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Graphene-based materials for tissue engineering☆

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ABSTRACT

Graphene and its chemical derivatives have been a pivotal new class of nanomaterials and a model system for quantum behavior. The material's excellent electrical conductivity, biocompatibility, surface area and thermal properties are of much interest to the scientific community. Two-dimensional graphene materials have been widely used in various biomedical research areas such as bioelectronics, imaging, drug delivery, and tissue engineering. In this review, we will highlight the recent applications of graphene-based materials in tissue engineering and regenerative medicine. In particular, we will discuss the application of graphene-based materials in cardiac, neural, bone, cartilage, skeletal muscle, and skin/adipose tissue engineering. We will also discuss the potential risk factors of graphene-based materials in tissue engineering. In conclusion, we will outline the opportunities in the usage of graphene-based materials for clinical applications.

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1. Introduction

Graphene is one of the crystalline forms of carbon, which is a single monolayer of sp^2 hybridized orbitals in a tightly packed two-dimensional (2D) honeycomb lattice (Fig. 1) [1]. Each carbon atom has three σ-bonds and an out-of-plane π-bond that can bind with neighboring atoms [1]. This atomic structure, combined with the electron distribution of graphene, results in high thermal and electrical conductivity, unique optical behaviors, excellent mechanical properties, extreme chemical stability, and a large surface area. Furthermore, by chemical and physical modifications, graphene sheets can be transformed into graphene-related materials such as single and multi-layered graphene, graphene oxide (GO), and reduced GO (rGO), each of which has unique tunable properties. Since its experimental discovery in 2004 [2] it has been widely used in various fields such as flexible electronics [3,4], supercapacitor [5], batteries [6], printable inks [7], optical, electrochemical sensors [8–10], and energy storage [11–13].

The field of tissue engineering involves the reproduction and regeneration of damaged tissues and organs [14,15]. To achieve its potential, engineered tissues require effective organization of cellular, morphological, and physiological features resembling those *in vivo* [16–18]. Therefore, the development of novel substitutes to create functional three-dimensional (3D) complex tissue constructs *in vitro* or regenerate damaged tissues *in vivo* are of great importance. To engineer functional tissues, the generated substitutes have to possess several key factors such as guiding cell growth and modulation, delivering bioactive molecules, generating proper physical and chemical signal cues, and stimulating mechanical properties of the native tissue. These factors can be aided by incorporating specific nanomaterials that possess the unique features and properties in between single atoms and continuous bulk structure.

Graphene is one of the most versatile nanomaterials due to its exceptional physical and chemical properties. Moreover, graphene can interact with other biomolecules such as DNA, enzymes, proteins, or peptides for regenerative medicine and tissue engineering. In recent years graphene and its chemical derivatives have emerged as a new class of nanomaterials and have been widely used in biomedical applications [19]. For example, while the excellent optical properties are suitable for bioimaging, graphene's large surface area and availability of free π electrons are useful in gene and drug delivery platforms [20–27]. In addition, outstanding mechanical strength, stiffness and electrical conductivity make graphene-based materials a good candidate for bone and neural tissue engineering [13,28–32].

In this review, we will highlight the recent applications of graphene-based materials in tissue engineering and regenerative medicine. In particular, we will emphasize on the applications of graphene-based materials in cardiac, neural, bone, cartilage, musculoskeletal, and skin/adipose tissue engineering. Although there is a great enthusiasm in using graphene-based materials in this field, there are still concerns regarding the potential toxicity and biocompatibility of these materials among the scientific and public communities. Therefore, we critically discuss this concern and propose potential solutions.

2. Properties of graphene and its chemical derivatives

Graphene can be produced by various approaches including chemical vapor deposition [33], mechanical cleavage of graphite [34], and electrochemical exfoliation of graphite [35]. Graphene can be further wrapped up to form zero dimension (0D) nanomaterials such as fullerenes, or rolled into nanotube (one dimension, 1D), or manipulated into 3D graphite [36]. Graphene sheets exist in bi-layers and multi-layers (<10), each possessing unique properties. Further increasing the number of layers significantly changes the properties of the material as a graphene stacks more than 10 layers behaves more like graphite [36], demonstrating that the interlayer structure and coupling between the layers determine key physical properties [37]. For instance, the stacking order, relative twist, and interlayer spacing govern the electronic, optical, and mechanical properties of multi-layered graphene [38–40].

Additionally, graphene the free-standing two-dimensionally carbon allotrope, each carbon atom in the 2D crystal is bonded to the three other adjacent carbon atoms forming a hexagonal aromatic structure [1]. This specific structure and its periodicity result in unique electrical and mechanical characteristics. The electron confinement in the orbitals are localized to neighboring carbon atoms to create the covalent σ-bonds [41,42]. The σ-bonds (C–C bonds) are responsible for the perfectly planar nature of graphene and determine its strong mechanical properties. Graphene's unique physical properties include hardness higher than diamond [43], elastic modulus as high as 1 TPa [43], thermal

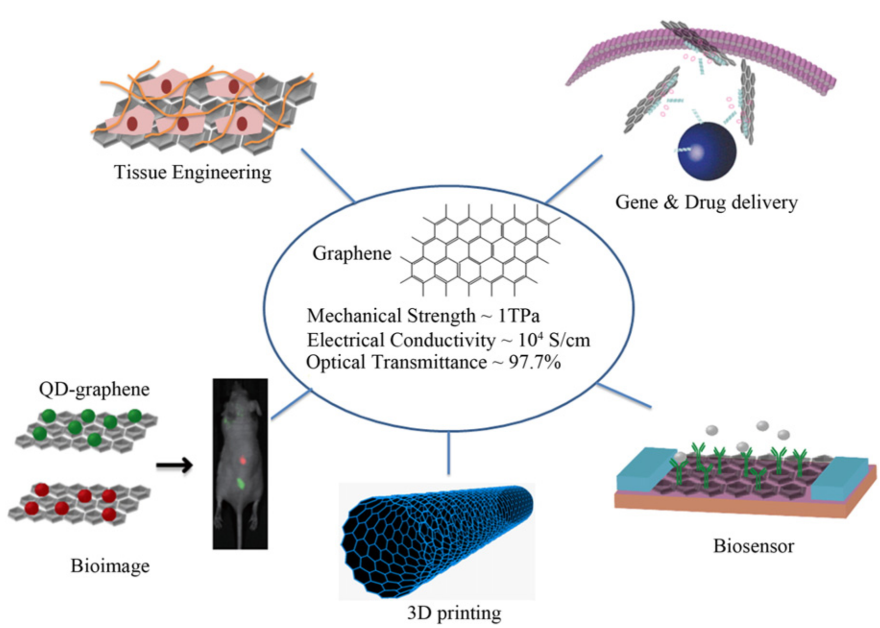

Fig. 1. The overall application of graphene-based materials for regenerative medicine and tissue engineering (Reprinted with permission of bioimage from [27] Copyright (2012) American Chemical Society).