How does Loss of the INPP4B affect breast cancer etiology and treatment outcomes?

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**Public Abstract:**

Triple-negative breast tumor is a subtype of breast tumor that is notorious due to early onset and aggressive behavior. The prognosis is particularly dire for this group of patients, and women diagnosed with triple-negative breast cancer often panic and feel helpless because of lack of targeted therapy that are available for other subtypes of breast tumors. Obviously there is a pressing need for a better understanding of disease mechanisms of triple-negative breast cancer, and for the development of new treatment options. Recent technological developments have allowed high-throughput and large-scale sample analyses directly using patient tumors, and such analyses have revealed potential molecular changes that contribute/drive disease onset and progression. One of the molecular changes that were observed with high frequency is loss of INPP4B, a molecular that function to terminate extracellular signals. Extracellular cues stimulate cells on the surface and cells relay such information by generating unique secondary messengers inside the membrane. Intracellular effector proteins can then bind to these secondary messengers and trigger a plethora of activities regulating fundamental cellular processes such as cell proliferation, survival, growth, differentiation, and cell migration. Prompt termination of these secondary messengers is critical for normal physiological responses. Inadequate removal of these signals may give rise to abnormally prolonged and amplified responses, resulting in various disease conditions including cancer. INPP4B is one of such terminators and loss of INPP4B has been found in multiple tumor types, including ovarian, lung, liver, bladder, and colon cancer. Importantly, loss of INPP4B protein has been observed in 60-90% of human triple-negative breast cancer. Aforementioned large-scale analyses also found other genetic mutations that are present in the same tumors where INPP4B-loss was found. In this proposed research, I will evaluate whether loss of INPP4B alone and in combination with other genetic changes drive triple-negative breast tumor formation, progression and/or dissemination. During the past three years, I also generated triple-negative breast tumors in mice that resemble human counterparts, and I will treat these mice with various drug/drug combinations to identify potential treatment options for triple-negative breast tumors. I expect that tumors resistant to particular treatment will eventually arise and I will investigate mechanisms underlying drug resistance. Since these mice closely mimics human patients, the information obtained here can be quickly and faithfully translate to human patients to provide a framework for designing targeted and personalized therapy toward this deadly disease. The goal is really trying to understand what drives triple-negative breast tumor formation, and how to treat these tumors given the information we comprehended.