prevention

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Public Abstract:
Breast cancer prevention is a promising approach to further reduce breast cancer incidence and mortality in the next decade. There is an urgent need to identify the fundamental forces driving the development of breast cancer and to identify novel approaches to block hose forces and thereby prevent breast cancer. Breast cancers typically contain thousands of mutations, and it is well accepted that breast cancer results in large part from the accumulation of multiple mutations in premalignant cells. Thus, the capacity of premalignant cells to generate and accumulate mutations, which is known as the "mutator phenotype," is one of the fundamental forces driving breast cancer development. The long-term goal of our research is to identify the molecules that cause the mutator phenotype and block the action of those molecules to prevent breast cancer. Recent studies showed that one of the molecules that cause the mutator phenotype in breast cancer is the enzyme APOBEC3B. This finding represents a breakthrough in breast cancer research. APOBEC3B is overexpressed (i.e., present at high levels) in more than 50% of breast tumors and more than 75% of breast cancer cell lines. Overexpression and aberrant activation of APOBEC3B can lead to unexpected clusters of mutations in breast cancers. This phenomenon of clustered mutations, termed kataegis (shower in Greek), leads to unique mutation signatures in breast cancer. In this application, we will try to answer several key questions: (1) At what stage of breast cancer development is APOBEC3B overexpressed and activated? (2) What causes APOBEC3B to be overexpressed and activated? (3) What are biological components in cells that are required to restrict APOBEC3B expression? (4) Can we identify chemical inhibitors of APOBEC3B expression that will switch off the mutator phenotype and thereby prevent breast cancer? We expect our project to lead to breast cancer prevention strategies with a number of innovative features: (1) The prevention strategies will be genetically based and therefore complementary to currently available preventive approaches such as diet changes and exercise. (2) The strategies will prevent both estrogen-receptor-positive and estrogen-receptor-negative cancers since the mutator phenotype is a driving force for both kinds of breast cancers. (3) The strategies will work at multiple stages of breast cancer development because the mutator phenotype fuels not only breast cancer initiation but also breast cancer progression, metastasis, drug resistance, and recurrence in breast cancer survivors. In summary, we believe the results from our study will have a significant impact not only by improving our understanding of breast cancer biology but also by leading to clinically applicable approaches to prevent breast cancer initiation and progression.