Materials Science & Engineering C 85 (2018) 37–46

Contents lists available at ScienceDirect

Materials Science & Engineering C

journal homepage: www.elsevier.com/locate/msec

Electrospun membranes of PELCL/PCL-REDV loading with miRNA-126 for enhancement of vascular endothelial cell adhesion and proliferation

Fang Zhou[a], Meiling Wen[a], Peiqiong Zhou[a], Yunhui Zhao[a], Xiaoling Jia[b], Yubo Fan[b,c], Xiaoyan Yuan[a,*]

[a] School of Materials Science and Engineering, Tianjin Key Laboratory of Composite and Functional Materials, Tianjin University, Tianjin 300350, China
[b] Key Laboratory for Biomechanics and Mechanobiology of Ministry of Education, School of Biological Science and Medical Engineering, Beihang University, Beijing 100083, China
[c] National Research Center for Rehabilitation Technical Aids, Beijing 100176, China

ARTICLE INFO

Keywords:
PELCL
REDV peptide
miRNA-126
Electrospun membranes
Vascular endothelial cells

ABSTRACT

Surface modification for rapid endothelialization of vascular biomaterials is known as an important way to prevent thrombosis and intimal hyperplasia. Moreover, therapeutical manipulation of microRNAs (miRNAs) expression *via* local delivery of miRNA mimics or inhibitors by electrospun ultrafine fibers has demonstrated the promise in tissue regeneration. In this work, a dual-functional electrospun membrane was developed by combining Arg-Glu-Asp-Val (REDV) peptide-modification of the fiber surface to enhance vascular endothelial cell (VEC) adhesion and encapsulation of miRNA-126 (miR-126) complexes in the electrospun fibers to accelerate VEC proliferation. The electrospun membranes were specially prepared by emulsion electrospinning of poly (ethylene glycol)-*b*-poly(L-lactide-*co*-ε-caprolactone) (PELCL) and REDV-terminated polycaprolactone (PCL) (50/50 mass ratio), in which miR-126 was encapsulated *via* REDV peptide-modified trimethyl chitosan-*g*-poly (ethylene glycol). By introduction of REDV-terminated PCL with lower molecular weight, the obtained electrospun fibers could be modified by REDV on their surface, and also achieve a relatively fast release profile of miR-126 in favor of VEC proliferation. Results of direct seeding VECs on the electrospun membranes indicated the enhanced cell adhesion and proliferation. The combination of REDV peptide-modification of the electrospun fibrous membranes and controllable miRNA release may provide a synergistic strategy of surface guidance and biochemical signals to support and modulate VECs for vascular tissue regeneration.

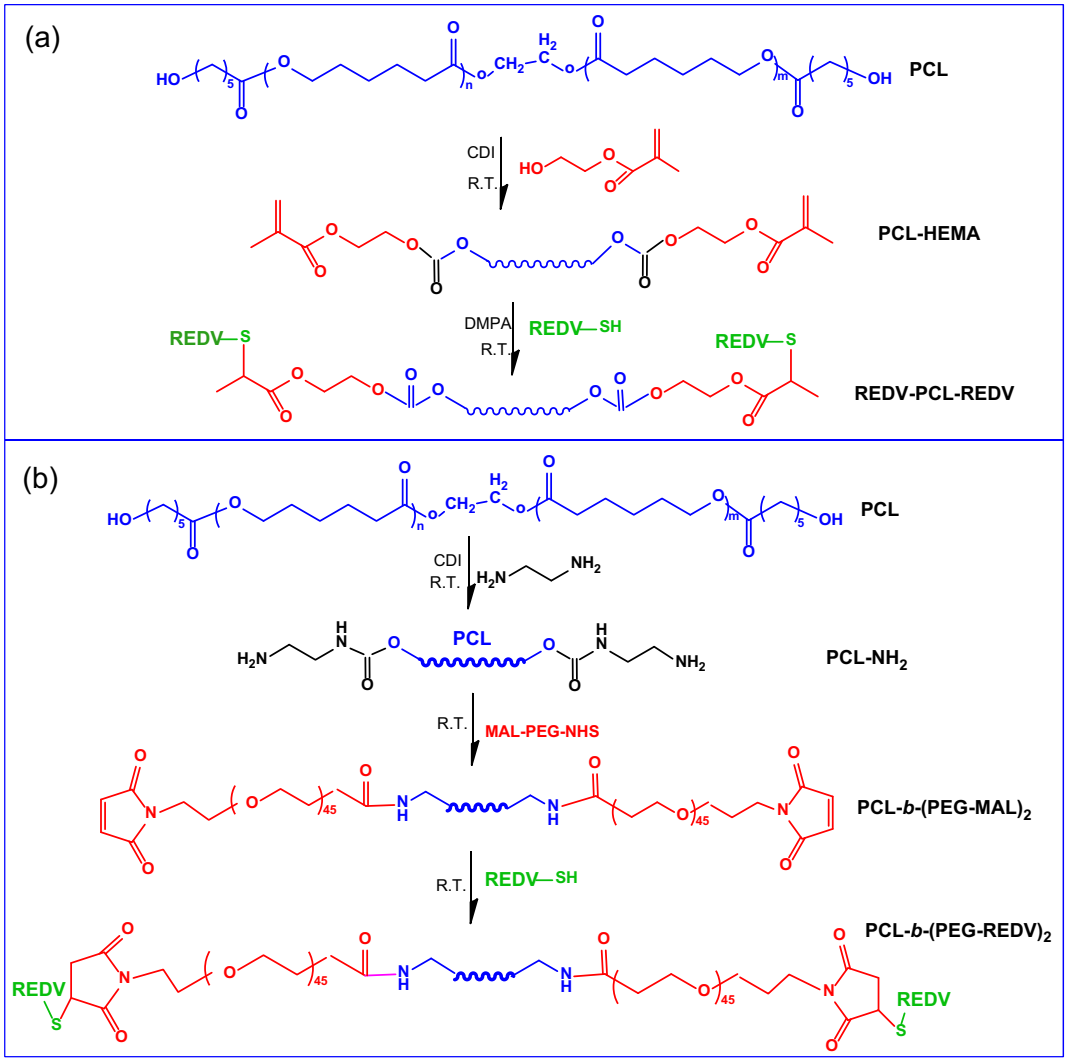
1. Introduction

Thrombosis generating on the surfaces of synthetic biomaterials by direct contact with blood limited the success of small diameter vascular grafts as an artery substitute in the cardiovascular system [1,2]. Rapid endothelialization has been considered as an efficient way to inhibit intimal hyperplasia and enhance patency of artificial vascular grafts [2,3]. Surface modification for rapid endothelialization of vascular biomaterials is known as an important way to prevent thrombosis and intimal hyperplasia for improving hemocompatibility and long-term patency of artificial vascular grafts [3–5].

Recently, RNA interference based on microRNAs (miRNAs) has drawn much attention in regenerative medicine for dealing with bone, cardiovascular and neuronal diseases, or against cancers that are related to aberrant gene expressions [6–11]. As post-transcriptional gene regulators, small and noncoding miRNAs have been demonstrated systematically *in vitro* and *in vivo* as therapeutic potentials to stimulate tissue regeneration [6–11]. In the field of vascular biology, miRNA-126 (miR-126) is considered as a master regulator of physiological angiogenesis that manipulates vascular integrity and angiogenesis *via* regulation of the signals of angiogenic growth factors, such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) [12–14]. According to the references, miR-126 targets sprouty-related protein (SPRED-1) and phosphoinositol-3 kinase regulatory subunit 2 (PIK3R2), both of which are VEGF and FGF signaling suppressors [14,15]. During vascular injury curing, miR-126 plays a key role in tissue repair by inducing angiogenesis and activation of re-endothelialization [12]. In our previous studies, it was found that miR-126 could be target-delivered to vascular endothelial cell (VECs) *via* Arg-Glu-Asp-Val (REDV) peptide-modified PEG-trimethyl chitosan (TMC-*g*-PEG-REDV) [16], and the local delivery of miR-126 to VECs by electrospun membranes could accelerate VEC proliferation for blood vessel regeneration [17]. In addition to release of miR-126 for rapid endothelialization, it was assumed that long-term supply of suitable

* Corresponding author.
E-mail address: yuanxy@tju.edu.cn (X. Yuan).

https://doi.org/10.1016/j.msec.2017.12.005
Received 26 June 2017; Received in revised form 7 September 2017; Accepted 7 December 2017
Available online 15 December 2017
0928-4931/



Scheme 1. Synthetic schemes of REDV-terminated PCL. (a) REDV-PCL-REDV; (b) PCL-*b*-(PEG-REDV)$_2$.

miRNA mimics would be required for the successful vascular tissue regeneration.

Since VEC adhesion onto the artificial scaffold is of importance at the early stage of endothelialization, many methods have been developed to provide the biomaterial surface with the ability to selectively adhere VECs [3–5]. Most of the approaches were related to immobilization of cell active peptides on the surface of artificial vascular grafts, which can promote VEC adhesion and *in situ* rapid endothelialization on the scaffolds [18,19]. REDV peptide was widely studied due to its ability to initiate cell-specific binding to VECs [19–22]. As a VEC-specific ligand, REDV peptide could mediate the migration of VECs *via* the integrin α4β1 subunit, but not allow the adhesion of smooth muscle cells (SMCs) and platelets [19,20]. The competitive growth of VECs over SMCs could be increased *via* the specific recognition of REDV on the cardiovascular stent [19,21]. Our previous research demonstrated that vascular scaffolds loaded with miR-126 complexes could facilitate VECs proliferation *in vitro* [17], but endothelialization *in vivo* still remains a challenge for long-term efficiency. So, it is necessary to make efforts to modify the fiber surface by REDV peptide for enhancing selective adhesion of VECs on the vascular scaffold that has encapsulated miR-126 complexes.

Active peptides can be coated, covalently grafted or immobilized onto the biomaterial surface by either physical absorption or chemical reactions [3,19,22]. Different from the reported methods, in this work, we prepared REDV peptide-modified electrospun membranes of poly (ethylene glycol)-*b*-poly(L-lactide-*co*-ε-caprolactone) (PELCL) by introducing REDV-terminated polycaprolactone (PCL) in the electrospun solution. During the electrospinning process, rapid solvent evaporation was generally accompanied with high molecular mobility of the electrospun polymer components, in which the lower molecular weight polymer tended to locate in the shell [23–25]. It was supposed that REDV-terminated PCL with lower molecular weight, in comparison with PELCL with relatively higher molecular weight, could move outward to the surface of the electrospun fibers as a result of higher molecular mobility. Electrospun ultrafine fibers are attractive as synthetic ECM analogues and as carriers for localized delivery of bioactive materials [16,26,27]. In this regard, TMC-*g*-PEG-REDV/miR-126 complexes are encapsulated in the electrospun fibers for target-delivery of miR-126 to VECs, in addition to REDV peptide-modification. Therefore, we prepared the electrospun membranes *via* emulsion electrospinning of blend solutions of PELCL/REDV-terminated PCL (50/50 mass ratio), in which TMC-*g*-PEG-REDV/miR-126 complexes were encapsulated. The dual-functionality of the electrospun fibrous membranes is expected to facilitate both adhesion and proliferation of VECs.

2. Materials and methods

2.1. Materials

PCL (14 kDa) and PELCL (LA/CL = 75/25, 70 kDa) were prepared