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Advanced optoelectronic nanodevices and nanomaterials for sensing inside single living cell

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ABSTRACT

In recent years, much attention has been gained on the study of single living cell with the development of biology, physics, electrophysiology, and nanotechnology. Researchers from biological and medical sciences regard the cell as a basic unit of life and the work of quantifying, imaging, and modulating living cells has been studied for decades. The dynamic changes in single living cell can reflect the changes and abnormalities of the organism. As such, it is extremely important to analyze living cells on an individual basis so as to illustrate the roles they play in these systems as well as their changes. In addition, the development of highly sensitive measurements applied in the field of analyzing single living cells, may contribute to clinical diagnostics. We present a summary of nanotechnologies resulting from the advances of intracellular analysis based on optoelectronic nanodevices and nanomaterials.

1. Introduction

The cell has been one of the most crucial focuses in life sciences since its first visualization by optical microscopy in the 17th century. Lamarck proposed that all living organisms were composed of cells containing a liquid form; an assumption which has been later verified by Schleiden and Schwann and explained by the current well-known cell theory. Today, an increasing number of researchers including cell biologists, electrophysiologists, biophysicists, and molecular biologists are involved in the study of the surroundings of the cell and contributed meaningfully to the exploratory work.

A single living cell (Fig. 1) is composed of complex biomolecules (DNA, RNA, intracellular enzymes, ions, among others) and subcellular structures (all kinds of organelles), which range from the micron to the nanometer scales. The cell nucleus (11–12 μm in diameter for mammalian cells) (Table 1) , is the biggest organelle in the cytoplasm, and can be metaphorically referred to as the brain of the cell that regulates the metabolism of other organelles. Currently, the cell nucleus has been subject to the most frequent studies concerning topics such as nuclear transfers [1–3], nuclear receptors [4–7] and nuclear matrix proteins [8–10]. Meanwhile, many diseases have been found to be linked to the lesions of organelles. As an example, damages in the endoplasmic reticulum (ER) could cause cardiovascular diseases followed by apoptosis. In addition, damages in the Golgi apparatus can cause to errors during the mitosis and potentially lead to a liver cancer. Furthermore, it has also been observed that Tay-Sachs and some rheumatoid arthritis are caused by the lost or a damaged lysosome. Three scientists who unveiled the transport system of the cell have been awarded with the 2013 Nobel Prize in Physiology or Medicine. According to a Chinese proverb "A journey of a thousand miles must begin with a single step; quantity will finally turn into quality", many diseases occur due to little changes at the molecular scale inside the cells. Therefore, it is of paramount importance to study the single cell at a subcellular level or even at a molecular level.

The different scales and complexity of the intracellular components impose limitations on the development of sensing techniques inside a single living cell. Optical microscopy for the observation of these biological components is limited by the diffraction of the light. For example, the cell microfilament skeleton is very dense and its image by fluorescence microscopy is very fuzzy. Therefore, a growing number of novel technologies such as patch-clamp, nuclear transfer, fluorescent biosensing, surface-enhanced Raman spectroscopy (SERS), single-cell qPCR and single cell gel electrophoresis (SCGE) are developed to analyze single-cells or subcellular organs.

The patch clamp technique, developed in late 1970s, has revolutionized experimental cardiac electrophysiology [11]. The technique has known substantial development and improvement over the time, for examples: action potential clamp [12–15], dynamic clamp [16–19], high-resolution scanning patch clamp [20–

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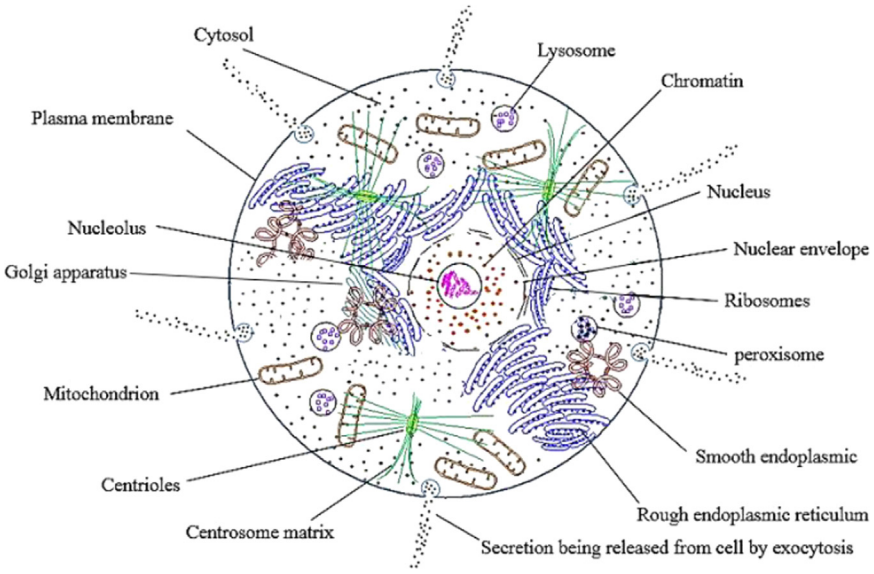

Fig. 1. The structure of a mammalian cell.

Table 1
Sizes and functions of organelles.

Organelle	Sizes	Functions
Nucleus	11–12 μm (for mammalian cells)	(1) Controls the center of the cell (2) Contains the hereditary information of the cell
Rough endoplasmic reticulum	–	(1) Provides membranous surfaces for chemical reactions (2) Connects to the nuclear membrane via a channel (3) Transports the messenger RNA
Smooth endoplasmic reticulum	–	(1) Produces vesicles (2) Provides proteins
Golgi complex	5–10 μm	Stores, modifies, and packages materials in vesicles
Mitochondrion	0.5–1.0 μm in diameter, 1.5–3.0 μm in length	(1) Responsible for the aerobic cellular respiration (2) Digests fat and sugar digestion in the cell (3) Releases energy in the form of ATP
Ribosomes	20–30 nm	Protein synthesis
Lysosomes	0.025–0.8 μm, 120–400 nm in myocardial cells	Digest enzymatically damaged cells, cell parts, or molecules Absent in plant cells
Vesicles	–	(1) Transport substances within the cell (2) Transport substances to the plasma membrane
Centrioles	–	Assist in the organization of microtubule systems Absent in plant cells
Microfilaments	6–10 nm	(1) Provide structural support for the cell (2) Involve in organelles and entire cell movements
Microtubules	15–24 nm in diameter, 6–9 nm in thickness	(1) Provide structural support for the cell (2) Involved in the organelles and entire cell movements
Cytoskeleton	–	(1) Internal framework of the cell (2) Provides the cell with structure and shape (3) Excludes macromolecules from some cytosols
Plastids	–	(1) Chloroplasts are sites for photosynthesis (2) Chromoplasts contain pigments giving color (3) Leukoplasts are often sites for starch storage Absent in animal cells
Vacuole	No basic shape or size	(1) Contains water and solutes, wastes, or nutrients (2) Provides hydrostatic pressure (3) Provides lysosome function in plant cells Absent in animal cells

22], planar patch clamp [23–27], and automated patch clamp [28–30].

It is known that the hereditary information of each cell remains identical to that of the zygote except during the cell differentiation step and for differentiated cells. Nuclear transfer (NT) was used to verify this concept originally through the cloning of animals from differentiated cells [31–33]. It was then used to understand the effects of congenital defects and of acquired changes during phylogenesis or in diseases [33].

With the development of optical technologies, the measurements of single-cells or subcellular level organs are achievable. Mathew et al. from the Harvard Medical School have reported a fluorescent biosensor (PercevalHR) designed for the imaging of energy status (ATP-to-ADP ratio) in live cells. The ATP: ADP ratio could regulate many metabolic activities, hence the significance to measure this physical index at single-cell level. In addition, this fluorescent biosensor can also record electric currents inside a single living cell contributing to the research of the coordinated variation between ATP:ADP and K_{ATP} channels [34].

SERS has become an effective means for sensing biological molecules at high resolution. Specifically, the high sensitivity of SERS provides the possibility for research inside the single living cells [35–37]. In addition, using SERS to measure the intracellular cell redox potential has been possible [38]. El-Said et al. from the Sogang University (Korea) used SERS to monitor the process of metal nanoparticles formation and to analyze the chemical

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