Review Article

Graphene-based nanomaterials in precision medicine for next-generation therapeutics: Emerging advances, therapeutic potentials, and translational challenges

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Abstract

Graphene, a two-dimensional substance with distinctive mechanical, optical, and electrical characteristics, has recently attracted considerable attention. Researchers have explored the use of graphene-based nanomaterials in various biomedical contexts, such as drug delivery, biosensing, tissue engineering, and cancer treatment. These materials hold significant promise for advanced therapeutic purposes, including precise cancer cell targeting through ligand functionalization and heat generation for photothermal therapy to eradicate cancer cells. Nevertheless, there are noteworthy challenges to overcome, with a primary concern being the potential toxicity of graphene-based substances due to uncertainties regarding their long-term effects on human health. Thus, it is imperative to rigorously assess the safety of these materials before their adoption in clinical applications. This review article consists of overviews of recent advancements in graphene-based nanomaterials for advanced therapeutics and discusses the associated obstacles. By comprehending both the potential benefits and limitations of graphene-based materials, we can continue to push the boundaries of biomedical research and potentially transform the field of therapeutics.

Keywords: Graphene-based nanomaterials, targeted therapy, photothermal therapy, biocompatibility, safety, clinical applications

Introduction

In recent years, significant research has been into the potential therapeutic applications of graphene-based nanomaterials (Rezwani et al., 2016). Graphene, a two-dimensional material known for its distinctive mechanical, optical, and electrical properties (Kenry et al., 2018), has demonstrated suitability for a broad spectrum of biomedical uses (Figure 1). This article reviews recent advancements in utilizing graphene-based nanomaterials for advanced therapeutic purposes (Q Li et al., 2013). One key advantage of graphene-based nanomaterials is their high surface area-to-volume ratio, facilitating substantial drug-loading capacities (Dreyer et al., 2010). These materials have found applications in drug delivery, where they can be customized with various targeting molecules for precise cancer cell targeting (Prabhakaran et al., 2009; Shirvats et al., 2014). Furthermore, graphene-based materials have been investigated for photothermal therapy, enabling heat generation to eradicate cancer cells (Sang et al., 2013). However, challenges persist concerning the use of graphene-based nanomaterials in therapeutics. A significant hurdle is a potential toxicity associated with these materials (Hench et al., 1998). Although graphene is generally considered biocompatible, there are lingering concerns regarding the prolonged impact of graphene exposure on human health (Fergal et al., 2011). Therefore, it is imperative to conduct comprehensive safety assessments of graphene-based nanomaterials before considering their application in clinical settings (Willerth and Sakiyama-Elbert et al., 2008). In conclusion, graphene-based nanomaterials hold immense promise for advanced therapeutic applications. With

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continued research and development, these materials can potentially revolutionize the realm of therapeutics by offering more effective and targeted treatments for various diseases (Pandey et al., 2016). Nevertheless, addressing the challenges linked to their use is vital, ensuring both safety and efficacy in clinical applications (Figure 1) (Shin et al., 2016).

Graphene: chemistry and importance

Graphene, a carbon allotrope arranged in a hexagonal lattice in a two-dimensional structure, gained prominence following its isolation and investigation in 2004 by Andre Geim and Konstantin Novoselov, who were subsequently honoured with the Nobel Prize in Physics in 2010 for their graphene-related research (Meena et al., 2015; Solanki et al.,2013). Graphene boasts numerous distinctive attributes, including extraordinary strength, exceptional electrical conductivity, and a vast surface area (Farid et al., 2016). These remarkable characteristics make it an appealing material for various applications, spanning electronics, energy storage, and biomedical fields (Zhu et al., 2010).

In biomedical research, graphene-based materials have been extensively examined for their potential in drug delivery, biosensing, tissue engineering, and cancer treatment (Zaaba et al., 2017). Graphene-based substances can be tailored with various targeting ligands, enabling precise cancer cell targeting. Additionally, they find utility in photothermal therapy for eradicating cancer cells (Staudenmaier, 2018). Nevertheless, lingering concerns persist regarding the potential toxicity of graphene-based materials, given that their prolonged effects on human health still need to be fully comprehended. Consequently, it is imperative to rigorously assess the safety of graphene-based materials before contemplating their application in clinical contexts (Fu et al., 2005).

Graphene oxide: chemistry and importance

Graphene oxide, a derivative originating from graphene, features surface oxygen functional groups (Pei et al., 2018). Its production involves the oxidation of graphite by applying potent oxidizing agents like potassium permanganate or sodium nitrate, followed by processes such as sonication or chemical reduction (Seabra et al., 2014). Graphene oxide possesses several characteristics that render it appealing for diverse applications, encompassing its extensive surface area, biocompatibility, and capacity to interact with biomolecules (Hu and Zhou, 2013). Its utility has been explored across various biomedical applications, including drug delivery, biosensing, tissue engineering, and cancer therapy (Lopez-dolado et al., 2016). A notable advantage of graphene oxide lies in its amenability to functionalization with diverse biomolecules like proteins, DNA, and peptides, enabling targeted drug delivery or biosensing (Langer and Vacanti, 1993). Additionally, it can be employed for photothermal therapy, where it generates heat to eliminate cancer cells (Langer, 2000). Nonetheless, apprehensions endure regarding the potential toxicity of graphene oxide due to the presence of oxygen functional groups, which can enhance reactivity and the potential for oxidative stress (Yeatts and Fisher, 2011). Consequently, a thorough evaluation of the safety of graphene oxide is essential before contemplating its use in clinical settings (Hummers and Offeman, 1998).

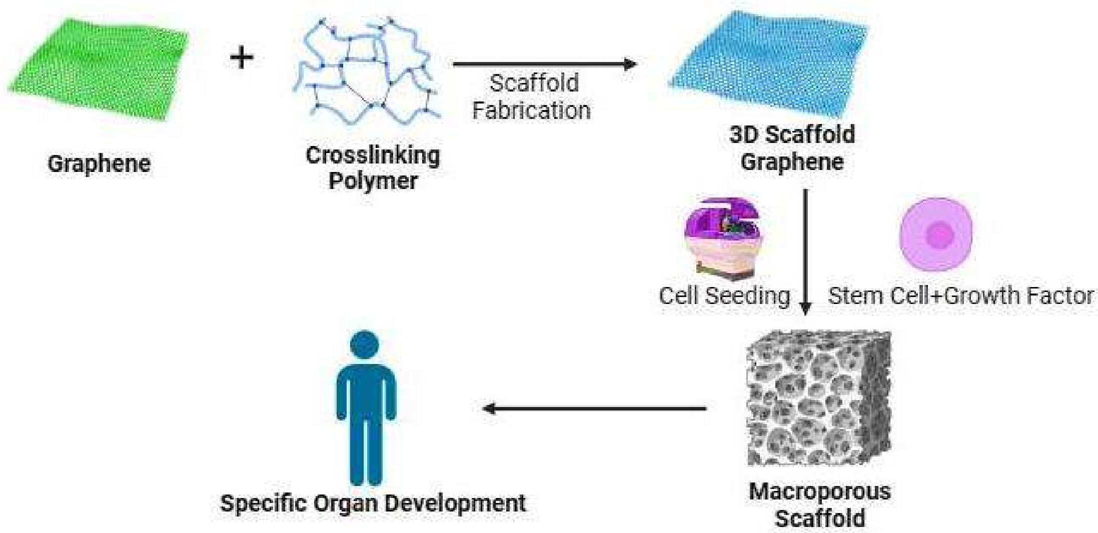

Figure 1: Schematic representation of tissue engineering using scaffold

Synthesis of graphene oxide

Graphene oxide can be synthesized using a modified approach based on the Hummers method, involving the oxidation of graphite with potent oxidizing agents like potassium permanganate or sodium nitrate (Scalera et al., 2014). This procedure usually comprises the following stages:

1. Formation of graphite oxide: Initially, graphite undergoes oxidation in a mixture of concentrated sulfuric acid and sodium nitrate, creating graphite oxide.
2. Further oxidation with potassium permanganate: The graphite oxide is subsequently subjected to additional oxidation using potassium permanganate, introducing oxygen functional groups onto the graphene sheets' surfaces.
3. Reduction: To transform graphene oxide back into graphene, chemical or thermal reduction methods are employed. Chemical reduction can be accomplished using reducing agents like hydrazine, sodium borohydride, or ascorbic acid. In contrast, thermal reduction involves heating the graphene oxide at elevated temperatures within an inert gas environment (Marcano et al., 2010; Sun et al., 2014; Yu et al., 2016; Henkel et al., 2013).

The resultant graphene oxide sheets typically exhibit a thickness on the order of a few nanometers and lateral dimensions spanning several micrometres. Oxygen functional groups on the graphene oxide's surface enhance its hydrophilicity and reactivity compared to pristine graphene, rendering it suitable for various biomedical applications (Table 1).

Properties (in therapeutic applications)

Graphene possesses several distinctive characteristics that render it appealing for medical treatments, as referenced in (Sarkar et al., 2010; Koshi et al., 2004; Wang et al., 2013):

1. Large Surface Area: With a substantial surface area relative to its weight, graphene is ideally suited for drug delivery systems and bio-detection.

2. Superior Electrical Conductivity: An electrical conductor, graphene is beneficial for bio-detection and serves as a heating medium for photothermal treatments.

3. Exceptional Mechanical Durability: Graphene is perfect for forming the foundation in tissue engineering and restorative medicine.

4. Biological Compatibility: Multiple studies have indicated graphene's compatibility with various cells and organic tissues, emphasizing its potential in biomedicine.

5. Adaptable Surface: Graphene's surface can be tailored with diverse biological molecules, including proteins, peptides, and DNA, paving the way for precision drug delivery and bio-detection.

6. Photothermal Abilities: Graphene's capability to absorb near-infrared light makes it a candidate for photothermal cancer therapies.

Graphene's inherent attributes make it a promising substance for various medical uses (Stevenson et al., 1996), spanning drug transport, bio-detection, tissue creation, and oncological treatments (Chae et al., 2013). Nonetheless, thorough scrutiny regarding the safety and effectiveness of graphene-infused materials is crucial before they are integrated into clinical practices.

Applications of graphene and its derivatives

In bone tissue engineering

Graphene has exhibited promising attributes due to its distinct characteristics like exceptional mechanical strength, superior electrical conductivity, and biocompatibility (Brodie, 1999). Here are specific ways graphene can be employed in this field (Hamlekhan et al., 2010; Causa et al., 2016):

Table 1: Illustration of different techniques for producing graphene oxide

Method	Oxidants used	Solvent used	Advantages	Disadvantages	References
Hummers	$NaNO_3$ $KMnO_4$	H_2SO_4	Water free and requires less time (2 h).	emits toxic gases with $NaNO_3$.	Marcano et al., 2010
Modified Hummers Method	$K_2S_2O_8$ KMNO$_4$ $KMnO_4$	H_2SO_4 H_3PO_4	Decreases toxic gases, avoided the use of NaNo$_3$, produces GO with same characteristics.	-	Sun et al., 2014
Brodies	$KClO_3$	HNO_3	Ease of fabrication.	Time consuming (3-5 d) and hazardous due to emission of toxic gases.	Yu et al., 2016
Staudenmaier	$KClO_3$	H_2SO_4 HNO_3	Faster method than Brodies (96 h), one vessel reaction with improved processing yield.	Time consuming and hazardous.	Henkel et al., 2013

1. Structural Frameworks: Graphene can craft three-dimensional frameworks resembling the natural architecture of bone tissue. Such structures offer mechanical stability and enhance cell attachment and growth.

2. For Controlled Substance Release: Graphene, when combined with drugs, growth factors, or specific biomolecules, can provide a regulated release, aiding in bone restoration.

3. For Bio-Detection: Using graphene, one can create biosensors to monitor aspects such as pH shifts, temperature variations, or other signals that hint at either bone development or deterioration.

4. For Electrical Impulses: Bone tissue can receive electrical stimulation via graphene, an approach recognized for advancing bone growth and healing.

5. For Imaging Enhancements: Graphene can act as a contrast medium in imaging methods like X-rays, MRI, and CT scans, shedding light on bone structure and density.

Studies indicate that materials derived from graphene can spur the osteogenic transformation of mesenchymal stem cells, bolster bone creation, and augment bone repair in test animals (Jiang et al., 2005). Nonetheless, comprehensive studies are imperative to grasp the underlying processes and verify graphene-related materials' safety in medical settings (Table 2).

In neuronal regeneration

Graphene has demonstrated promise in nerve tissue restoration due to its distinct characteristics, such as its biocompatibility (Mohan et al., 2016; Yang et al., 2013), ability to conduct electricity, and robust mechanical nature. Here are specific avenues where graphene can be applied for nerve regeneration:

1. Neural Structural Supports: Graphene can develop three-dimensional frameworks that resemble the makeup of authentic neural tissue. These structures can offer physical reinforcement and encourage cell attachment and growth.

2. Electrical Impulses: Leveraging graphene's electrical conductivity, it can stimulate neural tissues, which fosters nerve tissue rejuvenation.

3. Controlled Medication Release: By integrating drugs or specific biomolecules with graphene, there can be a regulated dispensation, aiding in nerve regeneration.

4. Bio-Detection: Graphene-based biosensors can monitor variations in neural activities or other markers that signal nerve tissue regeneration.

Studies indicate that compounds crafted from graphene can stimulate neural stem cells' neuronal differentiation, bolster neurite growth, and boost functional recuperation in animal studies involving spinal cord injuries and strokes (Feng et al., 2011). However, in-depth exploration is essential to decode the exact processes involved and to ascertain the safe application of graphene-infused substances in medical scenarios (Table 3).

In biosensors

Graphene displays significant promise for use in biosensors due to its unique attributes, such as its superior electrical conductivity, expansive surface area, and biocompatibility (Lee et al., 2011). Here is how graphene can be applied in biosensing:

1. Biomolecular Identification: By tailoring graphene with specific biomolecules or receptors, it can identify a range of biomolecules, including proteins, DNA, and RNA. The heightened sensitivity of graphene-infused biosensors can pinpoint disease markers at an early stage.

2. Spotting Environmental Contaminants: Sensors derived from graphene have the precision to detect environmental pollutants, such as heavy metals, pesticides, and certain gases, with notable accuracy and selectivity.

3. Medical Testing: For medical diagnostics, graphene-infused biosensors might be helpful in scenarios like monitoring glucose levels in diabetic individuals or recognizing infectious ailments.

4. Sensors in Wearable Tech: Integrating graphene-

Table 2: Different uses of graphene substances in the realm of bone tissue regeneration

Structure	Composition	Cells	Advantages	References
3D porous scaffold	r GO+ nano HA (*in-vivo* rats)	Rat bone MSCs	20% nHA+rGO scaffold significantly enhanced cell proliferation.	Wei et al., 2014
Scaffold by electrospinning	GO+ poly vinyl alcohol	Mouse osteoblastic cells	attachment and growth of cells were significant	Gaharwar et al., 2019
As film on polyster coated tissue culture plates	Graphene Oxide	MSCs	high mechanical strength, porosity	Rasoulianboroujeni et al., 2020
Hybrid structure (Bioinspired surface)	rGO+ poly dopamine	Mouse osteoblastic cells	*In-vitro* mouse osteoblastic cells shown high adhesion,	Wang et al., 2013

Table 3: Different graphene substances are used for nerve tissue restoration

Materials	Cells	Advantages	References
2D r GO nanomesh	H NSCs	More differentiated to neurons and glia by NIR stimulation compared to conventional rGO.	Singh et al., 2016
2D graphene (CVD grown)	Hippocampal cells of mouse	Boosting of neurite sprouting and outgrowth of cells.	Tang et al., 2012
3D porous GO scaffolds	embryonic neural progenitor cells	Viable and interconnected neural cells were formed with neurons and glial cells.	Krishnamoorthy et al., 2012
3D rolled GO foam	hNSCs	By electrical stimulation the neuronal differentiation and generation of neural fibers was seen on porous cylindrical like scaffold.	Wu et al., 2011
Nanostructured rGO microfibers	NSCs	formation of dense neuronal networks surrounding the microfiber compared to 2D graphene film.	Kurantowicz et al., 2017

derived sensors in wearable gadgets allows continuous tracking of various metrics, including heart rhythms, blood pressure, and body temperature.

5. Contrast in Imaging: Graphene-infused contrast materials can be utilized in imaging modalities like MRI and CT scans.

Studies have revealed that biosensors based on graphene exhibit high precision, specificity, and durability (Lin et al., 2014; Bai and Shi, 2007; Li et al., 2013; Zhang et al., 2017; Shi et al., 2018; Zhang et al., 2018), making them fit for a broad spectrum of uses (Lin et al., 2018). Nonetheless, in-depth investigations are essential to comprehend their efficacy's underlying principles and validate their safety in medical contexts (Yang et al., 2014; Chen et al., 2002).

In bioimaging

Materials derived from graphene exhibit significant promise in the realm of bioimaging. Here is a glimpse into how graphene is being utilized in this sector (Young et al., 2005; Ramakrishna et al., 2006; Baker et al., 2015):

1. Contrast Enhancement: Graphene oxide (GO) and reduced graphene oxide (rGO) boast notable photothermal and photoacoustic traits. It makes them apt contrast agents in bioimaging, enhancing the clarity of MRI and CT scans.

2. Fluorescence Imaging: Graphene quantum dots (GQDs), which are diminutive graphene nanoparticles, possess distinct optical attributes, rendering them suitable for fluorescent imaging applications. These GQDs can be conveniently tailored with biomolecules, such as antibodies, facilitating the focused imaging of cells or tissues.

3. Photoacoustic Visualization: Graphene-infused materials can be contrasting agents for photoacoustic imaging. This approach amalgamates ultrasound's precise spatial resolution characteristic with the pronounced contrast typical of optical imaging.

4. Biosensory Applications: Biosensors founded on graphene can identify biological entities like proteins, nucleic substances, and cells. These can be pivotal for the diagnosis, treatment, and monitoring of the progression of diseases.

In summary, the potential of graphene-oriented materials in bioimaging is undeniable, offering benefits like superior sensitivity, precise resolution, and biocompatibility (Zhang and Ma, 1999; Chen et al., 1999). Nonetheless, a deeper dive into research is essential to ascertain the safety and effectiveness of these materials when applied biologically.

In cancer therapy

Graphene, characterized as a two-dimensional structure with a singular layer of carbon atoms set in a hexagonal pattern (Discher et al., 2005), has demonstrated promise in cancer treatments (Gilbert et al., 2006). Here are some avenues through which graphene is being investigated for oncological interventions:

1. Medication Transport: Studies on Graphene oxide (GO) and reduced graphene oxide (rGO) indicate their potential as carriers for anticancer medications. These can enhance the solubility and bioavailability of the drugs, ensuring they are precisely delivered to malignant cells.

2. Photothermal Treatment: Graphene and its variants can absorb near-infrared rays and transform them into thermal energy. This mechanism, termed photothermal therapy (PTT), has proven successful in animal-based studies by causing cellular death in cancer cells.

3. Photodynamic Approach: In photodynamic therapy (PDT), light activates a photosensitizer, creating reactive oxygen species (ROS) that can eliminate cancer cells. Materials derived from graphene have shown potential as efficient photosensitizers in PDT.

4. Biosensory Detection: Graphene-infused biosensors can identify markers indicative of cancer with impressive

Table 4: Uses of graphene-based nanostructures in oncology

Material	Cells	Advantages	References
nanoGO+PEG+ Doxorubicin	*In-vivo* and *in-vitro* tumors	Demonstrated combined effects of chemotherapy and photothermal treatment, enhancing therapeutic outcomes.	Xie et al., 2012
nanoG0+folic acid Doxorubicin (DOX) + Polyvinylpyrrolidone	*In-vitro*	Demonstrated a complete 100% loading capacity for DOX and proved effective in targeted chemophotothermal treatment.	Rainer et al., 2009
PEG+nanoGO+SN38 (camptothecin analogue)	HCT-116 (human colon cancer cell line)	Demonstrated greater effectiveness compared to irinotecan (CPT-11) and showcased impressive water solubility, enhancing its ability to target and kill cancer cells	Feng et al., 2020
PEGlyalted rGO sheets	U87MG cancer cells	Demonstrated strong in-vitro photo ablation capabilities, cost-effectiveness compared to other near-infrared (NIR) photothermal agents, and notable doxorubicin loading on reduced graphene oxide (rGO).	Lin et al., 2020

accuracy and precision, potentially paving the way for early diagnosis.

Even though therapies grounded in graphene present significant potential for oncological applications, more profound research is mandatory to thoroughly comprehend their safety profile and effectiveness (Fernandes et al., 2011; Sahoo et al., 2010). It is crucial to recognize that graphene's introduction is relatively recent, and comprehensive studies regarding its prolonged effects on human health are ongoing (Table 4).

Biodegradability and biocompatibility of graphene

Graphene, a two-dimensional carbon structure, boasts unique physical, chemical, and mechanical attributes, making it a prime candidate for multiple biomedical uses. Nonetheless, when contemplating its in-vivo applications, the biodegradability and biocompatibility of materials based on graphene are of paramount importance (He et al., 2018; Lu et al., 2017). Biodegradability denotes a substance's capability to disintegrate into more minor elements that the body can metabolically process and excrete (Yang et al., 2013). Under standard physiological situations, graphene, recognized for its stability, does not naturally biodegrade (Gaharwar et al., 2014; Sharma et al., 2019). This stability can be a double-edged sword, contingent on the intended use. For instance, in drug delivery (Wu et al., 2011), a persistent material like graphene might offer prolonged drug dispersion over time (Tian et al., 2016; Xu et al., 2014). Conversely, biocompatibility encapsulates a material's potential to coexist with biological tissues without inducing adverse effects. Materials derived from graphene display a spectrum of biocompatibility, influenced by aspects such as their dimensions, contour, surface composition (Zhang et al., 2018; Jiang et al., 2018; Han et al., 2019), and modifications. Evidence suggests that these graphene-derived materials could induce oxidative stress (Dong et al., 2019; Tian et al., 2016), invoke inflammation, and be cytotoxic both in vitro and in vivo. However, by adjusting parameters like size, surface polarity, and alterations, the adverse effects of these materials can be curtailed (Liu et al., 2014; Bai and Shi, 2007; Li et al., 2013; Zhang et al., 2017; Shi et al., 2018). A method to enhance graphene materials' biocompatibility is by appending biologically friendly polymers, like polyethylene glycol (PEG) (Zhang et al., 2018; Liu et al., 2018; Yang et al., 2014). Such PEGylation can augment the consistency of graphene materials and lessen their toxicity by bolstering their water compatibility and mitigating protein interactions (Chen et al., 2002; Young et al., 2005; Ramakrishna et al., 2006; Baker et al., 2015).

Conclusion

Graphene-derived nanomaterials have emerged as a promising contender in advanced therapeutic avenues due to their distinct physical and chemical attributes. This review encapsulates the latest progress in employing these nanomaterials for therapeutic purposes, encompassing drug delivery, tissue engineering, biosensing, and bioimaging. A notable strength of these nanomaterials is their prowess as effective drug carriers. Graphene oxide (GO) and its reduced counterpart, rGO, demonstrate impressive drug-binding and prolonged release capabilities, positioning them as prime choices for drug delivery. Moreover, tailoring these materials with specific targeting agents, like antibodies and peptides, amplifies their precision and potency. Graphene-derived nanomaterials shine in tissue engineering due to their biocompatibility, robustness, and electrical characteristics, making them apt for roles like tissue scaffolds. Their distinct electrical nature also paves the way for innovative uses, including nerve stimulation and heart tissue engineering. Regarding biosensing and bioimaging, these materials have achieved substantial breakthroughs. With a vast surface area and superior electron mobility, graphene-centric biosensors offer unmatched sensitivity and specificity. Their strong photoluminescence and magnetic attributes make them viable for bioimaging techniques, such as fluorescence visualization and MRI. However, the journey has hurdles. The prospective toxicity of these materials remains a pivotal issue that mandates rigorous examination before clinical application. Another impediment is the cost-effective, large-scale fabrication of premium-quality graphene derivatives. The last few years have witnessed remarkable strides in graphene-based therapeutic tools. To harness their full potential in clinical settings, future research endeavors must tackle existing challenges and refine the efficacy of these nanomaterials.

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Conflict of interest

None

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