Susan G. Komen

Research Grants – Fiscal Year 2015

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Dynamics of cell fate decisions after breast cancer radiotherapy

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Lead Organization: Harvard Medical School

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Public Abstract:

Most breast cancer patients receive adjuvant radiation therapy. Despite its success, still many patients gain little or no benefit from this treatment, as evidenced from the elevated rates of locoregional recurrence, distant metastatic spread, and breast cancer deaths. Unfortunately, those patients will nevertheless suffer the short and long-term side effects of the inefficient radiation therapy. Currently there are no reliable tools to predict how different patients will respond to radiotherapy. In addition, breast cancers are known to be extremely heterogeneous; cells react differently and some are insensitive in response to a specific treatment, which might account for the diverse outcomes among patients. Our aim is to develop patient-specific strategies that maximize the damage in tumor cells while minimizing the damage to normal cells. Recent studies in breast cancer have shown that classical breast cancer subtypes have different sensitivity to radiation. Many efforts are directed to improve the classification of breast cancer subtypes by characterizing the genetic make-up of the particular tumor.

However, current therapies do not incorporate these differences, and instead follow a standardized protocol that consists of daily doses of radiation, over several weeks. The radiation beam induces DNA damage in both tumorous and nearby non-tumorous cells. Cells then initiate diverse cellular programs ranging from DNA repair and transient cell cycle arrest to terminal fates such as cell death and permanent cell cycle arrest. Despite its importance, the connection between breast cancer subtype and a specific cellular outcome remains largely unknown.

To address this challenge we have designed an experimental project at the single-cell level to quantitatively investigate the temporal response and fate of a collection of modified breast cell lines upon radiation. Most breast cancer studies are performed by averaging the behavior of a population of cancer cells. Such approaches cannot detect variation between cells and sometimes even mask the true behavior of single-cells. We will use a collection of breast cells carrying single genetic modification frequently found in breast cancer in combination with live cell imaging reporting on the state of each cell and test cells survival in response to a variety of fractionated DNA damages. We will develop computational tools for image processing and statistical analysis of single-cell data, and develop simple mathematical models connecting cellular states with cell-fate in response to various frequencies of radiation. This will be an interdisciplinary study integrating knowledge and skills from diverse disciplines including molecular biology, live-cell microscopy, radio-oncology, engineering and computational biology.