Medicinal chemist develops imaging tools to target degenerative diseases

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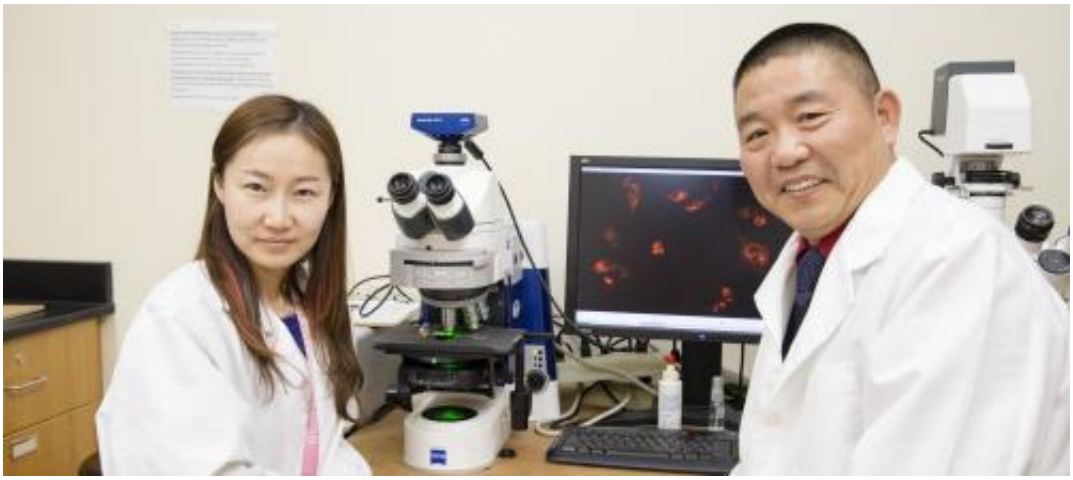

Doctoral student Yang Yang and pharmacy professor Xiangming Guan

Neurodegenerative diseases, such as Alzheimer's and Parkinson's, affect more than 6.4 million Americans, according to the Harvard NeuroDiscovery Center. That number may double in the next 30 years as the population ages, unless medical researchers figure out what's happening at a cellular and molecular level and develop ways to treat or prevent these debilitating conditions.

Aging and oxidative stress are the culprits, but the challenge is to determine which cells, and even subcellular structures, are affected, according to pharmacy professor Xiangming Guan. The medicinal chemist is developing imaging techniques that will help researchers

identify what might be contributing to the course a degenerative disease takes.

Tracking the body's natural antioxidant

Organic molecules called thiols play a major role in defending the body against oxidative stress, Guan explained. These antioxidants, which are present inside and outside of cells, counteract the effect of reactive oxygen molecules known as free radicals which are involved in oxidative stress. Free radicals can disrupt normal cell functions.

"Thiols are consumed during oxidative stress, so we see lower thiol levels," Guan said. "Therefore, the level of thiols is used as one of the indices that reflect whether there is oxidative stress."

Drinking alcohol, for instance, can damage the liver, Guan explained. Thiols can quench the toxic effect of alcohol, but once they are depleted, the body cannot defend itself. Similarly, damage to nerve cells can then lead to degenerative diseases such as Parkinson's disease and multiple sclerosis.

Improving analytical tools

Postdoctoral research associate Bhimanna Kuppast mixes experimental compounds that are designed to react with thiol on the cell surface and in mitochondria.

Through National Institutes of Health grants for nearly $800,000, Guan and his team developed the first imaging reagent that can determine thiol levels in intact living cells. Previous methods of determining thiol concentrations required the destruction of the cells and tissue.

"We found a compound which can determine thiol density in live cells in a quantitative way through a particular type of chemical reaction," he

said. In the presence of thiol, the chemical gives off fluorescence—the higher the thiol level, the higher the fluorescence. Decreased fluorescence means thiols have been consumed trying to protect the cell, meaning it is more likely to be damaged.

With a new three-year NIH grant for $327,500, Guan hopes to develop reagents that can selectively show thiol density in subcellular structures, specifically the nucleus and mitochondria.

"These are crucial subcellular organs," Guan said, comparing the function of cell mitochrondria to that of the heart.

Furthermore, cell nuclei contain DNA, which can be altered by oxidative stress.

"The distribution of thiols within the cell is not even," he said.

Medical researchers now use a centrifuge to separate subcellular structures because their weights are different. Thiol concentration in the mitochondria can be determined via this centrifugal method, but not the thiol distribution and density within the mitochondria, Guan pointed out.

In addition, "thiol levels in the nucleus cannot be accurately determined since thiols leak out during isolation."

Examining subcellular structures

When dealing with age-related degenerative diseases, Guan said, "There are a lot of unknowns." If Guan and his team are successful, scientists will have an analytical tool to monitor how thiols in subcellular structures affect degeneration.

For example, if researchers see a marked decrease in mitochondrial thiol before onset of Alzheimer's symptoms, Guan explained, "perhaps we can find a way to deliver thiol into the mitochondria to prevent or slow that down."

Furthermore, scientists can use this analytical tool to determine if an intervention protected the subcellular structure, Guan noted. He hopes to develop a nontoxic reagent safe enough to be used for diagnostic imaging, like an MRI.

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