Researchers learn why PSA levels reflect prostate cancer progression

January 13 2011

Researchers at the Duke Cancer Institute who have been studying prostate cancer cells for decades now think they know why PSA (prostate-specific antigen) levels reflect cancer progression.

"This is the first demonstration of a mechanism that explains why PSA is a bad thing for a tumor to produce," said senior author Sal Pizzo, M.D., Ph.D., chair of the Duke Department of Pathology. "I am willing to bet there is also a connection in cancerous cell growth with this particular biological signaling mechanism happening in other types of cells."

Using human prostate cancer cells in a laboratory culture, the team found that an antibody reacts with a cell surface receptor called GRP78 on the cancer cells to produce more PSA. The PSA arises inside of the cancer cell and then moves outside of the cell, where it can bind with the same antibody, called alpha2-macroglobulin (α2M).

The PSA forms a complex with the antibody that also binds to the GRP78 receptor, and that activates several key pathways which stimulate cancer cell growth and cell movement and block cell death.

The study bolsters the case for measuring PSA as a marker of tumor progression, as well as for monitoring for α2M antibody levels.

"The use of PSA to make the initial diagnosis of prostate cancer has become controversial over the past decade," Pizzo said. "I personally believe PSA is more useful as a progression marker, particularly with a

baseline value on record at the time of the original therapy. A rapidly rising value and/or a very high value is reason for concern. I also believe that monitoring the serum for the appearance of antibodies directed against GRP78 is also a good marker of progression."

Pizzo said that the findings could yield cancer therapies that block the α2M-PSA complex from stimulating the cell receptor signaling cascade, and that his laboratory is investigating possibilities. He said the findings also might yield new kinds of early-detection tests for prostate cancer.

The study will be published in the Jan. 14 edition of the *Journal of Biological Chemistry*.

Pizzo credits lead author and signaling pathway expert, biochemist Uma Misra, Ph.D., with deducing that PSA may be involved in a signaling feedback loop that promotes more aggressive behavior in the human prostate cancer cells.

"If you were a cancer cell, you would like to turn on cell growth, turn off the process of death by cell apoptosis and you'd like to be able to migrate, and when the α2M antibody binds with the protease PSA molecule, all of that happens," Pizzo said.

Years ago, Misra discovered the GRP78 receptor on the prostate tumor cell surface, the receptor that binds the α2M antibody and the α2M-PSA complex.

"We were surprised to find that this complex binds with the protein GRP78, because we thought the GRP78 molecule only lived deep inside the cell, where it was busy taking improperly folded proteins and helping them to fold properly," Pizzo said. "It was a surprise to find GRP78 on the cell surface, with other functions. Based on the dogma of the time, we didn't think that GRP78 could function as a receptor. Even when we

identified it, I doubted our findings."

Pizzo said that since Misra first made the observation about GRP78 working as a receptor, "it has turned into a cottage industry. GRP78 receptors have been discovered on many other cancer cells, including breast, ovary, liver, colon, melanoma and lung cancer cells."

"This is going to be a generic phenomenon to tumors," predicted Pizzo, who is also working to learn more about this receptor in other types of cancer cells. "Not all tumors will express GRP78 on their cell surfaces, but when they do, it probably will be a harbinger of a bad outcome."

"I think we will find that nature favors conservation and it makes sense that the body uses the same types of molecules for different purposes," Pizzo said. "We are beginning to see more of this in other studies, and I predict we will see many more instances."

Provided by Duke University Medical Center