Design of New Sensitive Targeted pH Probes for Mitochondrial, Acidic and Cytosolic pHs Determination by 31-P NMR and EPR

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BIT's 8th Annual World Congress of

Molecular & Cell Biology-2018

Time: October 16-18, 2018
Venue: Fukuoka, Japan
Website: http://www.bitcongress.com/cmcb2018/

Theme 303: Advanced Technologies for Molecular & Cell Biology

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Abstract

In the last decades, spectral techniques such as 31-P NMR and EPR have become privileged strategies for the non-invasive study of the biological events affecting the energetic metabolism and free radical-related processes, respectively. Using NMR, the variations of the cytosolic pH can be monitored though the pH-dependent chemical shift (δ) behaviour of the endogenous phosphate (Pi) resonance peak. However, due to its neutral pKa and poor sensitivity, the Pi 31-P NMR peak cannot precisely probe more acidic vacuoles participating in proton transport mechanisms, or alkaline organelles such as mitochondria. In our search for improved non-invasive pH probing at subcellular level, we recently developed a series of cell permeable α-aminophosphonates with pKa ranging 2–8 and showing a 4-fold improved NMR sensitivity (Δδ up to 11 ppm between the chemical shift of acidic and basic media) as compared to Pi. The same concept was applied to EPR pH measurement by using the 31-P coupling constant a_P of persistent nitroxide free radical probes. This led to the design, synthesis and evaluation of a series of non-toxic pH-sensitive (Δa_P up to 3-4 Gauss between acidic and basic media) and stable β-phosphorylated nitroxides. The presentation will cover the design and the biological applications in vitro and in vivo of selected pH probes in normal and pathological situations.