DNA nanoprobe for real-time imaging and simultaneous quantification of mitochondrial Ca^{2+} and pH in neurons induced by superoxide anion and aggregated amyloid beta

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Mitochondria play vital roles in cellular energy production, signal transduction and Ca^{2+} homeostasis, as well as the cell death. Besides, mitochondrial pH and Ca^{2+} are closely associated with cellular functions and diseases. Thus, simultaneous imaging and biosensing are essential for understanding inter-relationship between Ca^{2+} and pH in physiological and pathological processes. Herein, we created a highly selective DNA nanoprobe for real-time imaging and simultaneous quantification of pH and Ca^{2+} in mitochondria, in which a new Ca^{2+} fluorescent probe was synthesized and assembled onto a DNA nanostructure together with pH-responsive, inner-reference, and mitochondria-targeted molecules. This new nanoprobe powerfully tracked pH and Ca^{2+} dynamics at the same localization in response to superoxide anion ($O^{2\bullet-}$)-induced oxidative stress and aggregated amyloid beta (Aβ) stimulation with a temporal resolution of milliseconds. Using this new tool, we discovered that acid-sensing ion channel 1a (ASIC1a) channel plays a vital role in $O^{2\bullet-}$ and Aβ-induced mitochondrial Ca^{2+} burst, which may contribute to neuron death. Moreover, psalmotoxin 1 (PcTX1) effectively protects against neuron injury, providing a potential drug for $O^{2\bullet-}$ and/or Aβ-induced neuronal death. Using the DNA-assembled nanosensor for determination of pH and Ca^{2+} at the same localization, we demonstrated that mitochondrial Ca^{2+} is increased ~4-fold in neurons compared with HeLa cells, whereas mitochondrial pH exhibits no obvious difference between the two types of cells. Furthermore, experimental results demonstrated diverse mitochondrial Ca^{2+} and pH values in different regions of neurons. The close relationship between Ca^{2+} and pH in mitochondria was discovered. Mitochondrial pH value in neurons obviously increased with increasing Ca^{2+} concentration, which may be attributed to the function of the Ca^{2+}/H^{+} antiporter in mitochondria. On the other hand, the mitochondrial Ca^{2+} burst can be adjusted by the ASIC1a channel during cytoplasmic acidosis. O2•- induces transitory cytoplasmic acidosis, which may activate the ASIC1a channel in the mitochondrial membrane, resulting in alkalization and Ca^{2+} overload in mitochondria. Mitochondrial Ca^{2+} overload is possibly one of the important factors in $O^{2\bullet-}$-induced neuronal death. These results offer a new view for understanding the signaling pathway of ROS-induced oxidative stress and neuron injury. Aggregated Aβ is highly toxic to neurons. After stimulation by Aβ25-35, the pH value in the cytoplasm clearly decreased together with the Ca^{2+} burst, leading to acidification and Ca^{2+} overload in mitochondria through ASIC1a. PcTX1 protein protect neurons from death by preventing mitochondrial Ca^{2+} overload stimulated by $O^{2\bullet-}$ and aggregated Aβ, suggesting that PcTX1 is a potential drug for $O^{2\bullet-}$ and/or Aβ-induced neuronal death.

Speaker Biography

Yang Tian, PhD is a Professor of Analytical Chemistry in East China Normal University. She received her PhD degree in Electronic Chemistry from Tokyo Institute of Technology. After a Post-doctoral training at University of Tokyo, she was appointed as a Professor in the Department of Chemistry at Tongji University, China in 2005. Then, she joined in East China Normal University as a specifically appointed Professor since 2013. Her research expertise is molecular imaging, biosensor, and bio-nanotechnology for understanding neuroscience. She has coauthored over 70 papers and book chapters.

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