Biomaterials 146 (2017) 115–135

Contents lists available at ScienceDirect

Biomaterials

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

Review

AIEgens for biological process monitoring and disease theranostics

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ARTICLE INFO

Article history:
Received 29 June 2017
Received in revised form
29 August 2017
Accepted 2 September 2017
Available online 4 September 2017

Keywords:
Biological process
Diagnosis
Theranostics
Aggregation-induced emission
AIE

ABSTRACT

Biological processes are of great significance for the normal physiological functions of living organisms and closely related to the health. Monitoring of biological processes and diagnosis of diseases based on fluorescent techniques would provide comprehensive insight into mechanism of life and pathogenesis of diseases, precisely guiding therapeutic effect in theranostics. It largely relied on fluorophores with the properties of excellent photostability, large Stokes shift, high signal-to-noise ratio and free of aggregation-caused quenching (ACQ) effect. Luminogens with aggregation-induced emission characteristic (AIEgens) could serve as superior agents for biological process monitoring and disease theranostics. Herein, we review the recent results in the aspects of monitoring biological processes such as autophagy, mitophagy, mitochondrion-related dynamics, cell mitotic, long-term cellular tracing and apoptosis as well as the diagnosis of related diseases based on AIEgens in real time. As part of AIEgens and AIEgen-based nanoparticles with the functionalities of drugs, photosensitizers and adjuvants accompanied with imaging, they exhibit huge potential in theranostic systems for image-guided chemotherapy, photodynamic therapy, radiotherapy and so on. Collectively, these examples show the potentials of AIEgens for understanding disease pathogenesis, for drug development and evaluation, and for clinical disease diagnosis and therapy. Future research efforts focused on developing long-wavelength excitable and phosphorescence-emissive AIEgens with improved depth-penetration and minimized background interference for fluorescence and photoacoustic imaging, will extend the potential applications of AIEgens in *in vivo*.

1. Introduction

Biological processes are recognized as a series of biochemical reactions, events and molecular functions that occur in living organisms and are vital for a living organism to live [1]. These processes are specifically pertinent to the function of living cells, tissues and organisms. At molecular level, the actions of biomacromolecules are closely associated with the life. For example, protein-associated activities such as enzyme-catalyzed biochemical reactions in metabolism allow organisms to grow and reproduce, to maintain their structures and respond to environment [2]. The replication and transcription of nucleic acids are critical for the storage and use of genetic information as well as protein biosynthesis [3]. While in cells, subcellular organelles involve in many cellular processes and exert their specific effects on maintaining the normal physiological functions, such as lysosome-mediated autophagy for degradation of damaged substrates inside cells [4], nucleus-related gene expression, post-transcriptional modification and cell division [5], Golgi apparatus-assisted sorting, packaging, processing and modification of proteins [6], and mitochondrion-

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http://dx.doi.org/10.1016/j.biomaterials.2017.09.004
0142-9612/

associated energy generation [7]. Cell events such as differentiation and apoptosis also play critical roles in cellular renewal and maintain balance of the whole organisms [8,9]. Consequently, biological processes are of great significance for the normal physiological functions of living organisms and closely related to the health.

On the other hand, the deregulation and abnormality of biological processes could lead to severe diseases such as cancer, Alzheimer's disease and diabetes mellitus. Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body [10]. Alzheimer's disease seriously threatens the brain due to neurodegenerative disorders, which are mainly caused by the large-scale aggregation of β-amyloid protein to form plaques [11]. Diabetes mellitus is a group of metabolic diseases caused by the lack of insulin which is a hormone in bloodstream to convert the blood glucose to glycogen [12]. Supposing that disease-related biological processes, such as enzyme-catalyzed reactions, protein fibrosis, abnormal mitochondria dynamics, pathological apoptosis, cancer proliferation, invasion, and metastasis, could be monitored on-site and in-time, it would benefit the deep insight into pathogenesis of diseases and precisely guide therapeutic effect in theranostics. Therefore, development of techniques that enable real-time monitoring and long-term tracing biological processes with high resolution and sensitivity is of critical importance in both fundamental biological science and practical clinical applications.

To date, many techniques have been utilized in monitoring and visualizing biological processes. Electron microscopes such as scanning electron microscope (SEM) [13] and transmission electron microscope (TEM) [14] can provide very high image resolution but they are complicated in sample preparation and operation. Besides, the sample must be fixed on the substrate and investigated under vacuum, thus study on cell dynamic is hardly realized. Positron emission tomography (PET) [15] and computed tomography (CT) [16] are imaging techniques that are used to observe metabolic processes in the body, however, they have drawbacks of low resolution, radiation exposure risk, contrast medium harmful for health and complex equipment with high cost. Magnetic resonance imaging (MRI) [17] exhibits high resolution and sensitivity as well as label free, however the cost is very high and the throughput is rather low. The operation cost of ultrasound [18] is low and easy to access. Unfortunately, it bears very low resolution and signal-to-noise ratio. Because of these shortages, all of them are difficult to be used to monitor the biological processes *in situ*. Recently, emerging fluorescent techniques as new approaches have been widely used in biomedical domain especially in observation of cellular and molecular events [19–22], as they possess the advantages of high resolution, sensitivity and contrast, simple and fast operation, and real-time fashion. The Nobel Prizes in 2008 and 2014 were presented to the scientists who worked in the field of fluorescent materials and techniques.

Thanks to the enthusiastic effort by researchers, various types of fluorescent probes and techniques were developed for biological imaging. Fluorescent proteins (FPs) [23] show high selectivity and biocompatibility but they suffer from inevitable decomposition by enzymes, high cost and easy photobleaching. Quantum dots (Q dots) [24] enjoy high emission efficiency and facile biomodification, but their variety is limited and cytotoxicity is still a major concern. In comparison, organic fluorophores are relatively less toxic than the heavy metal-containing Q dots [25]. And their emission can be readily tuned by molecular engineering, however, conventional organic fluorophores encounter aggregation-caused quenching (ACQ) effect due to the π-π stacking [26]. As shown in Fig. 1A, fluorescein (**1**), in dilute water solution, displays strong

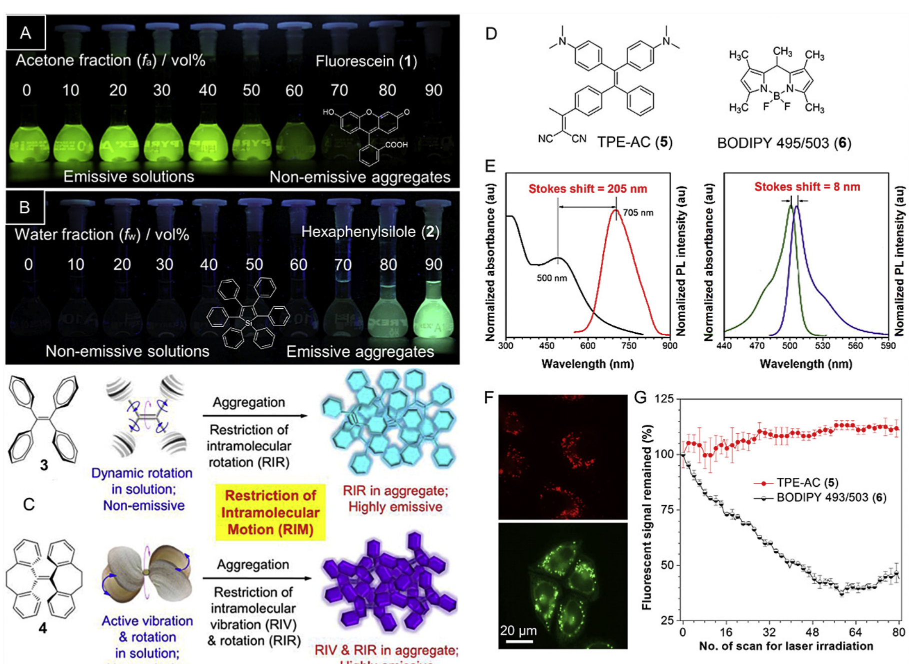

Fig. 1. (A and B) ACQ and AIE phenomena: fluorescent images of solutions and aggregate suspensions of (A) fluorescein (**1**, 15 μM) in water/acetone mixtures with different fractions of acetone (f_a), and (B) hexaphenylsilole (**2**, 10 μM) in THF/water mixtures with different fractions of water (f_w). (C) Restriction of intramolecular motion (RIM) mechanism for AIE: propeller-shaped tetraphenylethene (TPE, **3**) is non-emissive when dissolved but becomes emissive after aggregated, due to the restriction of the intramolecular rotations of its phenyl rotors. Shell-like annulenylidene (**4**) shows AIE activity, due to the restriction of the intramolecular vibration of its bendable vibrators. Images are taken from Ref. [26] with permission. (D) Structures of AIE-active TPE-AC (**5**) and ACQ-featured BODIPY 495/503 (**6**) for lipid droplet imaging. (E) Comparison on the Stokes shift of **5** and **6**. (F) Comparison on the background emission and specificity of **5** and **6** in lipid droplet imaging. (G) Comparison on the photostability of **5** and **6** under laser irradiation. Images are taken from Ref. [29] with permission.