Fluorescent proteins illuminating biomedical research

January 25 2009

Remarkable new tools that spotlight individual cellular molecules are transforming biomedical research. Scientists at the Gruss Lipper Biophotonics Center at the Albert Einstein College of Medicine of Yeshiva University have spearheaded their use in a series of papers, including one published today in the online version of *Nature Methods*.

These new tools are photoactivatable fluorescent proteins (PAFPs) and other advanced fluorescent proteins (FPs), several of which have been developed by Vladislav Verkhusha, Ph.D., associate professor of anatomy & structural biology at Einstein, and a member of the Biophotonics Center. PAFPs and FPs allow scientists to noninvasively visualize the structures and processes in living cells at the molecular level. It is now possible, for example, to follow cancer cells as they seek out blood vessels and spread throughout the body or to watch how cells manage intracellular debris, preventing premature aging.

These new fluorescent proteins add considerably to the biomedical imaging revolution started by the 1992 discovery that the gene for a green fluorescent protein (GFP) found in a jellyfish could be fused to any gene in a living cell. When the target gene is expressed, GFP lights up (fluoresces), creating a visual marker of gene expression and protein localization, via light (optical) microscopy. Three scientists won The 2008 Nobel Prize in Chemistry for their GFP-related discoveries. Fluorescent proteins of other colors have since been found in marine organisms such as corals.

While this form of imaging is invaluable, it is limited by the inherent nature of optical microscopy, which cannot image details of objects smaller than 200 nanometers or so. However, many cellular structures, which could hold the key to managing or curing disease, are a small fraction of that size — just a few nanometers or more.

Using a sophisticated combination of lasers, computers, and highly sensitive digital cameras, scientists have been able to surmount the barriers of optical imaging. The first generation of these new imaging devices, collectively known as super-resolution (SR) fluorescence microscopes, were able to capture images as small as 15 to 20 nanometers — the scale of single molecules. But this could be done only in non-living cells. The addition of PAFPs, more versatile versions of FPs, made it possible to do real-time SR fluorescence microscopy in living cells. Last month, *Nature Methods* selected SR fluorescence microscopy as the 2008 Method of the Year.

Dr. Verkhusha has developed a variety of PAFPs and FPs for use in imaging mammalian cells, expanding the applications of fluorescence microscopy. Among these are PAFPs that can be turned on and off with a pulse of light, FPs that can fluoresce in different colors, and FPs that have better resolution for deep-tissue imaging.

Most recently, Dr. Verkhusha developed a red PAFP called PAmCherry1, which has faster photoactivation, improved contrast, and better stability compared to other PAFPs of its type. "PAmCherry1 will allow improvements in several imaging techniques, notably two-color SR fluorescence microscopy, in which two different molecules or two biological processes can be viewed simultaneously in a single cell," explains Dr. Verkhusha. The findings were published today in the online version of *Nature Methods*.

Several studies have employed Dr. Verkhusha's PAFPs, revealing new

insights into a variety of biological processes. For example, one of his PAFPs was used to capture the first nanoscale images of the orientation of molecules within biological structures. "Such images could be useful in studying protein-protein interactions, the growth and collapse of intracellular structures, and many other biological questions," says Dr. Verkhusha. The results were published in November 2008 in *Nature Methods*.

In yet another *Nature Methods* study, also published in November 2008, Dr. Verkhusha contributed a novel PAFP to a new method of viewing individual breast cancer cells for several days at a time, providing new details on how cancer cells invade surrounding tissue and reach blood vessels, a process called metastasis. "Mapping the fate of tumor cells in different regions of a tumor was not possible before the development of the photoswitching technology," explains John Condeelis, Ph.D., co-chair and professor of anatomy and structural biology and co-director of the Gruss Lipper Biophotonics Center.

In addition, Dr. Verkhusha has developed new types of fluorescent proteins for use in conventional fluorescent microscopy. These new fluorescent proteins, called fluorescent timers (FTs), can change their color from blue to red over a matter of hours. "These FTs will enable scientists to study the trafficking of cellular proteins and to provide accurate insight into the timing of intracellular processes, such as activation or inhibition of gene expression or protein synthesis," says Dr. Verkhusha.

Together with another Einstein scientist, Ana Maria Cuervo, M.D., Ph.D., associate professor of developmental & molecular biology, anatomy & structural biology, and medicine, Dr. Verkhusha employed the FTs to demonstrate for the first time how a protein called LAMP-2A, which scavenges cellular debris, is transported to intracellular organelles called lysosomes, where the debris is digested.

Understanding this process, which maintains the health of cells and organs, may lead to treatments to keep elderly people's organs in prime condition. The findings were published in the January 11 issue of *Nature Chemical Biology*.

Source: Albert Einstein College of Medicine

Citation: Fluorescent proteins illuminating biomedical research (2009, January 25) retrieved 27 April 2024 from
https://phys.org/news/2009-01-fluorescent-proteins-illuminating-biomedical.html

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