Lay Language

It is estimated that there will be more than 300,000 new cases of breast in the United States alone in 2013 with close to 40,000 deaths. While overall cancer mortality rates have declined over the past twenty years, the need for new treatments and novel therapeutic targets is as prominent as ever. Increasingly, the strategy for combating cancer, especially multidrug resistant disease, is to simultaneously target the multiple arms through which the cancer arises and is maintained. Those targets revolve around what are considered to be the hallmarks of cancer: sustained tumor proliferation, evading growth suppressors, activating invasion and metastasis, inducing growth of new blood vessels, and resisting cell death.

One of the major proteins that contribute to the growth of cancer cells including breast cancer cells is Stat3. In addition to its actions in the nucleus as a transcription factor that stimulates the expression of genes involved in cell proliferation, Stat3 also is in the mitochondria of cells where it regulates the production of ATP, which provides the energy for cells to live and grow. Although considerable effort has been directed towards the discovery of drugs that can inhibit the actions of Stat3 in the nucleus, no attempts have been directed to manipulating the actions of that pool of Stat3 in the mitochondria. One of the reasons for a lack of interest in targeting potential therapeutics to disrupt the actions of mitochondrial-localized Stat3 is there has been limited understanding of how Stat3 functions in the mitochondria. Our recent studies have identified an important target for Stat3 in the mitochondria called cyclophilin D, which has an important role in maintaining mitochondrial integrity. Furthermore, our preliminary studies indicate that the growth and metastasis of breast cancer cells is clearly regulated by Stat3 in the mitochondria. The proposed studies in this application will allow us to better understand not only how Stat3 and its interactions with cyclophilin D regulate tumor growth, but also to examine how these two proteins may mediate resistance to doxorubicin, one of the primary drugs used to treat breast cancer. Completion of these studies will provide us with the information to identify new approaches to screen for other Stat3 controlled targets to inhibit the growth of breast cancer cells.