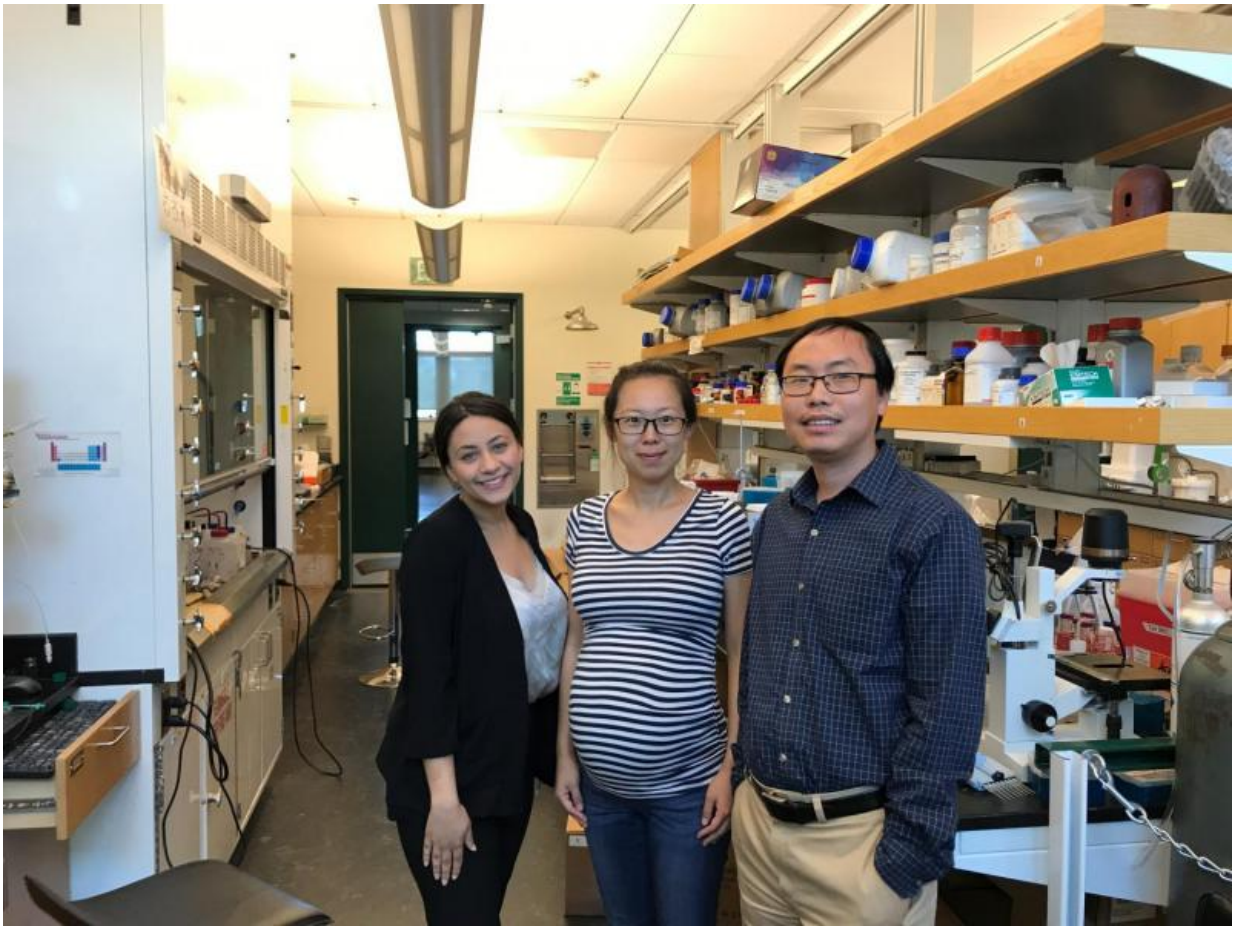
Biosensors light up cellular signaling processes

July 17 2017, by Sarah Nightingale



Lab members (left to right): Merna Makar, Yichong Fan, and Huiwang A.
Credit: ucr

Researchers at the University of California, Riverside have converted a naturally occurring fluorescent protein from corals into a biosensor that can be used to monitor the cellular thioredoxin (Trx) system, which is a promising target for cancer therapy.

Their paper, titled "Monitoring thioredoxin redox with a genetically encoded red fluorescent biosensor," was recently published in *Nature Chemical Biology*. The research team includes Huiwang Ai, an associate professor in Department of Chemistry; Yichong Fan, a graduate student in the Environmental Toxicology program and lead author of the paper; Merna Makar, an undergraduate student; and Michael Wang, a high school student who is gaining research experience at UCR.

The Ai lab develops novel molecular imaging tools to peer inside cells and understand their communications and signaling processes. One of their focuses is the spatio-temporal organization of redox signaling and its disruption under oxidative stress. Redox processes are a major regulatory component of cellular signaling in humans. Reactive oxygen species (ROS), which are oxidative chemicals generated by cells in response to various signals, play a dual pathophysiological role: on one hand mediating physiological signal transduction pathways, while on the other hand causing oxidative stress when their levels are high. Severe oxidative stress can lead to cell damage and death and a variety of diseases.

Thioredoxin (Trx) family proteins play critical roles in the regulation of cellular redox processes. Clinically, it has been shown that Trx levels are elevated in the plasma of patients with solid cancer and leukemia, and decreased when the tumor is surgically removed. The Trx system is thus a validated cancer drug target and drugs that inhibit the Trx system are now in clinical development with early promising results. In addition, the Trx system has been proposed as a drug target for certain bacterial and parasite infections.

The technical difficulty in direct monitoring the redox status of Trx in live cells has greatly hindered investigations on the roles of the Trx redox system and the interaction between Trx and other cell signaling components. Now, the Ai lab has addressed this gap by creating the first genetically encoded fluorescent biosensor that can directly monitor the redox status of Trx in live mammalian cancer cells. Combining protein engineering and fluorescence imaging techniques, the sensor they developed, named TrxRFP1, has successfully monitored compartmentalized redox dynamics of Trx caused by various cancer drugs across different cancer cell types.

This new sensor unlocks new opportunities for understanding the biology of cellular Trx, and moreover, for high-throughput screening of novel molecular modulators of the Trx system. Yichong Fan, a graduate student in Ai's lab, is currently working on rapid and quantitative screening of compound libraries using TrxRFP1 as an indicator. The screening may lead to the identification of potential inhibitors of the Trx system, which may have therapeutic applications.

More information: Yichong Fan et al. Monitoring thioredoxin redox with a genetically encoded red fluorescent biosensor, *Nature Chemical Biology* (2017). DOI: 10.1038/nchembio.2417

Provided by University of California - Riverside