Biosensors and Bioelectronics 85 (2016) 403–413

Contents lists available at ScienceDirect

Biosensors and Bioelectronics

journal homepage: www.elsevier.com/locate/bios

Construction of fluorescent polymeric nano-thermometers for intracellular temperature imaging: A review

Juan Qiao [a,b,1], Xiaoyu Mu [a,b,1], Li Qi [a,b,*]

[a] Beijing National Laboratory for Molecular Sciences; Key Laboratory of Analytical Chemistry for Living Biosystems, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China

[b] University of Chinese Academy of Sciences, 100049 Beijing, China

ARTICLE INFO

Article history:
Received 15 March 2016
Received in revised form
14 April 2016
Accepted 21 April 2016
Available online 6 May 2016

Keywords:
Fluorescent polymeric nano-thermometers
Intracellular temperature
Cell imaging

ABSTRACT

Multitudinous biochemical reactions occur in living cells, creating and releasing free energy to impel numerous cellular activities. Surplus energy is expelled as heat and resulted in elevated temperature, which induce control of gene expression, tumour metabolism and etc. Sensitive measurement of temperature on nanoscale in cells with ideal fluorescent probes is a great challenge in many areas. By taking the advantages of polymers in tunable critical solution temperature range and good biocompatibility, fluorescent polymeric thermometers (FPT) have drawn extensive attention because they are capable of accurate monitoring temperature with high spatial resolution at cellular level. This review offers a general overview of recent examples of FPT working in cells. The strategy for design and synthesis of the FPT has been highlighted. Furthermore, the applications of the constructed FPT for intracellular temperature variations under normal and external stimuli conditions have been discussed. Deep understanding of these aspects would lead to improvement in designing of unique FPT with real function and applications for intracellular temperature sensing. It will pave a new way not only for the study of intrinsic relationship between temperature and organelle function, but also provide the possibility for deep understanding of intracellular biological processes.

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1. Introduction

There is great interesting nowadays for investigation of temperature in nano-scale regime, including living cells and certain

* Corresponding author at: Beijing National Laboratory for Molecular Sciences; Key Laboratory of Analytical Chemistry for Living Biosystems, Institute of Chemistry, Chinese Academy of Sciences, Beijing 100190, China.
E-mail address: qili@iccas.ac.cn (L. Qi).

[1] Juan Qiao and Xiaoyu Mu contributed equally to this work.

http://dx.doi.org/10.1016/j.bios.2016.04.070
0956-5663/

parts of living animals (Nienhausa and Nienhaus, 2014; Wang et al., 2013; Roy et al., 2013), because the intracellular temperature variation pervades deep understanding of the most basic of physical, chemical, and biological phenomena (Frank et al., 2015). Furthermore, the events in living cells including the signal transduction (Xie et al., 2000), the energy conversion (Dufour et al., 1996), cell division (Brown and Rickless, 1949) and transmembrane transport of ions (Huang et al., 2010) are greatly affected by the variation of the intracellular temperature. As the source of energy in cells, significant thermogenesis was found in the hydrolysis process of adenosine triphosphate (ATP) (Lowell and Spiegelman, 2000). In mitochondria, part of the energy produced by ATP was expensed by the ions transmembrane transportation and the superfluous energy was released in the form of heat, which would cause the temperature increasing (Meis et al., 1998). The oxidative phosphorylation in mitochondria which related to ATP formation was also influenced by the intracellular temperature and the abnormal during the oxidative phosphorylation process would rise the intracellular temperature (Kadenbach et al., 2010). Consequently, the temperature monitoring and the intracellular thermal mapping can contribute to not only the explanation of cellular events, but also provide the possibility of finding many diseases at cellular level, which permitting the development of novel diagnostic and the rapeutic methods. For instance, from clinical viewpoint, the temperature in the pathological living cells is higher than normal cells due to their enhanced metabolic activity (Monti et al., 1986; Karnebogen et al., 1993). In a word, the intracellular temperature related to and influenced by the cellular events including gene expression, cell division, metabolism, and enzyme reaction. Thus measuring the cellular temperature would contribute greatly to understanding of the complicated biological processes.

Nevertheless, obtaining accurate temperature in the complex living cells with high spatial and resolution would be a challenging research topic. Moreover, detecting the intracellular temperature distribution maps would be one of the tremendous hotspot for the scientific community. Taking the size of the cells into account, only precise thermometry down to the nano-scale regime could reach the higher requirements in the temperature sensing and mapping in cells where the conventional thermometers could not reach. With the nano thermometric techniques development, some thermocouples (Wang et al., 2011) could measure the temperature variation down to micro and nanoscale. However, these methods would disturb of intracellular activity during the thermocouples introducing into cells. In general, the thermography technology would not injure the cells and could be applied for temperature sensing easily. Otherwise, a series of drawbacks, such as relatively low spatial resolution would obstruct the validation of these nanothermometers for temperature sensing and mapping at cellular level.

The rapid development of optical technology has made it possible to setup a variety of temperature sensing methods in living cells using fluorescence microscopy, which could overcome the inherent defects of the conventional approach due to its advantages: (i) a variety of fluorescence features, such as fluorescent intensity and fluorescence lifetime, changing with temperature could be recorded accurately by the fluorescence microscopy in the physiological temperature range; (ii) fluorescence microscopy method could provide excellent noncontact technology as thermometry in living cells due to its high spatial and temporal resolutions; (iii) fluorescence microscopy could obtain high-resolution optical images and has the ability to acquire in-focus images from selected depths. Thus the fluorescence microscopy including fluorescence imaging microscopy (Kiyonaka et al., 2013), two-photon fluorescence imaging (Maestro et al., 2010) and fluorescence lifetime imaging microscopy (FLIM) (Shang et al., 2013) have been applied for intracellular temperature sensing.

Generally, in intracellular property investigation with fluorescence microscopy, small molecule based organic dyes which possessing high fluorescent quantum yields are more popular applied. However, these fluorophores may also be limited by some drawbacks, including cytotoxicity, photostability and local environment dependence (Resch-Genger et al., 2008).

In recent years, with fast development of nanotechnology, a variety of novel materials have been reported and provide possibility to remedy limitation of small fluorescent molecule, which possess robust and photo stable fluorescent emission (Jaque et al., 2014; Guo et al., 2016; Baleizao et al., 2007; Haro-González et al., 2012; Brites et al., 2012; Wolfbeis, 2015; Peng and Chiu, 2015; Jaque and Vetrone, 2012; Shen et al., 2012; Wang et al., 2014). Among them, the nano materials such as quantum dots (Albers et al., 2012; Yang et al., 2011; Haro-González et al., 2013; Mishra and Huang, 2015), fluorescent polymers (Ye et al., 2011; Qiao et al., 2012), metallic nanoparticles (Shang et al., 2013), proteins (Kiyonaka et al., 2013; Donner et al., 2012), rare-earth doped nanoparticles (Jaque et al., 2013; Vetrone et al., 2010) and nanodiamonds, which have thermo-sensitive property on fluorescence emission in physiological range have been applied as nano-thermometers. The polymeric nano-thermometers, which have well biocompatibility, multifunctional reactive groups and could work at molecular level, are promising tools for intracellular temperature sensing and imaging. Although some reviews in area of thermo-sensitive polymers, temperature-induced polymer phase transitions and the polymeric thermally responsive nanoparticles (Gibson et al., 2013), solvatochromic dyes (Pietsch et al., 2011) have been reported, most of these reviews are focused on temperature sensing properties of nano materials in nano or micro scale. Otherwise, the intracellular temperature sensing and imaging using polymeric nano materials was less covered. Thus, in this review, we highlight recent progress in polymeric nano-thermometers and describe their advantages in design, synthesis, properties and special application for intracellular temperature sensing and imaging. Because composing and structure of polymer will determine the thermal responsive fluorescent properties, the polymeric nano-thermometers covered in this review have been divided into introduction, synthesis of the fluorescent thermo-sensitive polymers (including thermo-sensitive polymers, fluorescent dyes and their combination) and the intracellular temperature imaging (including introducing methods, fluorescent imaging technology, intracellular heat production and temperature imaging). In particular, progress in intracellular temperature variation model in temperature sensing based on fluorescent polymer material is stressed as a novel area to thermometry development. These fluorescent polymer nano-thermometers containing thermo-sensitive polymer and polarity fluorescent dyes are nowadays considered as excellent thermal fluorescent probes.

2. Fluorescent polymeric thermometers

Generally, the fluorescent polymeric thermometers could be classified as thermosensitive polymer based thermometers and nonthermosensitive polymer based ones.

2.1. Thermosensitive polymer based fluorescent thermometers

To realize the temperature sensing purpose and construct of polymeric nano-thermometers, usually, it should compose of thermo-sensitive polymer and fluorescent dyes (“indicator” dyes). The mechanism of the polymeric nano-thermometers could be summarized as following: the phase transition of thermo-sensitive polymers can be translated into the fluorescent dyes signal (Jaque