Susan G. Komen
Research Grants – Fiscal Year 2014

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Glycosylation as a link between breast cancer metabolism and tumorigenesis

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Public Abstract:
Many proteins inside living cells and organisms are subjected to chemical modifications that can alter their functions and contribute to disease, including breast cancer. One such modification, termed O-GlcNAc modification (or O-GlcNAcylation), involves the addition of a carbohydrate to proteins and is a main focus of my laboratory. This modification is a strong focus of my laboratory. O-GlcNAcylation levels are dramatically elevated in a variety of different cancers, including breast cancer, and is necessary for tumor formation. The levels of O-GlcNAcylation correlate with the grade of breast cancer (i.e., grade II-III has higher levels than stage I). Therefore, understanding the specific consequences of O-GlcNAcylation that promote tumor formation, and determining how to inhibit the increase of O-GlcNAcylation, are key steps towards novel breast-cancer treatments. Unfortunately, very little is known about HOW increased O-GlcNAc modification promotes breast-cancer tumor formation or WHY O-GlcNAcylation becomes elevated. We predict that answers to these questions will contribute to a more complete picture of breast cancer biology and provide opportunities for new, wide-reaching therapies. Toward this goal, we have developed a unique set of chemical tools to visualize and identify O-GlcNAcylated proteins. With these tools, we have made two important discoveries. (i) We have identified O-GlcNAc modification on key cell-death proteins that directly contribute to breast cancer. (ii) We have discovered that breast-cancer associated changes in metabolism increase O-GlcNAcylation levels, and we have identified a metabolic enzyme that regulates this process. We hypothesize that O-GlcNAc modification of cell-death proteins blocks their normal function and promotes breast cancer survival, so we further hypothesize that inhibiting the link between metabolism and O-GlcNAcylation levels will promote breast cancer cell-death. In our research, we will determine the consequences of O-GlcNAc on cell-death proteins in breast cancer cells. Simultaneously, we will develop drug-like inhibitors to exploit the link between metabolism and O-GlcNAcylation as a potential, new therapeutic strategy.