



Tailoring chemical and physical properties of fibrous scaffolds from block copolyesters containing ether and thio-ether linkages for skeletal differentiation of human mesenchymal stromal cells



Honglin Chen ^{a,1}, Matteo Gigli ^{b,1}, Chiara Gualandi ^c, Roman Truckenmüller ^a, Clemens van Blitterswijk ^a, Nadia Lotti ^b, Andrea Munari ^b, Maria Letizia Focarete ^{c,d,**}, Lorenzo Moroni ^{a,*}

^a Department of Complex Tissue Regeneration, MERLN Institute for Technology Inspired Regenerative Medicine, 6200 MD Maastricht, The Netherlands

^b Department of Civil, Chemical, Environmental and Materials Engineering, University of Bologna, 40131 Bologna, Italy

^c Department of Chemistry "G. Ciamician" and INSTM Udr of Bologna, University of Bologna, 40126 Bologna, Italy

^d Health Sciences and Technologies – Interdepartmental Center for Industrial Research (HST-ICIR), University of Bologna, 40064, Ozzano dell'Emilia, Bologna, Italy

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ABSTRACT

Bioactive scaffolds for tissue engineering call for demands on new materials which can enhance traditional biocompatibility requirements previously considered for clinical implantation. The current commercially available thermoplastic materials, such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(ϵ -caprolactone) (PCL) and their copolymers, have been used to fabricate scaffolds for regenerative medicine. However, these polymers have limitations including lacking of broadly tuning mechanical and degradable properties, and activation of specific cell-scaffold interactions, which limit their further application in tissue engineering. In the present study, electrospun scaffolds were successfully fabricated from a new class of block poly(butylene succinate)-based (PBS-based) copolyesters containing either butylene thiodiglycolate (BTDG) or butylene diglycolate (BDG) sequences. The polyesters displayed tunable mechanical properties and hydrolysis rate depending on the molecular architecture and on the kind of heteroatom introduced along the polymer backbone. To investigate their potential for skeletal regeneration, human mesenchymal stromal cells (hMSCs) were cultured on the scaffolds in basic, osteogenic and chondrogenic media. Our results demonstrated that PBS-based copolyesters containing thio-ether linkages (i.e. BTDG segments) were more favorable for chondrogenesis of hMSCs than those containing ether linkages (i.e. BDG sequences). In contrast, PBS-based copolyesters containing ether linkages showed enhanced mineralization. Therefore, these new functional scaffolds might hold potential for osteochondral tissue engineering applications.

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1. Introduction

A promising strategy for repairing damaged tissues and organs is to design scaffolds able to support and eventually control cell

activity, i.e. adhesion, proliferation and differentiation. Electrospinning is a simple technique capable of producing non-woven scaffolds made of continuous fibers with diameters ranging from few tens of nanometers up to several micrometers [1]. The resulting fibrillary networks mimic the morphology of native extracellular matrix (ECM), which serves to organize cells and provides signals for cellular responses [2].

Among the manifold of current commercially available thermoplastic materials used to fabricate three-dimensional (3D) scaffolds for regenerative medicine, aliphatic polyesters undoubtedly represent so far the most extensive studied class, since they combine good physico-chemical and mechanical

* Corresponding author. Department of Complex Tissue Regeneration, MERLN Institute for Technology Inspired Regenerative Medicine, 6200 MD Maastricht, The Netherlands.

** Corresponding author. Department of Chemistry "G. Ciamician" and INSTM Udr of Bologna, University of Bologna, 40126 Bologna, Italy.

E-mail addresses: marialetizia.focarete@unibo.it (M.L. Focarete), l.moroni@maastrichtuniversity.nl (L. Moroni).

¹ Equally contributing authors.

properties with assessed biocompatibility [3]. Poly(lactic acid) (PLA), poly(glycolic acid) (PGA), poly(ϵ -caprolactone) (PCL) and their copolymers are typically used [4] and their hydrolytic and enzymatic degradation under physiological conditions has been extensively proven [3]. Although these polymers have found many applications in clinical practice, the wide tuning of their mechanical, physico-chemical and biological properties is somehow limited [4]. For instance, the copolymerization of PLA with PCL enables to decrease polymer elastic modulus, thus obtaining more deformable materials that, however, are highly hydrophobic and display a very slow degradation rate. Hydrophilicity and hydrolysis rate can be significantly enhanced through copolymerization of PLA with PGA but, in this case, the rigidity of the material persists. This hampers the fabrication of 3D scaffolds capable of adapting to the needs of the specific tissue to be regenerated. Therefore, new polyesters with more flexibility in tuning their properties attract considerable attention in regenerative medicine.

In the last few years, an increasing number of researchers proposed poly(butylene succinate) (PBS) as a possible alternative to the above mentioned aliphatic polyesters due to the following advantages: (i) simple synthetic strategy through melt polycondensation; (ii) low cost of raw materials (1,4-butanediol and succinic acid), which can be also obtained from renewable resources [5]; (iii) high melting temperatures among poly(alkylene dicarboxylate)s ($T_m = 113$ – 115 °C); (iv) good thermal stability (thus a wide processing temperature range); (v) proven biodegradability and biocompatibility [6]. Furthermore, PBS is already commercialized by different companies for various applications such as compost bags and mulching films, but also fishery, civil engineering and construction and for common household goods.

Many efforts have been recently devoted to target PBS modification aiming to achieve better performances with respect to the intended application. For biomedical applications, composites have been realized by incorporating organic or inorganic fillers such as chitosan, collagen, calcium phosphate or hydroxyapatite along the PBS macromolecular chain [6]. A plethora of PBS-based blends and copolymers have been also obtained [6]. Among other copolymerization techniques, reactive blending is a versatile and solvent free approach which permits to prepare block copolymers of different molecular architecture by simply varying the reaction time [7].

Recent studies have demonstrated that the properties of scaffold, such as scaffold elasticity, structure and organization, and chemistry, can direct stem cell differentiation into specific lineages [8–10]. In this study, electrospun scaffolds fabricated from a class of block PBS-based copolyesters containing either butylene thiodiglycolate (BTDG) or butylene diglycolate (BDG) sequences, obtained by reactive blending, are presented. In particular, the possibility to use the synthesized copolymers as an alternative to conventional polyesters was explored to achieve enhanced control over stem cell differentiation. In these systems, the addition of heteroatoms along the macromolecular chains has been demonstrated to tune chain flexibility, thus affecting polymer crystallinity and mechanical properties of aliphatic polyesters [11,12]. Moreover, through this strategy surface hydrophilicity has been modified, due to the presence of electronegative oxygen and sulphur atoms [13–15]. All these factors significantly impact the biodegradation rate and biocompatibility of the final materials [16,17]. Scaffolds with tailored chemical composition and physical properties have been prepared and characterized. Their hydrolytic degradation profile has been evaluated under physiological conditions. Finally, we show that these copolymers may have the potential to steer stem cell differentiation towards skeletal lineages.

2. Materials and methods

2.1. Materials

Dimethylsuccinate (DMS), 1,4-butanediol (BD), diglycolic acid (DGA), thiodiglycolic acid (TDGA), and titanium tetrabutoxide (TBT) (Sigma–Aldrich) were reagent grade products. All the reagents were used as supplied with the exception of TBT which was distilled before use. Chloroform, dichloromethane (DCM), 2-chloroethanol (CE) and hexafluoro-2-propanol (HFIP) were purchased from Sigma–Aldrich and were used without any further purification.

2.2. Polymer synthesis

Starting homopolymers, i.e. PBS, poly(butylene diglycolate) (PBDG) and poly(butylene thiodiglycolate) (PBTDG) were synthesized in bulk by the usual two steps melt polycondensation, starting from 1,4-butanediol (BD) and DMS, DGA or TDGA, as reported elsewhere [11,12]. Two blends, PBS/PBDG and PBS/PBTDG, were obtained by melt mixing for 10 min equimolar amounts of PBS with PBDG and PBTDG, respectively, according to the procedures previously described [11,12]. Poly(butylene succinate/diglycolate) (P(BS₁₁BDG₁₁)) and poly(butylene succinate/thiodiglycolate) (P(BS₁₀BTDG₁₀)) copolyesters were obtained by melt mixing equimolar amounts of PBS with either PBDG (for 30 min) or PBTDG (for 45 min), respectively [11,12]. The reactions were carried out at 225 °C, under dry nitrogen atmosphere to prevent polymer degradation. Copolymer formation was catalysed by the residual titanium tetrabutoxide used for the synthesis of the parent homopolymers. The reactive blending provided two block copolymers (P(BS₁₁BDG₁₁) and P(BS₁₀BTDG₁₀)) with similar block length.

2.3. Scaffold and film preparation

PBS, PBS/PBDG and PBS/PBTDG blends, and P(BS₁₁BDG₁₁) and P(BS₁₀BTDG₁₀) copolymers were subjected to electrospinning to obtain 3D mats. Scaffolds were produced by using a customized electrospinning apparatus, comprised of a high-voltage power supply (SL 50 P 10/CE/230; Spellman), a syringe pump (KD Scientific 200 series), a glass syringe, a stainless steel blunt-ended needle (inner diameter = 0.84 mm) connected with the power supply electrode, and a grounded aluminium plate-type collector (7 cm × 7 cm). Polymer solution was dispensed through a Teflon tube to the needle which was placed vertically on the collecting plate at a measured distance (D). The scaffolds were produced at room temperature (RT) and a relative humidity of 40 ± 5%. The electrospun solution and the operating conditions for each polymer were selected after optimization experiments aimed at obtaining bead-free fibers and are reported in Table S1. Electrospun mats were kept under vacuum over P₂O₅ at RT overnight to remove residual solvents.

Films (0.2 mm thick) of PBS, blends and copolymers were obtained by compression moulding the polymers between Teflon plates, with an appropriate spacer, at 140 °C for 1 min under a pressure of 2 ton m⁻² (Carver C12, laboratory press).

2.4. Material characterization

Polymer structure and composition were determined by means of proton nuclear magnetic resonance (¹H NMR) spectroscopy, whereas the distribution of the co-monomeric sequences along the polymer chain was evaluated by ¹³C NMR spectroscopy. The measurements were carried out at RT by employing a Varian Inova 400-MHz instrument (Agilent Technologies, USA). Molecular weights

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