Application of polypyrrole-based biomaterials in tissue engineering*★

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Abstract

BACKGROUND: Polypyrrole (PPy) has been widely applied in biomedical fields due to its special electronic property. Past 20 years, there are an increasing number of studies on the application of PPy as a potentially electrically addressable tissue/cell support substrate for tissue/cell regeneration.

OBJECTIVE: To overall review the application of PPy in tissue engineering field, and to provide a new approach for the research and development of medical biomaterials.

METHODS: Pubmed and Chinese biomedicine literature database were searched using key word of "polypyrrole" for documents published between 1990 and 2010. Literatures related to application of PPy in tissue engineering field were included, and the repetitive articles were excluded.

RESULTS AND CONCLUSION: Totally 762 papers were searched by computer, according to the inclusive and exclusive criteria, 51 literature were reviewed. Currently, PPy has been widely used in the fields of cardiovascular tissue engineering, bone and muscle tissue engineering, as well as skin tissue engineering. Application of PPy and PPy-based biomaterials hold great potential in development of novel biomedical materials applied in tissue engineering due to their versatile functionality and superior biocompatibility.

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INTRODUCTION

Of all known conductive polymers, polypyrrole (PPy) has been one of the most investigated polymers for various applications in recent years. Especially in tissue engineering applications, thanks to its unique inherent advantage over convetional polymers, such as the controllable surface properties, high electrical conductivity. PPy has been widely studied as a cell growth substrate in culture *in vitro* models. Factually, PPy has been reported to support cell adhesion and growth of a number of different cell types so far, including endothelial cells[1-4], rat pheochromocytoma (PC12) cells[5-7], neurons and support cells (*i.e.* glia, fibroblasts) associated with dorsal root ganglia[8-9], primary neurons[10-12], keratinocytes[13], and mesenchymal stem cells[14]. Most of these studies demonstrated that PPy enhanced cell adhesion, migration and proliferation or improve cell-material interactions for all type of cells. Furthermore, the investigation of effects of its implantation *in vivo* on animal models have also been conducted in many independent studies with positive results[8,15-18]. With the development of biomedical material technology, PPy and its derivative polymers have been increasingly used for fabrication of tissue engineering scaffolds to bring the benefit of its versatile functionality to repairs and regeneration of damaged tissue. In this review, we summarize the recent researches regarding interaction between PPy based biomaterials and various biological tissues, and to make an evaluation of PPy future directions.

DATA AND METHODS

Retrieval strategy

Relative contents of searcher: The first author.
Retrieval time range: From 1990 to 2010.
Key words: Polypyrrole.
Database: Pubmed, http://www.ncbi.nlm.nih.gov/pubmed/ and Chinese biomedicine literature database, http://cbmwww.imicams.ac.cn.
Literature quantities: A total of 762 documents were searched.

Selecting criteria

Inclusive criteria: Application of polypyrrole-based biomaterials in tissue engineering.
Exclude criteria: Repetitive articles.

Quality assessment

A total of 762 documents were searched by computer including 11 written in Chinese and 751 in English. All data were screened by reading title and abstracts, and irrelevant articles were excluded.

RESULTS

The basic information of included data

Totally 51 articles were included in final manuscript, there were 17 articles concerning nerve tissue engineering[8,11,15,19-32], 15 related to cardiovascular tissue engineering[1-4,19,33-42], 9 related to bone and muscle tissue engineering[14,43-50], 9 concerning skin tissue engineering[13,51-58], and 2 regarding other tissue engineering[59-60].

Comprehensive analysis of literature evidence

PPy and nerve tissue engineering

In a series of *in vitro* and *in vivo* studies demonstrated that PPy possesses superior biocompatibility with nerve tissues. It was showed to promote the survival, proliferation, migration of Schwann cells and the neurite extension from dorsal root ganglia *in vitro* and perform better than most currently used biomedical materials, such as polyester and Teflon[15,19-20]. The *in vivo* test showed that there was only lightly inflammation when the PPy-silicone tube bridged

across the 10-mm gap of the transected sciatic nerve of rats[8]. The topographical characteristics of cell culture substrates are thought to play an important role in affecting biological behaviors of cells. Thus, surface morphological modification of PPy may lead to significant improvement of cell-material interaction. PPy patterned with 1 and 2 μm wide microchannels were shown to promote polarization of embryonic hippocampal neurons cultured on it, with a two fold increase in the number of cells with axons compared to cells cultured on unmodified PPy. Microchannels were also found to have an effect on the orientation of axon growth, promoting parallel or perpendicular alignment with respect to the microchannels but did not result in a significant increase in axon length from hippocampal cells, suggesting that surface topographical features have a more dramatic effect on axon-initiation mechanisms (*i.e*., polarization), but these effects become negligible once the axon is established and undergoes elongation[11]. Similarly, in Liu's study[21], a higher density of cells and more firm adhesion to the substrate were obtained on a PPy/SIBS(Poly (styrene-b-isobutylene-b-Styrene)) nanofibrous mat than those on pristine gold coated Mylar *in vitro* culture and not only the clear neuronal direrentiation of PC12 cells on the PPy/SIBS nanofibers, but also the particular growth of neurites from PC12 cells were induced in the inner layer of the 3D fibrous network after 144 hours of culture. In another *in vitro* culture longer neurites from PC12 were found to form on the aligned PPy–poly (lactic-co-glycolic acid) (PLGA) nanofibers than on the random PPy–PLGA fibers[22]. Moreover, stimulation of the cells on aligned PPy-PLGA fibers resulted in longer neurites and more neurite-bearing cells than stimulation on random PPy-PLGA fibers, suggesting that fiber alignment and electrical stimulation act together to enhance neurite extension of PC12 cells. Interestingly, cells stimulated with 10 mV/cm extended significantly longer neurites than cells stimulated with 100 mV/cm on both random and aligned fibers, suggesting a lower potential may be more favorable for promoting neurite outgrowth of PC12 cells. The similar phenomenon was also investigated by Huang *et al*[23]. They found that electric stimulation at low potentials (100 mV/mm) was found to significantly increase the proliferation of Schwann cells through the conductive polymer substrate while higher potentials (300–1 000 mV/mm) have detrimental effects. Furthermore, the transcription, expression, and secretion of nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF) in Schwann cells were analyzed to be dramatically increased by electric stimulation. They reasoned that the possible mechanism lies in the fact that electric stimulation is capable of modulating cell membrane permeability[24], membrane fluidity, and cytoskeletal structure[25].

To some extent the intrinsic irregular surface morphorlogy of PPy and PPy based biomaterials are supposed to contribute to the enhancement of adhesion, growth and proliferation of cells cultured on them. PPy-TEAP-PVA (Polypyrrole-Tetraethylammonium-perchlorate-Poly (vinyl alcohol) produced by grafting method was found to significantly enhance the adhesion of PC12 cells *in vitro*. Researchers reasoned that the porous and uneven surface morphology of the PPY-TEAP-PVA may account for such an enhancement by inhibiting cells on its surface from floating away in the medium. Furthermore, these pores can also act as a reservoir to deliver nutrients to the adhered cells[26]. The proposed mechanism was supported by research of Zhang *et al*[27].

Apart from the electrical conductivity and surface morphological property controllability, another attractive point for PPy to be applied in nerve tissue engineering lies in that it can be bioactivated with various biomolecules by grafting, entrapment method to exhibit diversified functionality. NGF could be immobilized onto PPy substrate using an intermediate linker upon exposure to UV light. The immobilized NGF was investigated to be active and capable of increasing neurite outgrowth from PC12 and dorsal root ganglia neurons. Surprisingly, it was determined that a surface NGF concentration of 0.98 ng/mm^2 produced similar neurite extension in PC12 cells compared to soluble NGF (50 ng/mL) after 2 days culture. Immobilized NGF maintained the effect on neurite length at 10 days after culture. However, the median neurite length on PPy-NGF was lower than that for unmodified PPy controls with NGF in solution. A possible explanation for this difference could be that PC12 cells exhibited restricted responses to immobilized NGF because of endosome signaling inhibition[28].

Macromolecules entrapped in PPy by electrochemical polymerization do not affect the original electrical property of PPy significantly while maintaining the same bioactivity as their counterparts in medium. The electrode surface modified by PPy entrapped with synthetic peptide DCDPGYIGSR was found to establish a strong connection with neuronal structure of guinea pig *in vivo* within 3 weeks and good recordings were obtained from the coated sites that had neurons attached. The impedances of PPy/DCDPGYIGSR coated sites were relatively stable for the first week of implantation. Though there was an increase in impedance modulus after 1 week, the impedance values were still low enough for detecting neuron activity. Moreover, the peptide entrapped in the polypyrrole film was investigated not to diffuse away within 7 weeks of soaking in de-ionized water[29]. Guinea pigs implanted with polypyrrole/para toluene sulfonate/neurotrophin-3 (PPy/pTS/NT-3) coated electrodes were showed to have lower electrically-evoked auditory brainstem response thresholds (EABRs) in implanted cochleae compared to non-implanted cochleae and greater spiral ganglion neurons (SGN) densities compared to animals implanted with PPy/pTS-coated electrodes. PPy/pTS/NT3 did not exacerbate fibrous tissue formation or affect electrode impedance. Simultaneous co-administration of electrical stimulation and neurotrophins provided greater SGN survival than either treatment alone. Furthermore, continuation of electrical stimulation beyond the period of neurotrophin delivery to the cochlea maintained the protective effects on SGNs[30]. In another electrical stimulated culture, it is showed that SGN explants grown on PPy/pTS/NT3 and subjected to 1 hour of biphasic current pulse stimulation had greater neurite outgrowth compared to explants grown on unstimulated PPy/pTS/NT3. In contrast, electrical stimulation of PPy/pTS did not enhance neurite outgrowth compared to unstimulated PPy/pTS. These results suggest that the enhanced neurite outgrowth observed from SGN explants is due to release of NT3 from the polymer rather than the electrical stimulus[31]. The similar results were also obtained in the research conducted by Evans *et al*[32].

PPy and cardiovascular tissue engineering

Rowlands *et al*[33] isolated vascular smooth muscle cells (VSMCs) from rabbit aorta and cultured them on conducting PPy substrates doped with hyaluronic acid (HA) and coated with collagen IV followed by Matrigel together with immortalised A7r5 cells (a smooth muscle cell line). Then, they were subjected to a 50 mA sinusoidal electrical stimulation with 0.05, 5 and 500 Hz. They found proliferation and expression of smooth muscle phenotype markers, smooth muscle α-actin and smooth muscle myosin heavy chain were increased in cultures stimulated at 5 and 500 Hz, whereas using a frequency of 0.05 Hz was found to be extremely detrimental to VSMCs.

Nishizawa *et al*[34] used PPy-coated microelectrode to analyze the effect of electrical stimulation on the chick embryonic cardiac myocyte to find it synchronously beated upon pulsation with the underlying PPy-coated microelectrode and determined a threshold charge of around 0.2 mC was needed to excite the myocyte sheet. They thought the PPy coating was effective for reproducible, noninvasive stimulation of cultured cardiac myocytes.

Surface property of PPy can be modified reversibly by chemical or electrochemical oxidation or reduction and induce interesting cellular responses. When aortic endothelial cells were cultured on fibronectin-coated polypyrrole in oxized state, they found cells spread normally and synthesized DNA. In contrast, when the polymer was switched to its neutral state by applying an electrical potential, both cell extension and DNA synthesis were inhibited without affecting cell viability[1-4].

Polyester fabrics were extensively applied in the surgical treatment of cardiovascular diseases. Surface modification of polyester fabrics with PPy may result in improved biocompatibility. Jakubiec investigated two PPy-coated polyester fabrics (PPy-Phos and PPy-Plas fabrics) prepared by different techniques (phosphonylation and plasma-activated polymerization) to find neither of the fabrics had an adverse effect on hemolysis and coagulation time or cause any acute systemic toxicity. In terms of acute PMN activation, as indicated by IL-8 mRNA expression, the PPy-Phos and PPy-Plas fabrics were superior to the polyester (PET) fabrics and Bionate 80A poly(carbonate urethane)[19]. The results of electrically stimulated culture indicated that highly conductive polypyrrole-coated polyester fabrics (100–200 Ω/square) induce undesirable effects on endothelial cell behavior in terms of cell growth, migration, and viability; elevated PMN activation in terms of CD11/CD18 integrin expression, and inhibitory effects on mononuclear cell metabolism in terms of IL-6 mRNA cytokine secretion. This study also pointed to an intermediate or optimal level of polypyrrole conductivity on polyester fabrics which would be in the range of 10^3 to 10^4 Ω/square. This optimal level of conductivity is associated with improved cellular response *in vitro*[35].

RGD was an amino acid sequences that has effect on the adhesion, morphology, growth, migration, and differentiation of a variety of cell types as a result of the interaction between the integrin family of cell surface receptors. Surface modification of PPy based biomaterials with the synthetic peptide containing RGD was showed to exert the same effects on the biological behaviours of endothelial cell as immobilized RGD. In Lee's research[36-37], PPyCOOH was successfully tailored by chemically conjugating an RGD-containing peptide, GRGDSP, onto the surface of Carboxy-endcapped PPy (PPy-α-COOH). This RGD-grafted-PPy-a-COOH demonstrated superior HUVEC adhesion and spreading compared with ungrafted controls and no significant change in conductivity compared to that of PPy was measured. This bioactive conductive platform provides a functional surface capable of tethering biomolecules that direct cell behavior without the drawback of reduced conductivity.

Surface modification of biomaterials which is aimed at improved blood compatibility is of great importance in cardiovascular tissue engineering currently. In recent years substantial studies were involved in this direction. Li *et al*[38] thought the entrapment method which PPy/Heparin were prepared by suffers from the same problems as the immobilization of other biomolecules through entrapment during the synthesis of electrically conductive polymer film. Specifically, firstly, this immobilization process significantly reduces the bioactivity of immobilized heparin due to the high hydrophobicity of PPy. Secondly, the steric constraints of the surrounding polymer may also reduce the conformational freedom of the immobilized heparin and at the same time, significantly reduce the accessibility of the blood, cells, or tissues to the immobilized heparin[39]. Thus, they proposed a surface graft technique by which heparin was activated with cyanuric chloride and then immobilized onto PPy *via* a modifier poly (ethylene glycol) methacrylate (PEGMA). In their research PPy/Heprain prepared by surface graft copolymerization with 5% PEGMA monomer concentration was analyze to be more biocompatible than that prepared using lower PEGMA concentration or no PEGMA at all. In the presence of heparin, platelet adhesion and activation on the composite (5% PEGMA) was further inhibited, which indicates that heparin can also suppress the platelet activator. Further, with electrical stimulation, the blood compatibility, in terms of plasma recalcification time and platelet adhesion of the pristine PPy film and the surface-modified films was improved (an increase of 60–120 seconds for plasma recalcification time) significantly. Mao *et al*[40] adopted a photocrosslink technique to immoblize the O-butyryl chitosan (OBCS) onto PPy films to obtain an Azide-OBCS-graftiging-PPy film. Results demonstrated that the Az-OBCS-grafting-PPy films offer the improved blood compatibility, showing much less platelet adhesive and fibrinogen adsorption compared to the control PPy surface, and the conductivity of Az-OBCS-grafting-PPy films did not decrease significantly compared to that of the unmodified PPy films. Surface modification of steel with PPy has been performed by Khan *et al*[41] for improvement of the blood compatibility of steel. A PPy derivative, namely, polypyrrole-N-succinimidyl ester (PPyNSE) was successfully electrocoated onto steel plate, followed by covalently attachment of bovine serum albumin (BSA) to PPyNSE to obtain a biomolecule-derivatized polymer coating with improved blood compatibility. From blood test results it was shown that there is a 10%–20% reduction in thrombus formation on BSA-immobilized coating as compared with bare metal and the coated surface is highly resistant to platelet adhesion.

Finally, polypyrrole-tissue hybrid biomaterials may represent a new direction in cardiovascular tissue engineering in the future. Khor *et al*[42] impregnated porcine pericardium with a pyrrole derivative, sodium 4-(3-pyrrolyl) butane sulphonate monomer with subsequent in situ chemical polymerization of the

monomer-rich tissue using $FeCl_2$ as initiator and obtained a black polypyrrole-tissue hybrid biomaterials. For cardiovascular application the biological and mechanical property of this novel biomaterial remained to be further explored.

PPy and bone and muscle tissue engineering

The good biocompatiblity of polypyrrole with osteoblastic cells was widely proved in considerable studies. Lakard *et al*[43] cultured human osteosarcoma cell line SaOs-2 (ATCC-HTB85) osteoblastic cells on PPy substrates and found they adhered and proliferated normally on all the PPy polymers tested and their morphology was the same as on the indium tin oxide (ITO) glass control, showing the non-toxicity of polypyrrole for osteoblastic cells. Moreno *et al*[44] showed osteoblasts growth on proper PPy/Polysaccharide (PPy/heparin and PPy/hyaluronic acid) substrates did not cause any cytoskeletal modifications. Moreover, the films with smooth surface morphologies were showed to allow good cell adhesion and proliferation, whereas those samples that exhibit irregular surfaces did not assure good cells response. Duan *et al*[45] determined the surface energy of PPy electrically coated Titanium (59.5 mJ/m^2) is higher than that of titanium (47.0 mJ/m^2) and the shear bond strength of this coating to Ti amounts to as high as (9.16±1.62) MPa. *In vitro* culture results revealed this coating supports the attachment, spreading and proliferation of osteoblasts. In their further studies they found the PPy films can accelerate oseoblast proliferation and differentiation osteoblasts in combination with positive electrical stimulation and the novel Ti surface modification strategy may have great potential for bone tissue engineering[46]. De Giglio *et al*[47] modified Ti surface with a PPy derivative PPy-3-acetic using electrical polymerization. The cell culture results of their studies indicate that adhesion and proliferation of osteoblast-like cells onto PPy-3-acetic-modified titanium substrates were comparable to those observed on glass cover slip after 24 hours. They also successfully immobilized RGD onto the surface of Ti/PPy using the graft technique developped in their laboratory and investigated the interactions between these composite and neonatal rat calvarial osteoblasts. They found the concentration of RGD solution in the synthesis may have an effect on cell adhesion onto substrates. For the concentration of the RGD-peptide of 5.1×10^{-4} mol/L, an increase in cell attachment of about 230% on Ti/PPy-RGD substrates compared with PPy and glass coverslip was recorded[48]. Jia *et al*[49] have doped rhBMP-2 into Ti/PPy coating by electrochemical synthesis and culture results indicated that the doped rhBMP-2 can still keep the ability of osteoinduction and promote the proliferation and differentiation of bone marrow mesenchymal stem cells. This novel composite biomaterial may find great promise in the development of a new generation of oral implantable devices.

Chemical constitution of dopant is thought to affect the biological behavior of cells grown on various PPy based substrates. To find an optimal combination for improved interactions with skeletal muscle cells, Gilmore *et al*[50] have assessed the benefits of doping the conducting polymer with major components of the extracellular matrix, including HA, chondroitin sulphate A (CS), and compare them to nonbiological molecules (dodecyl benzene sulphonic acid (DBS), poly (2-methoxy-5 aniline sulphonic acid) (PMAS), dextran sulphate (DS) and para-toluene sulphonic acid (pTS). They found no significant difference was observed between the polymers in their ability to support cell adhesion and proliferation and by 48h myoblast numbers were in general greater on the thin polymer film surfaces compared to their thick counterparts. Based on the lactate dehydrogenase assay results, they thought it would be reasonable to assume that PPy/pTS and PPy/HA, along with the majority of the remaining polymer films, were suitable candidates for muscle cell adhesion and proliferation. Their data suggests that in addition to surface morphology effects, the polymer-dopant chemistry of these conducting polymers influences the biological behaviour of cells grown on their surfaces.

The concentration of pyrrole monomer during electrical synthesis is another significant factor in influencing cellular response *in vitro* culture. Castano *et al*[14] found that the attachment, proliferation and calcified matrix deposition of mesenchymal stem cells cultured on PPy thin films made by admicellar polymerization using 20×10^{-3} mol/L Py was comparable with that on TCP. However, a slight increase in the monomer concentration resulted in a considerable decrease in the number of cells. They proposed that by changing the monomer concentration PPy films can be generated which do not only vary in thickness, but also induce drastically different cellular events.

PPy and skin tissue engineering

Shi *et al*[51] have conducted indepth, comprehensive studies on the biological behaviour of human cutaneous fibroblasts cultured on polypyrrole/polylactide (PPy/PLLA) substrates. They found the conductive PPy/PLLA membranes can support the adhesion and proliferation of human cutaneous fibroblasts in both the presence and absence of electrical stimulation. Further study showed that electrical stimulation mediated by PPy/PLLA conductors significantly increased interleukin-6 and interleukin-8 mRNA expression and dramatically enhanced the secretion of these two types of cytokines from human fibroblasts. They reasoned these electrical stimulation-induced effects are related to cell membrane structures[52]. In another study, they demonstrated that the fibronectin-bioactivated PPy membranes upregulated the adhesion and proliferation of human cutaneous fibroblasts compared to the control group while the BSA-rich PPy membranes had a negative impact on fibroblast culture by inhibiting both cell attachment and growth. Furthermore, the incorporation of proteins was indicated to decrease the conductivity of the PPy particles only slightly. Thus, bioactivated PPy/PLLA conductive membranes show potential in the introduction of targeted electrical stimulation[53].

Meng *et al*[54] also investigated how the addition of heparin affects the biological interactions of human cutaneous fibroblasts with PPy/PLLA composite. Fibroblast culture results indicated the density of the adherent cells was greater in the HE-containing membranes than in the membranes without heparin and all of the HE-containing membranes showed obviously higher MTT values than the non-heparin containing PPy/PLLA membranes. The membranes containing more heparin were also showed to result in dramatically higher MTT values. Meanwhile, the electrical stability of the conductive composites was showed to be significantly enhanced by dopant of HE. In another research[55], a PPy/PDLLA composite was

found to successfully sustain a biologically meaningful DC current in a physiological environment for 1 000 hours. It was indicated that the substrates experiencing medium range current stimulation, *i.e.*, initial current at 10 and 50 mA or 1.33 and 6.67 mA/mm^2, recorded a obviously higher number of viable cells compared with the other substrates. Surprisingly, at both low and high current conditions, the growth of cells was similar to those without electrical stimulation. The mechanism was yet to be explored.

Ateh *et al*[13] compared chloride, polyvinyl sulphate, dermatan sulphate, and collagen-loaded polypyrrole films in terms of the viability of keratinocytes cultured on them. By Alamar Blue assay the cell viability was respectively 47.22%, 60.44%, 87.71% and 22.65% of tissue culture polystyrene controls after 5 days. From their studies, they concluded that optimized polypyrrole films adequately support keratinocyte growth in submerged cultures with some improvements needed for organotypical cultures.

Mattioli-Belmonte *et al*[56] also investigated the growth of a human keratinocyte cell line on PPy films and found the behavior of the keratinocyte cell line was modulated by redox state and morphology of PPy-tosylate films with poor growth occurring on oxidized substrates but none on those that were overoxidized. They attributed this limited cell growth to surface tension and irregular roughness of the oxidized films, but they could not rule out the possibility that tosylate diffusion into the culture media worsened the culture results on overoxidized films. In their another study, they observed the poor adhesion of the same human keratinocyte cell line on this PPy films compared with the other substrates including the resorbable triblock polymer based on poly-L-lactide[57]. Researchers have also studied the effect of electrical stimulation on the cell behaviors of rat primary keratinocytes cultured on PPy[58]. Through a series of experiments with optimized cell culture media composition and PPy electrical stimulation potential, they found that under optimal conditions, including electrical stimulation for 2 hours at 100 mV, there was over a 20% increase in cell viability on PPy films electropolymerized on porous stainless steel filters, as measured by the MTT assay 3 days later, compared to standard culture methods.

PPy and other tissue engineering

To indentify PPy's suitability for development of a cell culture system which allows directing electrically stimulated cultured cells by using a modified electrode as the culture substrate, Aoki *et al*[59] cultured bovine adrenal chromaffin cells on PPy-coated indium-tin oxide plates (ITO) for 7 days. Culture results suggested that the cellular ability to synthesize and store catecholamines was not affected by PPy in culture with cells still exhibiting the secretory response comparable with the collegan coated glass slides cells even after 7 days, while the cells cultured on ITO significantly lost the responsiveness to acetylcholine after 7 days, either the intrinsic secretory mechanism or the acetylcholine-receptor function of which was influenced by ITO seemingly. Thus, they concluded PPy can be employed as conductive coating on ITO electrodes to protect the cells from the toxicity of ITO during the cell culture. In another investigation which compared PPy coated ITO with TCPS (tissue culture polystyrene) in terms of biocompatibility with rat hepatic cells[60], the results showed that the cells on PPy films grew faster and entered logarithmic growth phase earlier than those on TCPS resulting in the earlier formation of the largest cell density accordingly. Furthermore, rat hepatic cells could regenerate on PPy films and their growth could be accelerated under electrical stimulation.

DISCUSSION

Conducting polymers represented by PPy based polymers have aroused increasing attention from researchers engaged in the biomedical field nowadays. However, in spite of substantial research already conducted on PPy based polymers for tissue engineering applications, many challenges remain to be addressed in this field.

It is widely accepted that tissue and cell responses to PPy-based conducting polymers are likely to be modulated by a wide range of factors including synthesis conditions, dopant choice and surface modification strategy of post-synthesis which influence resulting surface chemistries, topography and biofunctionality, as well as the tissue or cell type considered. Because of the endless possible combinations, research results involved with these factors vary widely in the literatures. Furthermore, due to a lack of understanding of the exact mechanisms behind the influenced cellular responses and a consensus on the effect of electrical fields and current on biological tissue and cells, it seems pretty difficult to establish a precise correlation between surface property, chemical characteristics and applied current potential with improved cellular behaviors, as is essential for the future development of PPy based material in tissue engineering. Therefore, more research in this regard should emerge thereafter.

Regarding development of synthesis techniques, it is possible that surface modification post-synthesis with bioactive macromolecules such as synthetic peptides and diversified cell factor with cellular inductivity will prevail in the future leading to development of a new generation of smart tissue engineering materials. Other expected progress in PPy synthesis methods including fabrication of biodegradable PPy based conductive composites with degradable ester linkages[55], or from pyrrole monomers modified with ionizable/hydrolysable side groups at β-position[48], or N-position[61] and stretchable PPy films made with dopants that act as plasticizers[62] might also boost their potential in tissue engineering applications. Research in this area is still at an early stage and considerable technical issues are yet to be solved.

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聚吡咯类生物材料在组织工程中的应用*★

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摘要

背景：聚吡咯因其特殊的电学性质被广泛应用于生物医学工程领域。近 20 年来，在组织工程领域有越来越多的关于其作为施电细胞组织培养基底用于组织和细胞再生方面的研究。

目的：全面了解聚吡咯类生物材料在不同类组织工程中的应用，为今后该类材料在组织工程方面的进一步研究以及新型医学生物材料的研发提供思路。

方法：以“polypyrrole”为检索词，应用计算机检索 Pubmed 数据库，中国生物医学文献数据库 1990/2010 发表的相关文章。纳入与聚吡咯组织工程应用密切相关的文献，排除重复性研究。

结果与结论：共检索到 762 篇文献，排除无关重复的文献，保留 51 篇文献进行综述。目前聚吡咯类生物材料主要用于神经组织工程、心血管组织工程、骨及肌肉组织工程、皮肤组织工程等方面。这类生物材料由于其多功能性以及良好的生物相容性，对于未来新型组织工程材料的研发以及组织工程的进一步研究具有重大的价值。

关键词：聚吡咯；生物材料；应用；组织工程
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此问题的已知信息：聚吡咯类聚合物材料在神经、心血管、骨肌肉、皮肤及其他组织工程领域中的近 20 年来的研究。

本综述增加的新信息：对聚吡咯类生物医学材料未来的研究方向提出了一些新的见解。

临床应用的意义：通过对当前聚吡咯类材料在各个组织工程领域中的应用进行了回顾总结，为今后该类材料在组织工程方面的进一步研究以及新型医学生物材料的研发提供思路。