Susan G. Komen

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Characterizing the anti-tumorigenicity, structure, and biochemistry of proBMPs

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Public Abstract:

Breast cancer is the most common invasive cancer and the leading cause of cancer-related death among women. Despite significant progress in early diagnosis techniques like mammography and effective therapies like chemo-, radio- and immuno-therapies, treatments to prevent cancer cells from spreading and initiating new tumor growth in other tissues, a process called metastasis, are still lacking. A current concept is that metastasis is mainly due to a small population of cells in breast tumors called cancer stems cells (CSCs). These cells can break away from breast tumors, migrate to a distant site through the bloodstream, and start new tumor growth at a new location. Unfortunately, these breast CSCs are generally resistant to conventional chemo- and radio-therapies, making new therapies that specifically target these cells the most desirable to treat breast cancer patients. Previous research showed that a group of proteins called bone morphogenetic proteins (BMPs) markedly reduced the population of breast CSCs and hindered bone metastasis, making BMPs promising candidates for preventing breast cancer metastasis. BMPs are messenger molecules. They are secreted from some cells and bind to receptors on other cells. In this way, cells communicate with each other to coordinate proper development of different tissues and organs. There are other proteins in the body known as BMP antagonists, which can interact with BMPs and intercept the message delivered by BMPs. BMPs exist in two forms: mature BMPs and pro-form BMPs (proBMPs). In proBMP, a larger molecule known as prodomain connects to mature BMP. It has been established that prodomains help BMPs form properly, but whether they affect the anti-tumorigenic activity of BMPs has never been studied. We hypothesize

that prodomains may change how BMPs bind to receptors or protect BMPs from antagonists, both of which could make proBMPs more effective anti-metastatic reagents than mature BMPs. ¬In this study, we will compare the abilities of proBMPs and BMPs to specifically reduce the number of breast CSCs and prevent their migratory behavior. To better comprehend differences between proBMPs and BMPs, we will also study how prodomains affect the way in which BMPs bind to receptors and antagonists. We will determine the atomic and molecular structure of proBMPs to fully understand how the prodomain interacts with BMPs. These studies will enable profound understanding of how prodomains impact BMP binding to receptors and antagonists, and hence influence the anti-tumorigenic activity of BMPs. The results from this proposed work will be used to identify the most anti-tumorigenic BMP or proBMP and translate them into potent anti-metastatic therapies to improve the lives of breast cancer patients.