Sticky Situations:  
A Story of the Rebel Mammary Serine Protease Inhibitor


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Abstract:
In 2007 alone, an estimated 180,000 women and 2,000 men were diagnosed with breast cancer. Malignant cells in breast tissue rapidly reproduce and can metastasize, thus spreading cancerous cells throughout the body. If cells metastasize, they detach from the extracellular matrix (ECM), but if they remain attached to the ECM, cells cannot metastasize. This behavior has been linked to the expression of Maspin in mammary cells. Maspin, or Mammary Serine Protease Inhibitor, is a member of the serpin family, members of which deactivate serine proteases, enzymes that cleave proteins which contain serine residues. Serine proteases aid in many functions of the body, including blood clotting and digestion. Maspin adopts a classical serpin protein fold, but is classified as a non-inhibitory/non-classical serpin as it does not have any known serine protease targets to inhibit. Instead, the reactive site loop (RSL) of Maspin stimulates the adhesion of cells to the ECM. This action prevents the migration of cells, thus preventing metastasis. It has been found that the RSL of Maspin alone is capable of producing the increased adhesion of cells to the ECM. Recent research has determined that substituting alanine for arginine at position 340 in the RSL loop reduces the adhesion of cells to the ECM. Current research is attempting to determine the method by which Maspin functions, and which key amino acids on the RSL loop are responsible for increasing cell adhesion. With this new research, scientists are one step closer to developing an effective drug to control the metastasis of breast cancer cells.

I. Introduction:
Scientists and doctors around the world are working toward a cure for breast cancer, one of the most common types of cancer. These cancerous cells can spread to other parts of the body through a process called metastasis. Recent research has linked the metastasis of cells, or lack thereof, to a protein called Maspin. Maspin has been found to aid in the adhesion of cells to the extracellular matrix.

II. The Extracellular Matrix:
The presence of Maspin, which exists in breast tissue, has been found to correlate with the adherence of cells to the extracellular matrix, or ECM. The ECM refers to the structure in the region outside cells composed of fibrous proteins and complex carbohydrates. When cells adhere to this matrix, their mobility is severely limited. When cells detach from the ECM, they are able to move throughout the body. Maspin in cells has been found to increase the adherence of the cells to the ECM, reducing their ability to move. This may prevent cancerous cells from metastasizing.

III. The Model:
The nine alpha-helices have been highlighted in purple and the three beta-sheets in blue. Though the presence of these secondary structures defines members of the Serpin (Serine Protease Inhibitor) family, Maspin does not function like other Serpins. The key to its function is the Reactive Site Loop (RSL), which has been highlighted in orange. It has been found that the RSL alone is capable of increasing cell adhesion to the ECM.

IV. The Method:
In the picture below, scientists are attempting to determine which amino acids in the RSL of Maspin are responsible for preventing metastasis of cancerous cells. In order to do this, researchers are altering the amino acids in the protein to see what affect mutating specific amino acids has on the function of the protein. To accomplish this mutation, researchers mutate the DNA responsible for the production of the protein. The altered DNA is then placed inside cells, which then produce the desired mutation in the protein.

V. Data:
This graph displays the adhesion of MDA MB cells (breast cancer cells) to fibronectin, the molecule in the ECM to which cells adhere. The RQ mutant is where the arginine (R) in the RSL of Maspin was changed to glutamine (Q), and the RA mutant is where the arginine was changed to alanine (A). No Maspin was applied to the cells in the control. Since glutamine is similar in structure to arginine, it did not affect Maspin’s function. Alanine, which is much different in structure, diminished the adherence of cells to fibronectin.

VI. A Step Forward:
Scientists have discovered that a mutation in the RSL at position 340 diminishes Maspin’s ability to induce adhesion of cells to the ECM. Though arginine typically occupies this place in the loop, when Maspin is mutated to produce alanine in this position, it no longer prevents metastasis. From this, it is known that the arginine residue at position 340 plays a key role in Maspin’s function. With this discovery and ongoing research, science and medicine may be one step closer to a viable cancer treatment.