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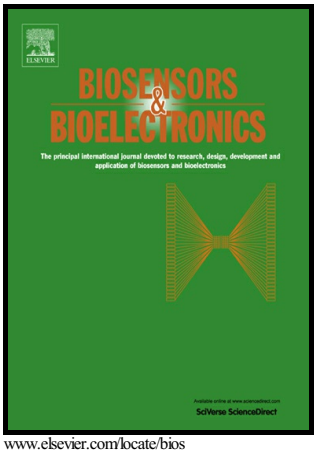

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Functional nucleic acids as *in vivo* metabolite and ion biosensors

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Abstract

Characterizing the role of metabolites, metals, and proteins is required to understand normal cell function, and ultimately, elucidating the mechanism of disease. Metabolite concentration and transformation collected from cell lysates or fixed-cells conceals important dynamic signaling information and differences between individual cells that often have profound functional consequences. Functional nucleic acid-based biosensors are emerging tools that are capable of monitoring ions and metabolites in cell populations or whole animals. Functional nucleic acids (FNAs) are a class of biomolecules that can exhibit either ligand binding or enzymatic activity. Unlike their protein analogues or the use of instrument-based analysis, FNA-based biosensors are capable of entering cells without disruption to the cellular environment and can report on the concentration, dynamics, and spatial localization of molecules in cells. Here, we review the types of FNAs that have been used as *in vivo* biosensors, and how FNAs are coupled to transduction systems and delivered inside cells. We provide examples from the literature that demonstrate their impact for practical applications. Finally, we comment on the critical limitations that need to be addressed to enable their use for single-cell dynamic tracking of metabolites and ions *in vivo.*

Keywords: biosensor; functional nucleic acids; aptamers; DNAzyme; riboswitch; molecular beacon

Introduction

The cell is the fundamental unit of life. Understanding the dynamic interplay between metabolites, metals, and proteins inside the cell, both in normal and diseased states, is a crucial research frontier (Newman et al., 2011; Purvis and Lahav, 2013; Armitage and Barbas, 2014). In particular, the detection and quantification of important molecules can provide insight on the dynamics and kinetics of physiological processes, disease progression, and reveal potential therapeutic targets (Zhang et al., 2013). A great deal has been uncovered about cell function, structure, and metabolic processes through imaging and analytical chemistry (Oikawa and Saito, 2012). For example, while not quantitative, early microscopy and immunocytochemistry provided information about the localization of and interactions between biomolecules (de Matos et al., 2010). Additionally, biomolecules and metabolites inside cells have been both identified and quantified using instrument-based analytical methods, including high-pressure liquid chromatography (Lu et al., 2006), gas chromatography (Vielhauer et al., 2011), mass spectrometry (Luo et al., 2007), and more recently, magnetic resonance imaging (Foster et al., 2008). This fundamental analytical research has provided information about metabolic processes in digested bulk sample (Carter et al., 2014; Trapnell, 2015).