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Electroactive polymers for tissue regeneration: Developments and perspectives

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ABSTRACT

Human body motion can generate a biological electric field and a current, creating a voltage gradient of −10 to −90 mV across cell membranes. In turn, this gradient triggers cells to transmit signals that alter cell proliferation and differentiation. Several cell types, counting osteoblasts, neurons and cardiomyocytes, are relatively sensitive to electrical signal stimulation. Employment of electrical signals in modulating cell proliferation and differentiation inspires us to use the electroactive polymers to achieve electrical stimulation for repairing impaired tissues. Electroactive polymers have found numerous applications in biomedicine due to their capability in effectively delivering electrical signals to the seeded cells, such as biosensing, tissue regeneration, drug delivery, and biomedical implants. Here we will summarize the electrical characteristics of electroactive polymers, which enables them to electrically influence cellular function and behavior, including conducting polymers, piezoelectric polymers, and polyelectrolyte gels. We will also discuss the biological response to these electroactive polymers under electrical stimulation. In particular, we focus this review on their applications in regenerating different tissues, including bone, nerve, heart muscle, cartilage and skin. Additionally, we discuss the challenges in tissue regeneration applications of electroactive polymers. We conclude that electroactive polymers have a great potential as regenerative biomaterials, due to their ability to stimulate desirable outcomes in various electrically responsive cells.

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1. Introduction

The biological electric field that the human body generates plays a pivotal role in wound healing due to the steady, direct current and electric potential, which drives cells to migrate to the point of injury [1]. Moreover, a voltage gradient, called "action potential", of −10 to −90 mV can trigger different cell types to change proliferation and differentiation by signaling across cell membranes [1,2]. The potential for harnessing the electric fields in cells to enhance growth and differentiation in biological systems has gained the attention of researchers. As is known, regeneration of damaged tissue begins with the growth and proliferation of cells [1,3]. Thus, to stimulate and enhance this regenerative process and thereby promote rapid healing of the damaged tissue, electroactive biomaterials are often considered for use as a tissue regeneration scaffold.

Electroactive materials provide a direct method for various forms of electrical stimulation to reach cells [3]. The electroactive materials include inorganic electroactive materials, metals and organic electroactive polymers. Recently, it is shown that specific amounts of electrical stimulation via electroactive materials could enhance the regeneration of cardiac [4], nerve [5,6] and bone through directing cell adhesion [7], growth, migration, apoptosis [8] and differentiation [9]. Thus, electroactive materials have the potential to evolve tissue healing and engineering treatments (e.g., bone [10,11] and nerve [12] regeneration). Particularly, electroactive polymers (EAPs) have received increasing attention (Figs. 1 and 2) because the human body contains many electrosensitive tissues such as bone, skin, nerve, heart and vessels [13]. In particularly, they have seen varied and extensive employment in tissue engineering (Table 1) because there are some advantages, such as the possibility of being constructed into varying shapes with attractive morphological features and a large selection of physical and chemical properties. To date, there are many reviews about the medical application of conducting polymers [5,14–16] and the tissue engineering application of piezoelectric materials [17,18]. However, there are few reviews for the application of electroactive polymers, including conducting polymers (CPs), piezoelectric polymers and polyelectrolyte gels, in tissue regeneration. This report will attempt to fill this gap.

2. Electroactive polymers

Under a stimulus, EAPs convert one form of energy into a more desirable electrical state, thus affording tremendous promise in emerging technologies for responsive prosthetics [69–71]. A typical characteristic property of EAPs is that they will undergo a large amount of deformation while under the pressure or being stretched. When electric charges are on the top of a polymer, a redistribution of charges within the polymer is observed; this is dependent on the polymer's ability of being responsively mobile [69]. The observed response of the polymer to an electric field is divided into two distinct categories. One is dielectric properties (dielectric constants and dielectric relaxation). Another is conductive properties (conductivity and dielectric strength) [70]. EAPs produce additional novel electrical properties, such as ferroelectric, photoconductive, piezoelectric, triboelectric, or pyroelectric characteristics [71]. Over the last ten years, EAP materials have garnered increasing attention as they are developed for different prospects in biomedicine such as tissue engineering scaffolds, drug delivery, biosensors, artificial muscles, actuators, power generators and various medical instruments and auxiliaries (Fig. 1) [72–74]. So, the interest in EAPs is increased because these "smart materials" have the ability to be responsive under varied external stimuli [75]. EAPs are unique in the biomedical field because they can convert different types of signals, such as mechanical, thermal, and magnetic, into electrical ones. This provides the opportunity to use EAPs in scaffolds for the stimulation of cell growth in tissue regeneration [8,76].

EAP history started in 1880 with the discovery of electromechanical coupling effects from the experiment where the rubber fixed at one end changed from charged to discharged [77]. Sacerdote [78] then conducted the same experiment and revealed the relationship between strain and electric field. In 1925 a piezoelectric polymer was identified [78]. Despite a lack of further work being explored, EAPs have become known for their reaction to electrical stimulation and the promise of practical and convenient applications. EAPs are readily categorized into two groups (electronic and ionic, Table 2) on the basis of the differing activation principles [79]. Electronic EAPs function by using the electrostatic forces of two electrodes to cause actuation to contract a polymer; this includes materials such as piezoelectric, electrostrictive, and ferroelectric. Ionic EAPs, on the other hand, function by displacing the ions contained in the polymer to cause actuation [80]. Examples of the ionic EAPs include polyelectrolyte gels, conducting polymers, and polymer-metal composites [72,79].

The most common applications of EAPs are in actuators and sensors. In recent years, the tissue regeneration applications of

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