Biomimetic chemical sensors using bioengineered olfactory and taste cells

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Biological olfactory and taste systems are natural chemical sensing systems with unique performances for the detection of environmental chemical signals. With the advances in olfactory and taste transduction mechanisms, biomimetic chemical sensors have achieved significant progress due to their promising prospects and potential applications. Biomimetic chemical sensors exploit the unique capability of biological functional components for chemical sensing, which are often sourced from sensing units of biological olfactory or taste systems at the tissue level, cellular level, or molecular level. Specifically, at the cellular level, there are mainly two categories of cells that have been employed for the development of biomimetic chemical sensors, which are natural cells and bioengineered cells, respectively. Natural cells are directly isolated from biological olfactory and taste systems, which are convenient to achieve. However, natural cells often suffer from the undefined sensing properties and limited amount of identical cells. On the other hand, bioengineered cells have shown decisive advantages to be applied in the development of biomimetic chemical sensors due to their promising prospects and potential applications in many fields such as biomedicine, food and drug industry, and environmental monitoring. By mimic the olfactory and taste transduction mechanisms, biomimetic chemical sensors have been developed using various non-biological materials such as conductive polymers, which are usually developed into sensor arrays to be applied in the construction of electronic noses or electronic tongues. Another strategy is to develop the biomimetic chemical sensors by the utilization of biological functional components such as tissues, cells or receptors originated from the biological olfactory or taste systems. Specifically, olfactory and taste cells can convert the chemical signals into specific cellular responses, which make them ideal candidates for the development of biomimetic chemical sensors. By the combination of olfactory and taste cells

Introduction

Biological olfactory and taste systems play an important role in sensing environmental chemical signals, which are natural chemical sensors that can provide essential information related to food, communication, and behavior. Biological olfactory and taste systems have unique performances for chemical sensing that are unmatched by any artificial devices so far. With the advances in the olfactory and taste transduction mechanisms, more and more efforts have been invested in the development of biomimetic chemical sensors due to their promising prospects and potential applications in many fields such as biomedicine, food and drug industry, and environmental monitoring. By mimic the olfactory and taste transduction mechanisms, biomimetic chemical sensors have been developed using various non-biological materials such as conductive polymers, which are usually developed into sensor arrays to be applied in the construction of electronic noses or electronic tongues. Another strategy is to develop the biomimetic chemical sensors by the utilization of biological functional components such as tissues, cells or receptors originated from the biological olfactory or taste systems. Specifically, olfactory and taste cells can convert the chemical signals into specific cellular responses, which make them ideal candidates for the development of biomimetic chemical sensors. By the combination of olfactory and taste cells
with various transducers, many kinds of biomimetic cell-based chemical sensors have been developed. At present, there are mainly two categories of cells that have been applied in the development of biomimetic chemical sensors, which are natural olfactory or taste cells, and bioengineered cells, respectively. Natural olfactory and taste cells are convenient to achieve but usually suffer from the undefined sensing properties and limited amount of identical cells. On the other hand, bioengineered cells usually require special treatment on the cells in order to achieve functional cells that can respond to the specific chemical signals and thus make them suitable to be used as sensitive elements in biomimetic chemical sensors. The decisive advantages of bioengineered cells for the development of biomimetic chemical sensors are mainly originated from the powerful capability of biotechnology in the reconstruction of the cell sensing properties. Bioengineered cells can be endowed with defined sensing features and generate the cellular responses that can be detected by appropriate transducers. In addition, bioengineered cells can be achieved in a mass-production manner to provide sufficient identical cells for the development of biomimetic chemical sensors. Here, we will briefly summarize the most recent advances of biomimetic chemical sensors using bioengineered olfactory and taste cells. The development challenges and future trends of bioengineered cell-based chemical sensors will be discussed as well.

**Biomimetic Chemical Sensors for Odorant Detection**

Bioengineered olfactory cells are usually achieved by the functional expression of olfactory receptors on the plasma membrane of cells that can be a heterologous cell system or primary olfactory sensory neurons. The expression of olfactory receptors makes the bioengineered cells can respond to the specific odorant molecules and generate the cellular responses via intracellular signal transduction pathway. The most commonly used olfactory receptor is ODR-10, which is an olfactory receptor of *Caenorhabditis elegans* and can specifically interact with its target molecule, diacetyl. A biomimetic chemical sensor has been developed by the utilization of bioengineered human embryonic kidney (HEK)-293 cells expressed with ODR-10 as sensitive elements and surface plasmon resonance (SPR) devices as transducers. The basic mechanism of this biomimetic chemical sensor is using SPR to detect the intracellular components changes originated from the specific interactions between ODR-10 and diacetyl. Upon the exposure of 0.1 mmol/L diacetyl, the responses of bioengineered cells can be detected by monitoring the changes in SPR signals. On the contrary, no significant SPR signal can be detected on the cells without ODR-10 expression upon the same diacetyl exposure. In addition, as for the bioengineered cells, the intensity of the induced SPR signals depended on the concentration of diacetyl in a certain range. However, the underlying mechanism of olfactory signal transduction in a heterologous cell system expressed with olfactory receptors is not yet completely understood, especially the intracellular component changes are not well defined and easy to be influenced by the other factors than the desired chemical signals, which make it difficult to interpret the data and make improvements.

The utilization of bioengineered primary olfactory sensory neurons as sensitive elements for biomimetic chemical sensors makes it possible to use the desired olfactory receptors for chemical sensing as well as to employ the natural olfactory intracellular signal transduction pathway to convert the chemical signals into electrical signals (action potential changes). A biomimetic chemical sensor was reported using the bioengineered primary olfactory sensory neurons expressed with ODR-10 as sensitive elements. Light addressable potentiometric sensor (LAPS) was used to detect the electrical responses of bioengineered cells to diacetyl. The responsive signals were further investigated by the analysis of extracellular potential firings features in frequency domains as well as in time domains. It is indicated that this biomimetic chemical sensor can respond to different concentrations of diacetyl with distinguishable responsive profiles as shown in Figure 1. This demonstrated that bioengineered olfactory sensory neurons can be successfully applied in the development of biomimetic chemical sensors, which has great potential to be applied in the

![Figure 1](image-url)
chemical signal detection as well as for the research of olfactory signal transduction mechanisms.

**Biomimetic Chemical Sensors for Taste Sensation**

Natural taste cells located in the taste buds can be divided into four types based on their differences in morphological features, which include type I (dark), type II (light), type III (intermediate), and type IV taste cells. Type II taste cells are responsible for sensing and transducing of sweet, bitter, and umami signals, which express the specific taste receptors that belong to G protein-coupled receptors (GPCRs). Type III taste cells express acid sensitive ion channels that can respond to sour stimuli and generate cell membrane potential changes. Recently, functional bioengineered taste cells have been utilized as sensitive elements for the development of biomimetic chemical sensors due to their unique capability of detecting target molecules and conversion of detected signals into cellular responses that can be monitored by proper transducers. Bioengineered taste cells can overcome the drawbacks of primary taste cells, which are usually originated from bioengineered cell lines expressed with defined types of taste receptors. Biomimetic chemical sensors have been developed based on the electrochemical measurements, in which human enteroendocrine NCI-H716 cells expressed with sweet taste receptors (gust T1R2 plus T1R3) and human enteroendocrine STC-1 cells expressed with bitter receptors were used as sensitive elements for the detection of sweet and bitter substances, respectively. The specific interactions between taste receptors and taste substances can lead to the morphological changes of bioengineered taste cells via intracellular taste signal transduction. Electrochemical impedance measurements were employed to detect the cellular morphological changes resulted from the specific interactions between taste receptors and taste substances by culturing the bioengineered taste cells on the surface of electrochemical sensors. It is indicated that these biomimetic chemical sensors can realize the specific detection of sweet and bitter substances in a quantitative manner.

An acid-sensitive biomimetic chemical sensor has been developed by the utilization of bioengineered human embryo kidney (HEK)-293 cells expressed with polycystic kidney disease-like (PKD) channels as sensitive elements. A micro electrode array (MEA) chip was employed to record the extracellular potential changes of bioengineered taste cells in response to a set of sour stimulations in a noninvasive way for a long-term. As shown in Figure 2, MEA chip can successfully record the special off-responses of PKD channels in response to a set of sour stimulations. On the contrary, HEK-293 cells without expression of PKD channels show no response to the same set of sour stimulations. It is suggested that this biomimetic chemical sensors cannot only be used for the acid detection, but also can be applied in the research of acid transduction mechanisms.

**Bioengineered Cell-Based Sensors for Chemical Receptor Assays**

More recently, a bioengineered cell-based sensor was developed in order to realize the label-free functional assays of chemical receptors based on the localized extracellular acidification measurement of LAPS chip, especially for the olfactory and taste receptors. Bioengineered HEK-293 cells expressed with a human taste receptor, hT2R4, or an olfactory receptor, ODR-10, was functionally assayed by the utilization of LAPS chip with a movable focused laser illuminating on the desired single cell (Fig. 3). It is indicated that both of chemical receptors can respond to their natural target molecules in a dose-dependent manner within a certain concentration range. On the contrary, HEK-293 cells without any chemical receptor expression show no response to the same chemical stimuli. In addition, the recorded signals were further demonstrated using MDL12330A, which can specifically inhibit the activity of adenylyl cyclase. It is demonstrated that this bioengineered cell-based biosensor have great potential to be used as a novel tool for the label-free functional assays of chemical receptors as well as other GPCRs.

**Conclusions and Prospects**

In the recent decade, biomimetic chemical sensors using bioengineered olfactory and taste cells have achieve significant progress due to the unique capability of bioengineered cells in chemical sensing, which can convert the
chemical signals into cellular responses. Bioengineered cells have been applied in the development of chemical sensors by the combination with various transducers such as LAPS, MEA, and electrochemical devices. Various transducers selected for the development of biomimetic chemical sensors mainly depend on the features of cellular responses. From the most recent advances, it can be concluded that biomimetic chemical sensors using bioengineered olfactory and taste cells have shown great potential and promising prospects, which cannot only be used for the specific chemical detection, but also used for the research of biological chemical sensing mechanisms. However, there are still some key issues need to be addressed in order to achieve further development and practical applications.

The main issue is that the preparation of stable bioengineered cells is usually costive and time-consuming. In addition, the expression efficiency of receptors in a heterologous cell system is usually low. This issue has great influences on their practical applications and gradually become the bottle-neck for further development. One of the future research trends should focus on how to achieve bioengineered cells in a cheaper and more efficient way to advance the development of biomimetic chemical sensors. On the other hand, the coupling between bioengineered cells and transducers has decisive influences on the sensor performances. In the future, the development of nano-technologies and microfabrication technologies may contribute to the coupling of bioengineered cells with transducers to improve coupling efficiency. Moreover, the development of biomimetic chemical sensors into the sensor arrays is also one of the promising development trends in order to achieve rapid, multiplexed, and high throughput measurement, which can be used as next generation of sensor arrays for the development of electronic noses and electronic tongues.

Figure 3. Schematic diagram of a bioengineered cell-based sensor for label-free functional assays of chemical receptors based on localized extracellular acidification measurement.  

Disclosure of Potential Conflicts of Interest
No potential conflict of interest was disclosed.

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