Medical Xpress

Protein handlers should be effective treatment target for cancer and Alzheimer's

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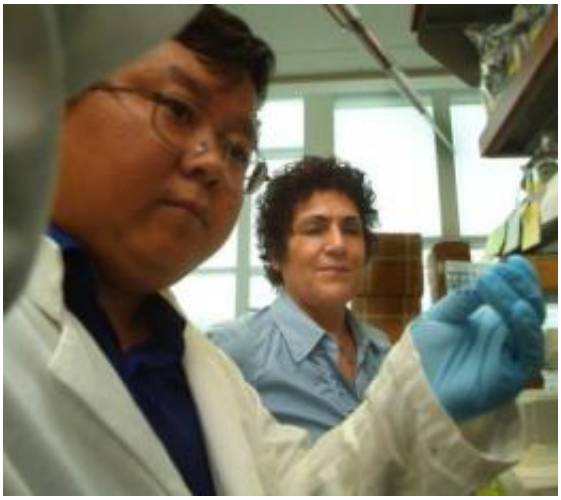

Dr. Xiongjie Jin (left), assistant research scientist, and Dr. Nahid Mivechi are exploring the role of molecular chaperones and heat shock factors in cancer. Credit: Medical College of Georgia

Cancer and Alzheimer's have excess protein in common and scientists say learning more about how proteins are made and eliminated will lead to better treatment for both.

Medical College of Georgia researchers Drs. Nahid F. Mivechi and Dimitrios Moskofidis have received two National Cancer Institute grants totaling nearly $3 million and a $982,800, four-year grant from the U.S. Department of Veterans Affairs in the last 12 months to support studies of proteins and the molecular chaperones that manage them from cradle

to grave.

Understanding the exact role molecular chaperones play in cancer and Alzheimer's should lead to better ways to intervene in both, says Dr. Mivechi, director of the MCG Center for Molecular Chaperone Biology/Radiobiology and Cancer Virology.

Everyone needs molecular chaperones which prompt genes to make proteins, move proteins around the body, fold them up into the proper shape to function properly and even haul them off when they no longer work. Cancer needs them even more for the endless cell replication required for tumor growth, Dr. Mivechi says. Essentially the opposite happens in Alzheimer's in which excess protein is a major component of the destructive brain plaque that is the disease's hallmark. Dr. Mivechi believes molecular chaperones, which typically slow in activity with age, are failing at their job so that proteins aggregate in the brain, contributing to Alzheimer's and other neurodegenerative diseases in which brain cell communication is interrupted.

The MCG center has evidence that disabling molecular chaperones or the heat shock factors that control some of them, disables tumor formation in the liver and probably the breast. Researchers are also now examining brain tumors as well as pancreatic and prostate cancer.

They also want to know whether ramping up the activity of molecular chaperone can essentially make them act young again and halt development of Alzheimer's, Parkinson's and other neurodegenerative diseases.

"We have to find the balance," Dr. Mivechi says of the center's concurrent work to find drugs that adjust the activity of molecular chaperones and heat shock factors. She theorizes these drugs would be used for limited periods to avoid trading cancer for an increased risk of

neurodegenerative disease or vice versa.

"A lot of drugs, such as chemotherapeutic agents, can kill cancer but they also kill normal tissue. That is a limiting factor. We are looking for better drugs," she says.

The MCG center is among the first to study molecular chaperones and heat shock factors in animals to better understand their role in these diseases. Drs. Mivechi and Moskofidis, a viral immunologist, have developed 20 mouse models missing different molecular chaperones or heat shock factors in the last decade to help explore the large family of molecular chaperones. For contrast, they also have a mouse that over expresses heat shock factor 1, or Hsf1, a major activator of molecular chaperones.

They are now focusing on developing mice that lack molecular chaperones or heat shock factors in targeted areas, such as liver or breast tissue, as well as mice in which these can be removed during cancer to determine what impact their loss has on active disease. They also are cross breeding the mice, to create one, for example, that also over expresses the molecule, Her2/Neu, which is over active in some of the most aggressive breast cancers. By comparing the resulting mouse to one that just over expresses Her2/Neu, they can examine the impact of Hsf1, Dr. Mivechi says.

"That is how these findings will translate to patients," Dr. Mivechi says. "We need to know, not only how deleting or augmenting molecular chaperones and heat shock factors affects disease development, but also how it impacts disease progression."

Their studies also will help researchers pinpoint which molecular chaperones and/or heat shock factors are associated with a specific type of cancer or neurodegenerative disease which will help in the design of

targeted therapies.

With the VA-funded study, for example, when they remove a specific molecular chaperone they find Alzheimer's-like disease accelerates dramatically in their animal model. They want to expand these studies to look at traumatic brain injury as well as other neurodegenerative diseases .

Source: Medical College of Georgia