Design and Synthesis of Cyanine Dyes for Selective Targeting and Imaging of Cellular Mitochondria

INDEX NO.: 76/18/Chem./25

Abstract: The development of selective organelle targeting agents with various imaging modalities is a promising approach for early detection and diagnosis of cellular organelle related deadly diseases. However, rational control for selective targeting of cellular organelles using small molecule fluorescent probes has remained a challenge due to the highly complicated cellular environment. Among all other cellular organelles, mitochondria are unique and indispensable, which not only harness energy through ATP production but also play a pivotal role in regulating cellular protein homeostasis, oxidative metabolism and maintaining intracellular redox balance. In contrary to other cellular organelles, mitochondria are arduous to target because of their distinctive double layer membrane and exceptionally negative inner mitochondrial membrane (IMM) potential [$(\Delta\Psi_m)_{normal} \approx -150$ to -180 mV] that act as barriers for the ingestion of molecules. Moreover, in cancer cells IMM potential [$(\Delta\Psi_m)_{cancer} \approx -220$ mV] is much more hyperpolarized compared to normal cells. In my research work, I have utilised the aforementioned extraordinary biophysical membrane property and hydrophobic nature of mitochondria for the development and synthesis of symmetrical as well as unsymmetrical cyanine fluorophores and their peptide conjugates for selective targeting and imaging of cellular mitochondria. A water soluble lipophilic cationic dual targeting NIR unsymmetrical cyanine-5 probe conjugated with maleimide and mitochondria targeting triphenylphosphonium (TPP^+) functionalities has also been developed for selective targeting and labeling of cysteine (Cys) exposed proteins inside the live cell mitochondria. These cyanine dyes exhibit high photostability, NIR absorption/emission, high molar extinction coefficient, narrow absorption/emission band, high fluorescence lifetime, and high fluorescence quantum yield. Mitochondrial target specificity of all the fluorophores is demonstrated by colocalization experiments carried out with the commercially accessible mitochondrion-tracking probes. Moreover, the mitochondria targeted NIR cyanine/peptide conjugates reaches the critical aggregation concentration inside the mitochondria of cancer cells due to the strong negative inner mitochondrial membrane potential [$(\Delta\Psi_m)_{cancer}$ -220 mV] and self-assembles to form amyloid fibrils or other nanostructures at the target site, which is responsible for the mitochondrial dysfunction and cytotoxicity. The narrow excitation and emission bands also make these probes a perfect choice for multicolor cellular imaging.

Samit Guha 22/07/2022

Signature with Seal of the Supervisor

Dr. Samit Guha
Assistant Professor
Department of Chemistry
Jadavpur University
Kolkata-700032, India

Pranab Chandra Saha
22/07/2022

Full Signature of the Candidate