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Review

Tissue engineering of electrically responsive tissues using polyaniline based polymers: A review

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ABSTRACT

Conducting polymers have found numerous applications as biomaterial components serving to effectively deliver electrical signals from an external source to the seeded cells. Several cell types including cardiomyocytes, neurons, and osteoblasts respond to electrical signals by improving their functional outcomes. Although a wide variety of conducting polymers are available, polyaniline (PANI) has emerged as a popular choice due to its attractive properties such as ease of synthesis, tunable conductivity, environmental stability, and biocompatibility. PANI in its pure form has exhibited biocompatibility both *in vitro* and *in vivo*, and has been combined with a host of biodegradable polymers to form composites having a range of mechanical, electrical, and surface properties. Moreover, recent studies in literature report on the functionalization of polyaniline oligomers with end segments that make it biodegradable and improve its biocompatibility, two properties which make these materials highly desirable for applications in tissue engineering. This review will discuss the features and properties of PANI based composites that make them effective biomaterials, and it provides a comprehensive summary of studies where the use of PANI as a biomaterial component has enhanced cellular function and behavior. We also discuss recent studies utilizing functionalized PANI oligomers, and conclude that electroactive PANI and its derivatives show great promise in eliciting favorable responses from various cell lines that respond to electrical stimuli, and are therefore effective biomaterials for the engineering of electrically responsive biological tissues and organs.

1. Introduction

The field of tissue engineering aims to regenerate or repair lost or damaged tissues with the help of biomaterial scaffolds, cells, and growth factors [1]. The scaffold should mimic the properties and structure of the organ it aims to replace and essentially acts as an artificial extracellular matrix to support cell survival and growth. Over the years, numerous studies have demonstrated that cells respond to various biomaterial properties. Characteristics such as wettability, mechanical stiffness [2,3], elasticity [4], and surface topography [5,6] have been identified as having significant influence over the behavior of seeded cells including migration, differentiation, and structural reorganization. In a similar manner, electrical signals too can influence cellular behavior and function.

The effects of electrical stimuli on tissues have been known since the 1960's when Bassett and colleagues showed that low intensity direct electrical currents influenced the mechanism of bone formation in adult dogs [7]. Others have reported that the application of pulsed electrical field stimulation on mouse osteoblast cells resulted in a significant increase in DNA synthesis [8], whereas a uniform electrical field influenced the clustering and distribution of membrane proteins on the cell–substrate interface, and was able to control the direction of cell locomotion in two fibroblast cell lines [9]. Further studies have also reported on the effects of applied electric fields on the migratory behavior of keratinocytes, vascular endothelial cells, and corneal epithelial cells [10–12]. Recently, electrical stimulation of myoblasts seeded on three-dimensional collagen scaffolds was shown to influence myogenic differentiation and deposition of type I collagen in a skeletal muscle construct [13], whereas electrical stimulation of cardiomyocytes seeded on collagen/Matrigel™ scaffolds induced their alignment and coupling, leading to synchronous contractions [14]. It is therefore evident that electrical stimuli can evoke desirable cellular responses, especially from cells belonging to

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electrically excitable tissues such as skeletal muscle, nerve, cardiac tissue, and bone. In general, majority of the biomaterial scaffolds employed in tissue engineering and electrical stimulation studies are electrically resistant in nature. Indeed literary evidence suggests that utilizing electroactive materials in scaffolds could greatly improve the functional outcomes of such studies.

Some efforts in this regard have been made through the incorporation of conductive particles such as carbon nanofibers [15] and gold nanowires [16] in scaffolds to modulate cellular behavior. The inclusion of these conductive elements makes it possible for the transmission of electrical signals (supplied from an external source) throughout the cell seeded scaffold. The use of gold and carbon based particles in implantable scaffolds could potentially be problematic since these materials are non-biodegradable and their long-term effects *in vivo* are largely unknown. Owing to the lack of solubility, a further drawback is the inhomogeneous distribution of the conducting particles in the two phase composite system. This issue can be overcome by employing conducting polymers, which can be dissolved in organic solvents and blended with other polymers before being processed, for example by electrospinning, into porous scaffolds. Blending of the conducting polymer into another polymer system ensures homogenous distribution of the conducting polymer molecular chains throughout the composite blend, which translates into electrical signals being effectively transmitted throughout the entirety of the composite, more importantly reaching all seeded cells and consequently modulating their behavior.

Polyaniline (PANI) offers a viable option to induce electroactivity in biomaterial scaffolds and substrates, and its popularity for use in biomedical and tissue engineering applications can be judged from the increasing number of research publications on the subject in the past decade. Such significant interest and available knowledge in the field of polyaniline for tissue engineering applications has motivated the preparation of the present review in which we discuss different aspects of PANI such as its biocompatibility, conductivity, processability, and antibacterial effect, properties that make it an attractive biomaterial component. The effect of PANI on cellular behavior in conjunction with electrical stimulation, and its application in skeletal, cardiac, and nerve tissue engineering are also discussed. Additionally, the review also touches upon the novel area of functionalized aniline copolymers which are simultaneously conducting and biodegradable, hence rendering them desirable for use as biomaterials in the field of tissue engineering.

2. Polyaniline

An early inherently conducting polymer was reported in 1977 when MacDiarmid, Shirakawa and Heeger recognized an 11 orders of magnitude increase in the conductivity of polyacetylene upon doping with iodine [17]. Since then, conducting polymers have witnessed an immense increase in scientific and technological interest, mainly due to their tunable electrical properties, ease of synthesis, and environmental stability. Conducting polymers have a conjugated backbone (alternating single and double bonds), which gives rise to an extended π network [18]. Movement of electrons within the π network is what gives the polymer, metal like semiconductive properties [19]. Polypyrrole, PANI, polythiophene and poly (3,4-ethylenedioxythiophene) (PEDOT) are just a few of the many conductive polymers that are employed in technological applications today. For instance, PANI finds applications in the microelectronics industry including photovoltaic cells [20], light emitting diodes [21], and electrochromic displays [22]. In the biological field, conductive polymers were shown to be compatible with cells and other biological molecules [23], and have thus found applications as substrates for cellular stimulation, DNA synthesis and protein secretion, as biosensors and bio-actuators [24], and recently as tissue engineering scaffolds [25]. Interest in conducting polymers for application in tissue engineering increased after Wong et al. used polypyrrole to show that application of an electrical potential can non-invasively control certain aspects of cellular behavior such as spreading, DNA synthesis, and differentiation [23]. Subsequently, numerous studies have highlighted advantages, and proposed the use of conducting polymers for nerve [26], bone [27], and cardiac [28] regeneration, among others [29].

Polyanilines are a class of conducting polymers which can exist in three different oxidation states, namely the completely reduced leucoemeraldine base, the completely oxidized pernigraniline base, and the emeraldine base consisting of alternating oxidized and reduced repeat units in its structure, as shown in Fig. 1 [30].

PANI is generally synthesized by either chemical or electrochemical methods [31]. The advantage of electrochemical methods is that uniform, high purity films of PANI can be deposited and collected on a metal electrode. The techniques used for electrochemical synthesis include potentiostatic (constant voltage), and galvanostatic (constant current) polarization, and cyclic voltammetry [32]. However, PANI is most commonly synthesized using chemical methods by oxidative polymerization of aniline in aqueous media in the presence of an oxidizing agent. Other chemical methods for synthesizing PANI include emulsion, dispersion, solution, interfacial, metathesis, and self-assembling polymerization [18].

Ever since conducting polymers such as polypyrrole were found to be compatible with cells and biological tissues, efforts to identify and establish the feasibility of other conductive polymers such as PANI for use in biomedical applications have been on the rise. Once the biocompatibility of PANI was established both *in vivo* and *in vitro* [33], research on PANI focused on designing materials for applications where it is in direct contact with biological tissues. Thus, PANI based composites have been employed in various biomedical applications including scaffolds for tissue engineering

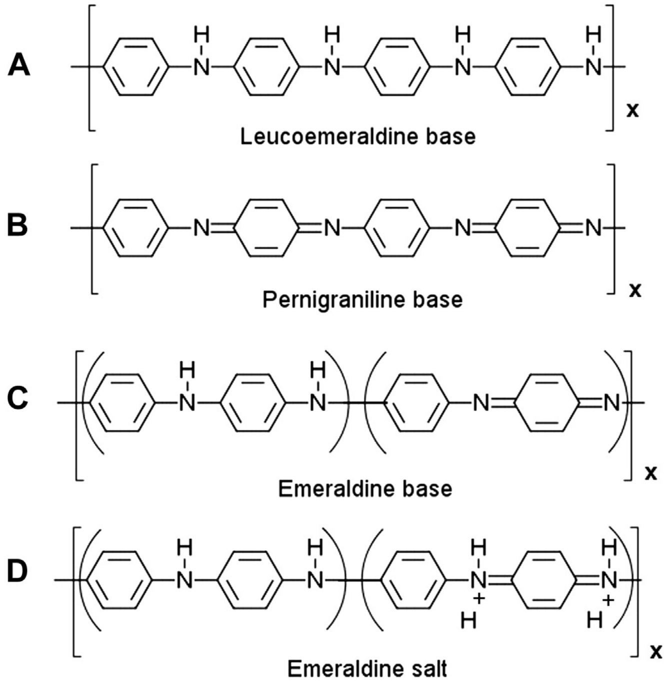

Fig. 1. Oxidation states of polyaniline, (A) the completely reduced leucoemeraldine base, (B) the completely oxidized pernigraniline base, (C) the half oxidized-half reduced emeraldine base, and (D) the doped, conductive form of emeraldine base, emeraldine salt.