Public/Lay Abstract

The work proposed herein describes a novel attack on the problem of metastatic breast cancer (BrCa), which is responsible for the majority of breast cancer-associated deaths. Over the past 15 years, it has become clear how carcinoma cells in general and BrCa cells in particular are able to physically travel from within primary tumors to distant sites throughout the body, doing so largely via the circulation. This, on its own, does not empower such cells to launch metastatic colonies in such distant tissues, since the last step in the multi-step "invasion-metastasis cascade" requires these cells to thrive and proliferate in the unfamiliar tissues in which they have landed. These disseminated cancer cells have arisen in the mammary gland, but now are located within foreign tissues to which they are poorly adapted at the moment of arrival. This lack of adaptation requires that such cells must significantly change their biological behavior to enable them to exploit and thrive within these tissues. How they do so, has been an enigma.

This shortfall in understanding the last step of the multi-step formation of metastases represents a critical gap in our insight into the formation of life-threatening metastases. It is clear that only a tiny fraction of disseminated BrCa cells succeed in spawning metastatic colonies—perhaps one in 100 thousand or one in a million, testifying to the difficulties that these cells encounter in successfully adapting to the foreign tissues in which they have landed. Currently there is no clear explanation of precisely how this adaptation is accomplished. The presently proposed research rests on a hypothetical model that describes in detail how disseminated BrCa cells succeed in developing the abilities to thrive in distant tissues. Equally important, this experimental model, once developed, will allow us and, by extension, many other BrCa researchers to explore the spectrum of changes that the different subtypes of BrCa cells must undergo in order to launch aggressively growing metastatic tumors.

An enumeration of these changes holds the prospect of providing, for the first time, the identities of signaling pathways within BrCa cells that undergo changes during the process of adaptation to growth in foreign tissues, such as the bone marrow, lungs and liver. Identification of these pathways will offer the prospect of developing an entirely novel set of anti-metastasis therapies that target these pathways, thereby undermining the ability of disseminated BrCa cells to continue proliferating within the tissues in which they happen to have landed. Such novel therapies, once developed, will contrast to the conventional therapies applied to date to patients who are suffering advanced metastatic disease. These conventional treatments are designed to kill BrCa cells throughout the body by interfering with the proliferation (growth) and survival signals within these cells. Regrettably, however, metastatic BrCa cells often develop resistance to the conventional treatments, requiring a novel approach to attacking and eliminating these cells from specific organ sites throughout the body.

To summarize the anticipated benefits of the proposed research: It will provide (i) a validated theoretical model that describes with precision how BrCa cells contrive to thrive in distant tissues; (ii) an experimental protocol that our group and others can employ that will make it possible to survey, for the first time, the spectrum of adaptations that BrCa cells must make in order to launch metastases in various specific tissues; (iii) the identities of signaling pathways operating within disseminated BrCa cells that undergo changes in various distinct tissues sites of dissemination; (iv) the changes that are shared in common by BrCa cells that have adapted to grow in distinct sites of dissemination, such as the bone marrow, liver, lungs and brain; (v) the identities of adaptations that BrCa cells from the four distinct subtypes of mammary carcinoma must make in order to launch metastases; (vi) the nature of the signaling pathways that are altered within BrCa cells in order to spawn metastatic colonies and, potentially, the identities of specific molecules and signals within these cells that can be targeted therapeutically by various types agents currently available and to be developed in the future.