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Investigation of the Mechanism of Inhibition of Thiosemicarbazone Inhibitors of Cathepsin L

The major cause of death from cancer is not the initial formation of a tumor but the spread and growth of cancerous cells to distant locations. This process is called metastasis and requires the degradation of the extracellular matrix surrounding the tumor, access of the tumor cells to the circulating blood or lymph, egress from circulation, and colonization of distant tissues. Specific proteolytic enzymes (enzymes that degrade proteins) play an essential role in this process and are often produced in large amounts by metastatic cancer cells. Cathepsin L is one such enzyme and is the target of our investigation. Most cathepsin L is found in cells where it degrades proteins extensively in some cases, while in other examples it processes them to a limited extent to regulate cell growth. Cathepsin L is also secreted from cells where it degrades proteins in the extracellular matrix under normal and pathological conditions. In many cancers, the secretion and activation of cathepsin L is accelerated. Our basic premise is that blocking the action of cathepsin L will delay or arrest cancer metastasis. A long-standing collaboration between the Trawick Research Group and the Pinney Research Group at Baylor University has resulted in the discovery of a privileged library of small-molecule inhibitors of cathepsin L. The most promising compounds are thiosemicarbazone derivatives that demonstrate potent (nanomolar range) inhibition of cathepsin L. Some of these compounds are selective for cathepsin L in comparison to related enzymes (cathepsin B and cathepsin K), and have been shown to inhibit the migration and invasion of cancer cells through Matrigel^{TM}, which is a substitute for the extracellular matrix – hallmarks of an anti-metastatic agent. To advance these compounds for potential therapeutic application, it is essential that we understand (1) the mechanism of inhibition of cathepsin L (which we will investigate through advanced kinetic studies); and (2) the specific mechanism of inhibition of cancer cell migration and invasion through Matrigel^{TM} (addressed through cell signaling studies).