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Role of polymers in the design of 3D carbon nanotube-based scaffolds for biomedical applications

María C. Serrano*, María C. Gutiérrez, Francisco del Monte

Instituto de Ciencia de Materiales de Madrid (ICMM), Consejo Superior de Investigaciones Científicas (CSIC), C/ Sor Juana Inés de la Cruz 3, 28049 Madrid, Spain

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ABSTRACT

Since pioneer works by Iijima in 1991, carbon nanotubes (CNTs) have received a great deal of attention as confirmed by the increasing number of papers in the topic. Their unique and attractive properties have made them extensively demanded materials for a wide variety of technological applications, including their promising use as scaffolds in tissue engineering. In this review, we focus on the role that polymers (both natural and synthetic) play on the fabrication of three-dimensional (3D) CNT-based scaffolds for biomedical applications, with emphasis on biocompatible fabrication strategies such as freeze-casting, electrospinning and gel formation. These 3D matrices may be an interesting and alternative platform to circumvent structural limitations and toxicity problems of bare CNTs by the use of biocompatible dispersant polymers that allow the preparation of substrates better resembling native extracellular matrices. In any case, due to the relevance of CNT toxicity in this context, we also discuss significant works concerning cell and tissue responses to CNTs in dispersion, highlighting: (1) the asbestos-like behavior of CNTs, (2) surface functionalization as a tool to reduce CNT toxicity and (3) CNT biodistribution from the blood stream and posterior excretion. In this sense, literature revision has evidenced major toxicity issues related to: (a) the inherent insolubility and tendency to aggregate of pristine CNTs, (b) the rigidity of their structures that makes them resemble asbestos, (c) the presence of residual metal impurities or amorphous carbon from their synthesis, and (d) the depletion of culture media components due to the adsorptive properties of CNTs. Nevertheless, as expected for almost any material, we also illustrate how dose plays a key role in the biological responses induced. Overall, this critic review is expected to help research community working on polymers and CNTs, as well as other carbon nanomaterials such as graphene, to identify useful guidelines that help advancing the use of 3D CNT-based scaffolds in biomedical applications.

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* Corresponding author at: Laboratory of Neural Repair and Biomaterials, Hospital Nacional de Parapléjicos, Finca de la Peraleda s/n 45071 Toledo, Spain. Tel.: +34 925 247758; fax: +34 925 247 745.
E-mail address: mslopezterradas@sescam.jccm.es (M.C. Serrano).

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1. Introduction

Carbon nanotubes (CNTs) have devoted a great deal of attention in the past two decades due to their unique and attractive properties, as demonstrated by the increasing number of papers in the topic (Fig. 1). CNTs are an allotropic form of carbon defined as hollow cylinders exclusively composed of graphitic carbon sheets generally rolled as either a single- (SWCNTs), doubled- (DWCNTs) or multiwalled structure (MWCNTs) [1,2]. As nanomaterials, CNT diameter must be always comprised within the nanometer scale (0.5–2 nm for SWCNTs, *ca.* 3 nm for DWCNTs and 2–100 nm for MWCNTs), but their length easily reaches microns. The small CNTs can be rolled up in different ways, thus resulting in armchair, zigzag and chiral types [3]. Three major methods have been used for the mass production of highly purified CNTs [4]: arc-discharge [5], laser ablation [6] and chemical vapor deposition (CVD) [7], the last one being the most commonly used. CVD involves the growth of CNTs as a vertically aligned structure by using a gaseous carbon supply (hydrocarbon feedstock) and a metal catalyst (*e.g.*, nickel) at high temperatures (typically >700 °C). They can be later removed, or not, from this structure depending on the desired use [8], and then incorporated into a wide variety of composites. In regards to their attractive features, CNTs have exceptional mechanical properties, with a reported Young's modulus higher than 1 TPa and tensile strengths up to 63 GPa (10–100 times higher than steel) [9,10], and thermal stability up to 2800 °C under vacuum [11]. Electrical conductivities of 92 S cm^{-1} have been described [12]. The exceptional mechanical, electrical and thermal properties mentioned above are caused by the sp^2 hybridation that maintains the carbon atoms bonded to each other in the CNT structure [1]. Other attractive properties of CNTs include: an ordered structure, lightweight, high aspect ratio, high surface area, adsorptive properties, intrinsic near-infrared optical adsorption, Raman scattering resonance, photoluminescence, and photo-acoustic properties.

Since their discovery a few decades ago [13,14], an extensive progress has been devoted to use CNTs as brick elements for the development of advanced materials with remarkable characteristics. In this sense, the incorporation of CNTs into composite materials benefits from their mechanical, thermal and electrical properties, among others, while reducing their limitations. Particularly, the fabrication of diverse CNT-based polymer composites in the last decade has opened their use in a wide collection of applications, including flexible electrodes in displays, electronic paper, antistatic coatings, bullet-proof vests, protective clothing, and high-performance composites for aircraft and automotive industries [15,16]. More recently, CNTs have also shown utility in the emerging field of nanobiotechnology. In this context, CNTs have been already exploited for the preparation of biosensors [17–19], field emission devices [20], gas storage systems [21], tips for atomic force microscopy [22], nano-surgical needles [23], and fuel-powered artificial muscles [24], among others. In the area of tissue engineering [1,25–27], they have been extensively explored for bone regeneration [28–31], nerve tissue repair [32–36], and blood contacting materials [37,38]. Last but not least, the adsorptive properties of CNTs, along with their high aspect ratio, have encouraged their application as molecular carriers in a variety of delivery systems, including drugs, proteins, DNA, and even small interference RNA [39–46].

Despite their attractive potential, important limitations arise when using CNTs for biomedical applications. Particularly, CNT toxicity still remains as a major issue limiting their biological use [47], as well as the mechanical and structural restrictions of substrates exclusively constituted by CNTs. In an attempt to aid both aspects, polymers have been extensively explored as a more permissive and versatile platform for the integration of CNTs in biological systems. Results in this sense have permitted the fabrication of an ample repertoire of 3D architectures (*i.e.*, scaffolds), thus benefitting CNT toxicity when involving the use of biocompatible dispersant polymers. In the particular context of tissue regeneration, 3D scaffolds have been pursued to serve as matrices that resemble the geometry, chemistry and signaling environment of the natural extracellular matrix (ECM) and its role of offering structural support and a favorable environment for tissue growth and vascularization [48]. Importantly, 2D culture systems fail reproducing

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