

Review

Advances and Potentials of Graphene Materials in Tendon-Bone Interface Healing: A Review

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Abstract

In the field of orthopedic sports medicine, the healing of the tendon-bone interface (TBI) has always been challenging. This is due to the unique gradient fibrocartilage transition zone structure of the TBI, which limits the gradient tissue regeneration ability from the tendon to the bone and easily leads to TBI regeneration disorders. This unsolved problem has always been widely concerned. Low-dimensional biological materials represented by graphene materials, due to their high specific surface area, good mechanical properties, excellent biocompatibility, bionic topological structure and multimodal regulation capabilities, provide new solutions for the regeneration of TBI. In this article, we focus on reviewing the biological characteristics of graphene materials, the potential research value of graphene materials in regulating cells related to TBI healing, the application prospects of graphene-based composite biomaterials in TBI, as well as the challenges and prospects faced, aiming to provide theoretical references for related research on TBI healing.

Keywords: Tendon-bone interface, graphene, materials, macrophages, fibroblasts.

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Introduction

In the field of orthopedic sports medicine, the incidence of shoulder and knee injuries is high. Among these, the most common injuries include rotator cuff tears and knee cruciate ligament tears. Arthroscopic tendon repair or ligament reconstruction has become the current mainstream option for treating these types of injuries due to the advantages of less trauma, fewer complications, and faster recovery. However, postoperative re-tears or re-ruptures remain a frequent clinical issue [1,2], primarily due to the complex fibrocartilaginous transition zone structure at the tendon-bone interface (TBI), which subsequently leads to impaired regeneration at this interface [3]. In order to reduce surgical complications, scholars have added high-strength suture materials to allogeneic tendons in anterior cruciate ligament reconstruction [4], autologous tendon grafts in acromioclavicular ligament reconstruction [5], and biological materials to promote TBI healing in rotator cuff repair [6]. The

failure rate of surgery can be reduced by adding implants or biomaterials. Of note, the risk of infection associated with the application of biological implants during tendon-ligament repair is also a clinical challenge to be addressed, and studies have shown that postoperative infection significantly reduces patient limb function [7,8]. Such complications not only hinder the recovery of motor function and activities of daily living [9] but also increase the risk of second revision surgery, which will pose a heavy burden on the health of patients, the medical insurance system, and the social economy [1]. Therefore, novel biomaterials are needed to enhance the biomechanical strength of TBI and simultaneously activate the endogenous tissue regeneration program to promote the healing of TBI, the success rate of surgery and the life quality of patients can be systematically improved [1].

Among the biomaterials used in related surgeries, the traditional poly (lactic-co-glycolic acid) (PLGA) is a

degradable functional polymer organic compound, which is an important choice for clinical applications in this field due to its combination of good biocompatibility, biodegradability, and processing properties [10]. It is widely used in the pharmaceutical industry in medical suture, tissue healing [11], controlled drug release [12], tendon repair [13], tissue engineering, and bone internal fixation materials, and other related fields [14,15]. However, in general, the three-dimensional (3D) space size of PLGA is much larger than that of a nanometer scale, and PLGA has strong hydrophobicity and weak interaction with hydrophilic biomolecules or cells [16,17]. The mechanical strength, toughness, and other properties of PLGA materials make it difficult to meet the requirements of tissue repair with high mechanical performance demands. In practice, it is often necessary to composite with other materials to enhance the overall mechanical properties, suitable for the use of clinical repair standards [16]. In addition, the acidic substances produced by the degradation of PLGA may cause the pH value of the local microenvironment to decrease, trigger inflammatory responses, affect the adhesion and growth of tissue cells, and thereby affect tissue repair [18,19]. To overcome the inherent limitations of PLGA materials and improve their interface integration with host tissues, a low-dimensional nanocomposite material modification strategy can be adopted to functionalize and enhance PLGA [20].

Low-dimensional biomaterials have many advantages over traditional biomaterials in terms of biocompatibility, biological activity, and functionality. They mainly include zero-dimensional structures, one-dimensional structures, and two-dimensional structures [21]. Their nanoscale size enables them to contact cells in a larger and closer area and simulate the extracellular matrix microenvironment. Low-dimensional biomaterials have significant promotion effects on cell adhesion, proliferation and differentiation, while their special structure makes them not easily recognized by the body's immune system as foreign objects, which effectively reduces the occurrence of immune reactions and creates a more suitable microenvironment for the repair of damaged tissues [22]. Two-dimensional biomaterials, represented by graphene, have excellent mechanical properties, high strength, and good flexibility, and can adapt to the complex environment in the body while maintaining structural stability. They have good biocompatibility and adsorption ability and are of great research significance in the field of tissue regeneration and biomedicine [23–25]. To further improve the properties of graphene, various graphene derivatives have been developed, such as graphene oxide (GO) and reduced graphene oxide (rGO) [26,27], and fluorinated graphene (FG) [28]. It provides a new idea for TBI healing. Although graphene materials have shown great potential and have been widely studied in other fields of orthopedics, such as bone defect repair and artificial joint material improvement [29], due to their unique physicochemical properties, good biocompati-

bility, however, in TBI healing, which is a special and critical tissue connectivity region, its application is still in the exploratory stage. This review focuses on the current status and prospects of Graphene materials in the biomedical field of TBI healing, from the mechanism of action to preclinical functionalization, to provide a theoretical reference for related research.

Biological Characteristics of Graphene and its Derivatives

Graphene and its derivatives, as a typical representative of two-dimensional materials, exhibit a series of prominent characteristics. These include a high specific surface area, tunable porosity, excellent mechanical properties, and favorable electrical conductivity, along with strong surface affinity toward organic molecules [23,30,31]. Graphene and its derivatives have broad application prospects in the field of bone repair due to their functionalizable modification and good biocompatibility [7,24,30,32] (Fig. 1).

The high specific surface area and porous structure of Graphene and its derivatives can provide a large number of active sites; at the same time, the structure can mimic the microenvironment *in vivo*, which can promote the process of cell adhesion, proliferation and differentiation. These properties strengthen cell-cell interactions and promote cell-scaffold synergies, laying the foundation for relevant biological applications [30,33,34]. Graphene can be made into highly oxidized forms of GO and rGO under reducing conditions by chemical modification, and thermal or chemical treatment of reducing agents will change many properties of GO [35,36], such as changing hydrophilicity and dispersion in aqueous solution, reducing surface charge, adjusting conductivity, etc [31,37]. Chemically modified GO and rGO on different surfaces can change their hydrophobicity and hydrophilicity, thereby controlling their biological interaction potential [38]. The surface charge of Go plays a crucial role in cellular uptake and endocytosis; higher surface charge leads to greater repulsion between particles and lower aggregation, which also allows graphene and its derivatives to easily enter cells [39,40].

Carboxylation modification endows GO with excellent water solubility and abundant enzyme immobilization sites, laying the foundation for its diverse biomedical applications in biosensing, catalysis, imaging, and drug delivery. Graphene and its derivatives have excellent mechanical properties. By changing the degree of functionalization of hydroxyl and epoxy groups on the GO surface, the tensile strength decreases with the increase of functionalization. It is possible to customize the mechanical properties of GO through targeted surface and edge functionalization. Functionalized modification on GO surfaces enables a wider range of controlled applications in nanocomposites [41].

The graphene oxide-polyethylenimine (GO-PEI) derivative shows controlled porosity and structural clarity

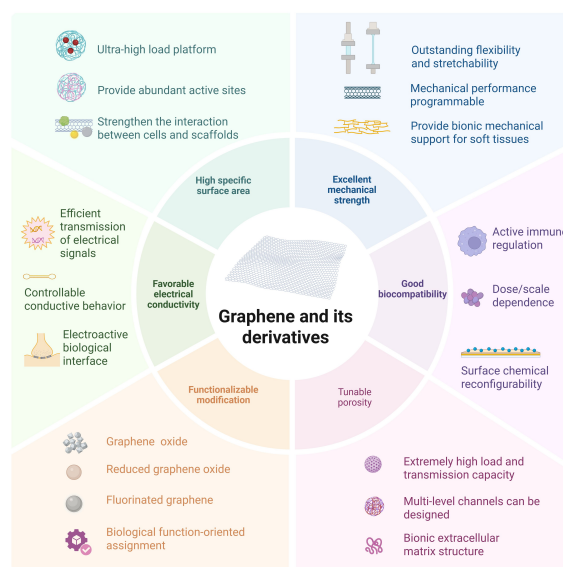


Fig. 1. Biological characteristics of graphene and its derivatives. (Created in BioRender. Xu, J. (2026) <https://BioRender.com/96166g4>.)

to provide better support for cell growth, which can restore cell proliferation and mitochondrial activity to controlled levels [33]. Polycaprolactone porous scaffolds, in which GO was added, increased cell attachment and proliferation and promoted the secretion of bone morphogenic protein-2 (BMP-2) and osteopontin [34]. GO can cause cells to show good cell viability and promote cell adhesion, while also upregulating the expression of regenerative factors such as transforming growth factor β (TGF- β) [42,43].

The injection application of GO may also trigger severe oxidative stress and inflammation, a potential risk that has been confirmed by relevant studies [44]. To mitigate such adverse effects of GO, modulation through surface functionalization is one of the effective strategies; for example, composites constructed by loading GO on the surface of TiO₂ nanotubes can significantly regulate macrophage polarization processes in the inflammatory microenvironment [45].

When stimulated with lipopolysaccharide, mouse monocyte-derived macrophages cultured on GO-modified titanium dioxide nanotubes (TNT) exhibited suppressed inflammatory responses and significantly enhanced M2-type polarization. This effect may stem from reduced intracellular reactive oxygen species (ROS) levels [45]. Graphene multifunctional collagen composite scaffolds can enhance cell viability, proliferation, and adhesion, and have excellent osteogenic and antibacterial properties, and graphene and its derivatives can promote osteogenesis and antibacterial effects. The transverse size of GO plays a key role in activating macrophages and stimulating pro-inflammatory responses in cells and animals. GO with a larger lateral size has a stronger adsorption capacity on the surface of

the cytoplasmic membrane, and accordingly, its probability of being phagocytosed by the cell is lower; at the same time, this type of large-size GO has a more significant activation effect on the NF- κ B signaling pathway. Smaller transverse-size GO sheets are more likely to be absorbed by cells, and larger transverse-size GO promotes more polarization of M1-type Macrophages. It is related to enhancing the production of inflammatory cytokines and the recruitment of immune cells [37].

rGO improves the antibacterial properties of nanocomposites. The photocatalytic disinfection rate of the rGO composite material photocatalyst against *Escherichia coli* was 99.92% within 180 minutes, and against *Staphylococcus aureus* was 99.85%. This improvement in antibacterial performance is due to the key role played by rGO, which not only promotes the efficient transport of electrons but also, the sharp edges of rGO can mechanically damage the cell membranes of bacteria [46]. A study has shown that the regulated discharge of cerium ions in cerium oxide nanoparticles supported by rGO can achieve spatiotemporal regulation of the cellular microenvironment and optimize the tissue repair process [36]. Antibacterial research indicates that in cerium/reduced graphene oxide (Ce/rGO) samples, the antibacterial efficacy against *Staphylococcus aureus* and *Escherichia coli* is enhanced. This is attributed to the synergistic effect of the antibacterial properties of rGO and the activity of cerium nanoparticles [36].

Fluorination serves as an effective surface modification strategy, regulating the interaction between graphene-based nanomaterials (GBNS) and biological systems by imparting unique carbon-fluorine (C-F) bonds. The core

of this modification lies in the synergistic effect of interfacial forces and fluorine chemistry, ultimately enabling partially FG to exhibit both enhanced antibacterial capabilities and superior cell compatibility compared to pristine graphene and FG [47]. Fluorinated graphene oxide (FGO) has good hydrophilicity, which is a significant biocompatibility advantage, and the ability to load hydrophobic therapeutic drugs onto its hydrophilic substrate, FGO nanosheets, which shows potential for use in targeted drug carriers [28,48].

In the field of biomaterials, graphene and its derivatives have attracted much attention due to their structural support function, electrical microenvironment regulation ability, and biological signal transduction activity. Such materials can not only be used as excellent conductive scaffolds to promote the directional arrangement, differentiation and collagen synthesis of cardiomyocytes, skeletal muscle cells and tendon cells, but also provide a new way for tissue repair without exogenous electrical stimulation due to their high electrical conductivity and biocompatibility. The core mechanism is that graphene-based materials can activate the electrophysiological response based on transmembrane potential and ion concentration by simulating the endogenous electrochemical gradient, thereby promoting cell migration, proliferation and directional differentiation [49–51]. Therefore, graphene-based conductive scaffolds can achieve tendon repair by promoting tenocyte differentiation and collagen synthesis.

GO and its derivatives have shown good application value in various therapeutic scenarios and drug delivery fields by virtue of their rich and diverse physicochemical and structural characteristics, becoming one of the promising material choices in this field (Table 1).

The Potential Research Value of Graphene Materials in the Regulation of Cells Related to TBI Healing

TBI is a hierarchical transition structure composed of tendon, non-calcified fibrocartilage, calcified fibrocartilage, and bone tissue. TBI efficiently coordinates mechanical transmission and biological function between soft and hard tissues through continuous changes in composition and mechanical properties [52]. Such as tenocytes, fibroblasts, chondrocytes, and osteocytes [53], these cells play their own roles in different areas and participate in the physiological function and repair process of TBI in coordination [3]. The healing of tendons and ligaments to the bone surface remains a therapeutic challenge due to the complex structure, composition, cell population, and interface mechanics of the TBI [54]. Biomaterials with good biocompatibility are urgently needed to improve mechanical strength and promote TBI healing to reduce surgical failure rate and improve limb function of patients [1,55].

During TBI healing, various cell types collaborate through directed differentiation and proliferation to pro-

mote the repair of TBI structures [56]. Extracellular biophysical factors can initiate cell signaling through mechanotransduction and promote cellular responses such as cell adhesion, migration, proliferation, gene/protein expression, and differentiation [57]. Graphene and its derivatives can promote cell differentiation and proliferation in TBI [58].

The 3D topological structure generated by graphene modification can effectively simulate the natural cellular microenvironment and enhance the adhesion of stem cells. Meanwhile, the interconnected pores are conducive to bone penetration, the formation of capillaries, and the transportation of nutrients. Furthermore, the simultaneous presence of micropores and mesopores significantly promotes the adsorption of extracellular matrix (ECM), thereby ensuring the adhesion of cells [59].

The highly ordered nanochain GO (Nano-GO) surface can regulate cell behavior, generate immediate perception of nano-topographic features by cells, cause dynamic cell interactions through cytoskeletal reorganization, and participate in cell adhesion, migration, alignment, proliferation, as well as cell morphological evolution [57] (Fig.2). Studies have shown nanofiber structures composed of a graphene matrix can promote TBI healing of the rotator cuff [60] and this mechanism of promoting TBI healing involves the regulation of a variety of cells, such as macrophages, mesenchymal stem cells (MSCs), and fibroblasts [61–63].

Macrophages, as the core participants of the immune response, play a key role in the process of tissue healing and can differentiate into pro-inflammatory M1-type and anti-inflammatory M2-type macrophages [64]. It plays a key role in different stages of tissue healing by dynamically regulating the inflammatory response and tissue repair [65,66]. Macrophage functions involve cell debris removal, secretion of cellular inflammatory factors, and shaping of the immune microenvironment, and interaction with MSCs [67,68]. The imbalance between M1-type and M2-type macrophages affects tissue regeneration or healing, and the promotion of tissue regeneration or healing can be achieved by modulating the phenotype of macrophages through chemical, physical, or biological treatments [30,64,69,70]. Promoting the polarization of macrophages to M2-type helps to reduce immune inflammatory response and accelerate the tissue repair process around the implant [66].

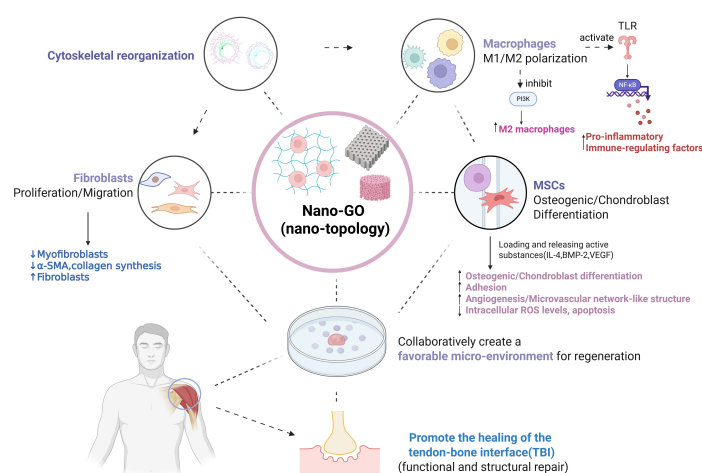
Regulation of Macrophages

The biological characteristics of graphene materials allow them to promote cell adhesion, proliferation, and differentiation, which are beneficial for cell-cell and cell-scaffold interactions [33,34]. The interaction between graphene and macrophages, cytokines/chemokines produced by macrophages through TLR-and NF- κ B-related signaling pathways, additionally, these graphene factors can modulate the phenotype of immature macrophages by reshaping their actin cytoskeleton, thereby reducing extracellular matrix adhesion and phagocytosis, which induces

Table 1. Biological characteristics of graphene materials.

Biological characteristics	Specific performance	Mechanism	References
High specific surface area and porous structure	Provide a large number of active sites to simulate the <i>in vivo</i> environment.	Promote cell adhesion, proliferation, and differentiation, and facilitate the interaction between cells and between cells and scaffolds.	[30,33,34]
Functionalizable modification	Chemically modified to GO, rGO, FGO, etc.	GO/rGO affects cell uptake and signal transduction by regulating surface charge and hydrophilicity. FGO can be used as a targeted drug carrier with both hydrophilic and hydrophobic drug-loading ability.	[28,35,36,39,40]
Adjustability of mechanical properties	The tensile strength decreased with the increase in the degree of functionalization, and mechanical properties were customized by surface hydroxyl/epoxy group modification.	GO nanocomposites can be functionalized to optimize their mechanical strength and are suitable for tissue engineering scaffolds.	[41]
Antibacterial property	rGO enhances antimicrobial capacity either by mechanical disruption of cell membranes or by synergistic nanoparticles.	Ce/rGO inhibited the growth of <i>Staphylococcus aureus</i> and <i>Escherichia coli</i> , and some FGO had better antibacterial ability than the original graphene.	[36]
Immunomodulatory capacity	Regulate macrophage polarization (M1/M2 balance)	GO-TNT nanotubes reduce ROS generation and promote M2 polarization; larger transverse sizes of GO promote M1 polarization, and smaller sizes are easily taken up by cells.	[37]

Highly ordered Nano-GO surfaces can regulate cell behaviors

**Fig. 2. Regulatory effects of graphene materials on cells.** (Created in BioRender. Xu, J. (2026) <https://BioRender.com/a6pzzcb>.)

significant morphological changes [71]. Functional tissue repair is often limited by inflammation and fibrosis. Activated M2-type macrophages have emerged as potential therapeutic targets for optimizing graft-host interactions, but efficient induction methods need to be developed. A study has shown that bifunctionalized GO can induce the polarization of M2a-type and M2c-type macrophages, and these two M2 subsets play pleiotropic inflammatory regulatory roles, coordinating inflammatory response and tissue remodeling [72]. Delivery of plasmid encoding interleukin-4 (pIL-4) or plasmid encoding interleukin-10 (pIL-10) via GO functionalized vectors successfully induced M2a-type or M2c-type subphenotypes characterized by negative regulation of immune effector processes and positive regulation of type 2 (Th2) immune responses. M2a exhibits the characteristics of IFN-responsive macrophages, which can inhibit the viral life cycle and promote myogenesis and osteogenesis. M2c, on the other hand, is characterized by interleukin-10 (IL-10) signaling, anti-fibrosis, and neutrophil-mediated antibacterial responses [72].

GO nanocomposite coating is a promising surface modification material in the field of TBI. Titanium dioxide nanotube (TNT) with GO (TNT-GO) serves as a novel nanocomposite coating that promotes macrophage M2-type polarization by reducing ROS production [45]. This coating exerts a positive immunomodulatory effect on tendon healing by coordinating the IL-10 and the tumor necrosis factor- α (TNF- α) [73]. The imbalance between M1-type and M2-type macrophages affects tissue regeneration or healing, and GO nanomaterials can promote M1/M2-type macrophage balance and promote a slight shift to M2-type macrophages involved in tissue repair [74]. Macrophages play a crucial role in the host response, and their M2-type macrophage polarization helps to reduce biomaterial implantation-induced foreign body response and promote tissue regeneration, and the synergistic effect of electrical stimulation (ES) and graphene microgroove can effectively promote the M2-type macrophages phenotype polarization by inhibiting macrophages actin polymerization and downstream Phosphatidylinositol 3-Kinase (PI3K) signaling pathways [75].

GO coatings are biocompatible and GO-coated surfaces have been found to manipulate macrophage polarization and inflammatory cytokine expression through the Toll-like receptor (TLR) pathway [34,76]. Under physiological conditions, GO-coated titanium (Ti-GO) activates macrophages and induces mild inflammation, with slightly elevated levels of proinflammatory cytokines and increased expression of TGF- β 1 and tumor stromal M genes, and Ti-GO attenuates the inflammatory response by down-regulating proinflammatory cytokines in an environment that mimics acute inflammatory conditions [76]. GO nanomaterials regulate the role of macrophages, which provides a valuable reference for the study of complex microenvironments related to TBI regeneration, and may benefit in TBI repair.

Regulation of MSCs

MSCs play multiple regulatory roles in the process of TBI healing. Their functions involve multiple links such as immune regulation, cell differentiation, paracrine effect, and tissue repair [68,77,78]. In addition, macrophages also interact with MSCs [68]. Exosomes are beneficial for tissue repair and regeneration [79], and bone marrow mesenchymal stem cells (BMSCs)-derived exosomes can promote extracellular matrix remodeling, osteogenic differentiation, angiogenesis, and stemness of tendon-derived stem cells, thereby accelerating TBI healing in rotator cuff tears. In promoting TBI healing in a mouse model of rotator cuff injury, adipose-derived and bone marrow-derived mesenchymal stromal cell exosomes (ADSC-Exos and BMSC-Exos) demonstrated comparable efficacy [79]. MSCs are incorporated in biomaterial implants that can be used for TBI healing [80]. For instance, previous studies on animal rotator cuff tear repair models using PLGA scaffolds loaded with bone marrow mesenchymal stem cells (BMSCS-PLGA) have found that BMSCS-PLGA scaffolds implanted at the rotator cuff TBI can increase collagen expression histologically and enhance the biomechanical properties of regenerated tendons biomechanically [81]. However, the mechanical strength and toughness of PLGA materials are difficult to meet the high mechanical performance requirements for tissue repair, and the bone induction ability of PLGA materials themselves is limited. Therefore, it is often necessary to combine it with other materials for reinforcement to improve its application in orthopedics [16,82]. To improve the shortcomings of PLGA materials, some researchers have combined the advantages of graphene derivatives and used electrospinning technology to prepare a complex of graphene and PLGA materials. They conducted *in vitro* cell experiments and *in vivo* experiments on rotator cuff repair animal models. This study shows that the use of GO-PLGA composite materials can more effectively promote the proliferation of BMSCs and accelerate osteogenic differentiation compared with the use of PLGA alone. Histologically, the use of GO-PLGA composite materials leads to better collagen arrangement at the rotator cuff TBI and better biomechanical properties [82].

The microenvironment established by M2-type macrophages is conducive to the osteogenesis of BMSCs *in vivo* and *in vitro*, and coated with graphene oxide-hydroxyapatite (GO-HA) nanocomposites can significantly enhance osteogenic differentiation of BMSCs [73]. The GO coating used can improve the adhesion of MSCs and also promote angiogenesis. GO framework shows excellent vascular endothelial growth factor (VEGF) binding performance, which can effectively promote cell proliferation and induce the formation of a microvascular network-like structure when co-cultured with outgrowth endothelial cells (OEC) [83].

Graphene can promote the osteogenic differentiation of human adipose-derived mesenchymal stromal cell

(ADSC) by regulating cell adhesion and cytokine-receptor interaction, inflammatory responses, and possibly the status of histone H3 and H4 through epigenetic regulation [84]. GO-coated titanium (Ti-GO) surfaces exhibited good biocompatibility, with the ability to stimulate the expression of osteogenic genes and extracellular matrix mineralization in human mesenchymal stromal cells (hMSCs) [76]. BMSCs exhibit remarkable osteogenic and chondrogenic differentiation potential [79]. Further studies indicate that gelatin methacrylate (GelMA) hydrogels functionalized with graphene oxide (GO-GelMA) loaded with bone-forming peptide-1 (BFP-1) effectively promote the osteogenic differentiation of BMSCs [85]. Moreover, this composite hydrogel system demonstrated potent osteogenic induction activity in rat models, significantly promoting the osteogenic differentiation of rat BMSCs (RBMSCs). The incorporation of GO not only optimized the hydrogel's mechanical properties but also effectively reduced its swelling rate [86].

The controlled-release hydrogel composite system constructed by GO can realize programmed loading and sustained release of interleukin-4 (IL-4) and BMP-2, and significantly enhance the osteogenic differentiation efficacy of BMSCs [66].

Sustained release of growth factors in GO-bonded hydrogel complexes accelerates chondroblast differentiation of hMSCs, and it has been shown that with GO addition, the hydrogel scaffolds (GO/PDLLA) (graphene oxide nanosheets within a photopolymerizable poly-D, L-lactic acid/polyethylene glycol) exhibit enhanced initial mechanical strength and maintain the release of transforming growth factor TGF- β 3 for 4 weeks [87]. The addition of GO and calcium phosphate (CaP) coating to polycaprolactone (PLC) (PLC/GO/CaP) can improve the hydrophilicity, swelling behavior, mechanical properties, and cell proliferation properties of composite scaffolds. Compared with the no GO or CaP group, the PLC/GO/CaP scaffold group containing mouse bone marrow stem cells (mBMSCs) not only has no obvious cytotoxicity but also has no obvious cytotoxicity. Furthermore, it can further promote the osteogenic differentiation [88]. Composite 3D graphene-based biomaterials, with distinct hierarchical pore structures (micropores to macropores), can induce the differentiation of human umbilical cord mesenchymal stem cells (hucMSCs) towards osteoblasts [59].

Osseointegration at the bone-implant interface is a complex biological process, including an inflammatory response involving immune cells and osteogenic differentiation mediated by a variety of cell types. GO can precisely regulate the material-cell interface interaction by functionalizing the surface of implants. For instance, GO-modified titanium surfaces can enhance the osteogenic differentiation of BMSCs and the M2-phenotype polarization of macrophages, thus endowing bone biomaterials with good bone immunomodulatory properties [87]. On the other

hand, incorporating 1.5 wt.% GO with polyvinyl alcohol (PVA) significantly enhances the viability and IL-6 secretion levels of human osteoblasts while reducing apoptosis rates and intracellular ROS levels [88]. And, the use of this strategy to modulate the biological interface not only reduces the toxic effects of GO but also preserves the strengthening properties of GO tissue engineering scaffolds. Graphene and its derivatives are involved in the functionalization of MSCs, and GO promotes bone differentiation of MSCs [89]. Graphene and its derivatives are involved in the functionalization of MSCs, which provides a broad application prospect for the regeneration of TBI.

Regulation of Fibroblasts

In the process of TBI healing, fibroblasts, as key participants, play a role in different repair stages by dynamic ECM remodeling, inflammatory microenvironment, and mechanical adaptability [65,90,91]. As the core cellular component of connective tissue, fibroblasts synthesize and secrete extracellular matrix, including key structural proteins such as type I and III collagen, maintaining tissue structure, and repairing damage [92–94]. It has been confirmed that the application of autologous dermal fibroblasts in the TBI significantly reduces the retear rate in patients with rotator cuff tears [95]. Fibroblasts can interact with BMSCs, tendon stem progenitor cells (TSPCs) [96], and macrophages [65,97] to jointly participate in TBI healing [92,98].

In response to tissue injury or inflammatory stimuli, fibroblasts are activated and differentiate into myofibroblasts through phenotypic transition [97,98]. Myofibroblasts play a key role in scar formation. Although the transformation of fibroblasts into myofibroblasts is widely considered to be the key step in tissue repair and wound healing, recent studies have revealed that macrophages can also trans-differentiate into myofibroblasts through the TGF- β /Smad3 signaling pathways, which can further aggravate skin scar formation [99]. The phenotype of fibroblasts can be directed by regulating the arrangement of nanofibers and the content of hyaluronic acid in the hydrogel [100]. In previous studies, myofibroblasts were usually regarded as terminally differentiated cells. However, existing evidence suggests that a reversible activation state is preferred. Therefore, the strategy of using myofibroblasts in a quiescent state may be an effective approach for anti-hypertrophic scar treatment. Graphene quantum dots (GQDs) have become a research hotspot in the field of nanobiomedicine due to their unique properties. GQDs have shown significant anti-scar effects, improved scar appearance, collagen reduction, and rearrangement by inhibiting the excessive proliferation of myofibroblasts. GQDs inhibit α -SMA expression, collagen synthesis, cell proliferation, and migration, and induce myofibroblasts to become quiescent fibroblasts [101]. The hybrid interface of GO and collagen type I (COL-I) effectively inhibits the differentiation of fibrob-

lasts into myofibers. Meanwhile, the structure and roughness of the GO coating interface can be easily adjusted at the nanoscale to induce M1 polarization of macrophages without generating excessive pro-inflammatory factors [102]. Human fibroblasts proliferated on the surface and pores of polylactic acid nanofiber scaffolds encapsulated in zirconia (ZrO_2)/hydroxyapatite/GO and grew significantly with composition changes, and the substantial proliferation of fibroblasts on scaffolds may suggest the use of these scaffolds for tissue engineering [103]. The effect of graphene and its derivatives on fibroblasts is expected to provide research value for TBI healing and remodeling.

Different cell types such as macrophages, MSCs, and fibroblasts are involved in TBI healing. Synergistically promote the repair of TBI structures through directed differentiation and proliferation [56]. Graphene, with their unique structure, are less likely to be recognized by the human immune system as foreign substances, thereby effectively reducing the occurrence of immune responses and creating a more suitable microenvironment for the repair of damaged tissues. They have a significant promoting effect on cell adhesion, proliferation and differentiation [22]. Composites with graphene, such as PRP, hydrogels, biological scaffolds, and internal fixation materials support have shown good performance in various application environments.

The Application Prospects of Graphene-Based Composite Biomaterials for TBI Healing

TBI is a difficult problem in orthopedic repair. Traditional biomaterials often face challenges such as insufficient mechanical properties, uncontrollable growth factor release, and susceptibility to infection. Graphene materials can significantly enhance the osteogenic activity of platelet-rich plasma (PRP) through functional modification, enhance the mechanical and differentiation-promoting properties of hydrogels, endow 3D-printed scaffolds with antibacterial and osteogenic dual functions, and improve the biological integration of orthopedic implants (Table 2).

PRP

PRP is enriched in a variety of growth factors and has been shown to be effective in promoting TBI healing [104,105]. Studies have shown that GO can regulate the ultrastructure and mechanical properties of PRP gel. *In vitro* experiments showed that GO/PRP gel had good biocompatibility and could promote the proliferation, osteogenic and chondrogenic differentiation of BMSCs [58]. In a large rabbit supraspinatus tendon model, this composite significantly enhanced the mechanical properties of the nascent tendon and accelerated TBI healing [58]. In addition, loading PRP with GO/alginate gel has excellent plasticity. Its porous structure and water content can maintain the activity of platelets and the growth factors they release in PRP, thereby promoting collagen synthesis and angio-

genesis, and accelerating the tissue repair process. Due to its high specific surface area, excellent mechanical properties, and good biocompatibility [30,112], graphene is an ideal PRP loading matrix, so the composite of GO and PRP shows significant application potential in the field of TBI regeneration.

Hydrogels

Graphene can improve the physical properties of biomaterials and promote tissue repair [58]. The 3D network structure of cross-linked polymers inside the hydrogel can provide a suitable multifunctional nanocomposite hydrogels that may be a novel therapeutic strategy for TBI healing. Graphene hybrid hydrogels may provide important ideas for the application of hydrogels in tissue regeneration [23]. microenvironment and physical and chemical inducing signals for cell proliferation and differentiation. However, the application and promotion of hydrogels in the field of tissue regeneration are severely limited by their poor mechanical properties (manifested as high fragility) and limited porosity [23,100]. The introduction of graphene and hydrogels can not only significantly enhance the mechanical properties of hydrogels, but also help to reduce the cytotoxicity of GO. Graphene-mixed hydrogels show excellent stretchability, high toughness, and good biocompatibility [23].

Meanwhile, their nanostructures are similar to the spatial characteristics of soft tissue extracellular matrix, which can play a synergistic role and enhance their biochemical characteristics. It has shown excellent regenerative capacity of skin and tendon tissue [23,86]. The graphene oxide (GO)-carboxymethyl chitosan (CMC)/poly (ethylene glycol) diacrylate (PEGDA) (GO-CMC/PEGDA) interpenetration network hydrogel was demonstrated to promote new bone formation and tissue repair through immune regulation of the local microenvironment [66]. Due to its short half-life in the body, TGF- β is rapidly cleared, which limits its wide application. The incorporation of GO nanosheets into photopolymerizable poly-D, l-lactic acid/polyethylene glycol (PDLLA) hydrogel enables sustained release of the cartilage-inducing factor TGF- β 3. This GO fusion hydrogel scaffold (GO/PDLLA) not only exhibits significantly enhanced compressive modulus and improved mechanical properties but also sustains TGF- β 3 release for up to four weeks. This 3D GO composite hydrogel growth factor controlled-release system effectively promotes chondrogenic differentiation of human MSCs [87]. Ca^{2+} -TArGO (CTAG) /GelMA hydrogel was synthesized by combining Ca^{2+} with GO by metal chelation, which has good biocompatibility and can induce polarization of macrophages to M2-type macrophages, enhance migration and proliferation of BMSCs, promote angiogenesis, inhibit osteoclast formation, and promote osteogenesis [106]. Graphene-based hydrogels not only exhibit excellent mechanical properties

Table 2. Preclinical functionalization of graphene materials.

Application types	Specific examples	Preparation methods	Specific performance	Mechanism	References
PRP	GO/PRP complexes	GO with the PRP gel mixture formation	Good biocompatibility and improved mechanical properties	Promote the proliferation of BMSCs, osteogenesis, and chondrocyte differentiation, and improve TBI healing of supraspinatus tendons in rabbit models	[58,104,105]
Hydrogels	GO-CMC/PEGDA	Chemical cross-linking to construct a 3D network	Immune regulation of local microenvironment	Promote new bone formation and tissue repair	[66]
	GO/PDLLA photopolymeric hydrogel	Incorporation of GO resulted in the sustained release of growth factors	Compression modulus increased, and TGF- β 3 was released for up to 4 weeks	Accelerate the cartilage differentiation of human MSCs	[87]
	Ca ²⁺ -TArGO/GelMA hydrogel	Metal chelation combines GO with Ca ²⁺	Excellent biocompatibility and induced polarization of macrophages to M2-type macrophages	Enhance the migration and proliferation of BMSCs, and promote angiogenesis and osteogenesis	[106]
Biological scaffolds	PLA/GO/TCP scaffolds	3D-printed PLA enhanced by GO and TCP	High porosity promotes cell adhesion and proliferation	Improve the cell adhesion, proliferation, and differentiation of hWJ-MSCs and promote osteogenesis	[107]
	The Ti–6Al–4V scaffold is coated with GO	The surface is coated with GO to enhance hydrophilicity	Irregular microporous structure promotes protein adsorption	Upregulate osteogenic genes, increase ALP activity and mineralization nodules formation, and ultimately promote osteogenesis	[108]
	Curcumin-loaded GO-collagen composite scaffolds	Physical adsorption combines GO with collagen	Synergistic osteogenic and antibacterial properties	Enhance cell vitality and inhibit Staphylococcus aureus and Escherichia coli	[109,110]
Orthopaedic implant materials	GO-SPEEK	Porous structure adsorption GO surface functionalization	High bactericidal efficiency, promotes osteogenic adhesion differentiation	Inhibit Gram-negative/positive bacteria and enhance ECM mineralization	[111]
	GO/COL-I hybrid coating	Nanoscale regulation of the GO and collagen interface	Anti-fibrosis and induction of macrophage polarization	Inhibit the differentiation of fibroblasts into myofibroblasts and reduce foreign body reaction	[102]

and structural integrity, but also have structural and chemical properties that are conducive to cell growth and tissue regeneration. As cell-friendly and tissue-friendly tough hydrogels, graphene-based hydrogels have great potential in the field of TBI healing.

Biological Scaffolds

3D-printed scaffolds have great potential in the field of regenerative medicine due to their good biocompatibility and biodegradability. Graphene-derivative 3D-printed scaffolds have good mechanical properties and can help tendon and ligament regeneration. 3D-printed tendon/ligament scaffolds based on polylactic acid (PLA)/graphene nanosheet composites. The ability of tendon regeneration is maintained by increasing the expression of specific genes [109]. 3D-printed PLA/graphene oxide/ β -tricalcium phosphate (PLA/GO/TCP) functional scaffold enhanced by GO and TCP can improve cell adhesion, proliferation, and differentiation of Wharton Jelly mesenchymal stem cells (hWJ-MSCs) and promote osteogenesis [107]. The 3D-printed highly porous Ti-6Al-4V scaffolds coated with GO were irregularly porous and highly hydrophilic. The functionalized scaffolds promoted protein adsorption and cell growth, increased alkaline phosphatase (ALP) activity, mineralized nodule formation, and up-regulation of osteogenic genes in MC3T3-E1 pre-cells. Ultimately, it promotes osteogenesis [108].

Infection remains a problem for bioimplant materials [7]. To reduce the risk of infection after intraosseous implantation, researchers combined curcumin-loaded GO with collagen to develop a multifunctional collagen composite scaffold that has excellent osteogenic and antibacterial properties. The pro-osteogenic and antibacterial effects of graphene and its derivatives were further confirmed [110]. Studies have shown that silver nanoparticles ((f-EG) + Ag) can be introduced into 3D-printed PLA/graphene nanoplatelets composites by functional modification to enhance their antibacterial properties against *Staphylococcus aureus* and *Escherichia coli* [109]. The biomimetic topological biological scaffolds based on GBNS have good mechanical properties, protein adsorption, and cell growth, and can play a role in promoting osteogenesis and antibacterial properties, which has shown a broad application prospect in the study of extracellular matrix remodeling related to TBI.

Internal Fixation Materials

Based on PLA/graphene nanocomposite fibers, the functionalized enhanced interface and anchored small concentrations of Ag as antimicrobial agents have good mechanical properties and thermal stability. Using textile engineering and additive manufacturing techniques, these nanocomposite fibers were successfully processed into 3D scaffolds with finely controlled dimensions, demonstrating their potential for application in ligament tissue engineering

[113].

The foreign body reaction after implantation of medical devices is a major clinical problem restricting their long-term biocompatibility and functional integration. The materials currently used in implants are mainly non-organic metals, and a lack of biocompatibility and absence of immune regulations may lead to long-term post-implantation fibrosis [102]. The hybrid interface constructed of highly biocompatible GO and COL-I can synergistically inhibit the transformation of fibroblasts into myofibroblasts and induce the polarization of macrophages without excessive production of proinflammatory factors by adjusting the structure and roughness of the coating interface at the nanoscale. Meanwhile, this hybrid biological interface also has high mechanical strength compared with nanomaterials or extracellular matrix as an anti-fibrotic interface [102].

Poly-ether-ether-ketone (PEEK) is a medical plastic that can be used in orthopedic implants, but its antibacterial properties and biological activity are poor. Sulfonation of PEEK using a porous structure of adsorbing GO (GO-SPEEK) has shown a good bactericidal effect against both Gram-negative and Gram-positive bacteria. In addition, the surface of GO-SPEEK can promote osteoblast adhesion, proliferation and differentiation, and enhance the mineralization ability of ECM. With the maintenance of mechanical properties, enhanced surface biological mineralization ability, cell-material interaction, and efficient bactericidal activity, GO-SPEEK is expected to be widely used in the field of orthopedic implants [111].

Carbon fiber-reinforced poly-ether-ether-ketone (CFR-PEEK) is a composite material composed of carbon fiber sheets, whose modulus can be precisely adjusted to match the characteristics of bone tissue. However, CFR-PEEK is biologically inert and fails to promote bone tissue attachment. Graphene was stably coated on the CFR-PEEK surface. *In vitro* and *in vivo* experiments showed that Graphene-carbon fiber-reinforced poly-ether-ether-ketone (G-CFR-PEEK) had good cytocompatibility and promoted osteogenesis [114]. Selective PEEK implants combined with graphene can induce directional cell adhesion and osteogenic differentiation. This indicates that it has a new application prospect in the field of implant materials for promoting TBI healing [114].

The Ligament Advanced Reinforcement System (LARS) ligament effectively solves the problems of insufficient supply and early mechanical properties of autologous tendon due to its good mechanical properties and no donor-site complications in shoulder, elbow, and knee ligament and tendon repair [115–117]. Among them, the most widely used ligament is LARS made of polyethylene terephthalate (PET) [118,119]. However, PET also has some disadvantages, such as reactive synovitis after implantation and difficulty in attaching and wrapping host cells on PET fibers. To overcome the disadvantages caused by the biological inertness of PET and to improve the interaction between PET

Table 3. Efficacy and limitations of different composite materials in TBI healing.

Composite material type	Representative composite systems	Therapeutic efficacy	Limitations	References
Platelet-Rich Plasma (PRP) composite system	GO/PRP gel. GO/Alginate/PRP gel.	Excellent biocompatibility; promotes BMSCs proliferation, osteogenic and chondrogenic differentiation. Enhances neotendon biomechanical properties and accelerates TBI healing in rabbit supraspinatus tendon models. Porous structure and high water content facilitate wound collagen synthesis, angiogenesis and repair.	PRP growth factors show obvious batch variations in activity and concentration, leading to unstable <i>in vivo</i> repair efficacy. Growth factors have short <i>in vivo</i> half-life and rapid clearance; single system fails long-acting sustained release. Low mechanical strength of gel cannot meet fixation and weight-bearing demands for high-load TBI.	[38,58]
Hydrogel composite system	GO-CMC/PEGDA hydrogel. GO/PDLLA hydrogel. Ca ²⁺ -TArGO/GelMA hydrogel.	Improves pure hydrogel brittleness and porosity, enhances tensile properties, toughness and strength. Nanostructure mimics soft tissue ECM, promotes cell proliferation, differentiation and skin/tendon regeneration. Enables 4-week TGF- β 3 sustained release, facilitates hMSC chondrogenic differentiation. Induces macrophage M2 polarization, enhances BMSC migration and proliferation, promotes angiogenesis, osteogenesis and inhibits osteoclastogenesis. Modulates local microenvironment via immunoregulation, promotes new bone formation.	Pure hydrogels exhibit inherent brittleness and insufficient porosity, limiting tissue ingrowth and load-bearing. GO concentration has a strict threshold; excess induces residual cytotoxicity and local inflammation. Hydrogel crosslinking and degradation fail to precisely match TBI gradient healing.	[23,66,86,87]
Biological scaffold system	3D-printed PLA/graphene nanoplatelets. PLA/GO/TCP functional scaffolds. GO-coated Ti-6Al-4V scaffolds. GO-collagen/curcumin/silver scaffolds.	3D-printed highly porous biodegradable scaffolds for ligament/bone regeneration. Enhanced mechanical properties, upregulated tendon-related genes and preserved tendon regeneration. Improved hWJ-MSCs/MC3T3-E1 adhesion, proliferation, differentiation, elevated ALP activity and mineralized nodule formation, promoted osteogenesis. Drug-loaded or silver-modified scaffolds exert antibacterial and osteogenic functions, lowering implant infection risk.	3D-printed scaffolds: poor pore uniformity/connectivity, limiting cell/vascular ingrowth. GO doping/coating: agglomeration, reduced mechanics/biocompatibility. Scaffold degradation mismatches tendon-bone healing, causing collapse/barrier. Uncontrolled silver/curcumin release: cytotoxicity, tissue irritation risks.	[7,107,109,110]
Orthopedic implant material system	PLA/graphene nanocomposite fibers. GO/COL-I hybrid interfacial coating materials. GO-SPEEK modified materials.	Nanocomposite fibers offer superior mechanical/thermal stability, forming customizable 3D scaffolds for ligament engineering. GO/COL-I interface inhibits myofibroblast differentiation, regulates macrophage polarization, alleviates inflammation, fibrosis and foreign body reactions, retaining mechanical strength. GO-SPEEK displays broad antibacterial activity, promotes osteoblast functions and ECM mineralization, balancing mechanics and bioactivity.	Traditional metals and PEEK lack bioactivity; GO-only modification fails efficient osseointegration. Weak GO-substrate interfacial bonding induces delamination, inflammation and fibrosis. Insufficient large-animal and long-term data for silver antimicrobial <i>in vivo</i> metabolism and toxicity.	[102,111,113]

and host tissue, PET should be surface modified [120–122].

A variety of modification methods have been introduced to improve the surface of PET materials, so as to promote the survival, attachment, proliferation and directional differentiation of seeded cells. Researchers have prepared graphene-coated PET artificial ligaments. Graphene coating significantly enhances the proliferation and differentiation of MC3T3 cells into osteogenic cell lines on fibrous PET scaffolds. After the implantation of graphene-coated grafts into bone tunnels, the bone healing process is accelerated. Graphene coating may facilitate early recovery after artificial ligament reconstruction [120].

Although the direct application research of graphene in the field of tendon-bone healing is limited and its application in biomaterials (such as PRP, hydrogels, scaffolds and implants) has some limitations [23,104,105,109,110], its excellent efficacy in animal models has provided valuable inspiration for TBI healing strategies (Table 3). With its unique mechanical strength, high specific surface area, and good biocompatibility, graphene and its derivatives provide a new strategy for optimizing regenerative materials. Through its synergistic effect, graphene and its derivatives provide a multi-dimensional solution for promoting TBI healing, showing broad clinical translation prospects.

Challenges and Prospects

With the widespread use of GBNS, concerns about their safety have gradually emerged. Studies have shown that GBNS can have different effects on various cell lines and organisms under different exposure conditions, and increased cytotoxicity at high concentrations can aggravate apoptosis and DNA damage, so the importance of dose-dependent effects should be considered when assessing the safety of GBNS [123]. *In vitro* evaluation of the mechanism of toxicity of functionalized rGO derivatives showed that rGO derivatives increased the levels of IL-1 β and TNF- α in THP-1 cell supernatant, and the functionalized rGO materials can exhibit some cytotoxicity [39,123]. The mechanism studies show that this type of toxicity is closely related to the induction of mitochondrial dysfunction and resulting in increased cell death.

Its toxic mechanisms primarily involve the activation of oxidative stress, manifested as elevated ROS levels and decreased superoxide dismutase (SOD) activity. Furthermore, the surface charge characteristics of GO—such as quantity and polarity—are also considered key factors influencing its biological toxicity. In the future, it is possible to establish a graphene-based nanomaterial for drug delivery that is almost non-toxic to cells by altering the surface charge of GO [39]. The ideal drug delivery system needs to be optimized in multiple aspects such as size, shape, encapsulation efficiency, plasticity, biocompatibility, biodegradability, and cost-effectiveness. The biological advantages of graphene-based materials have a profound application prospect in drug delivery, which further suggests that it is

particularly important for us to study how to reduce the biological toxicity of GBNS.

A toxicological study has shown different oxidation states (oxygen/carbon ratio) modulate the dispersion properties of graphene nanomaterials, such as GO is hydrophilic, and rGO is hydrophobic, which may affect their biological interactions, including differences in absorption patterns, ROS production, global gene expression [38]. In brief, the distinct GO/rGO surface oxidation states resulting in unique hydrophobicity/hydrophilicity modulate their cellular uptake, gene regulation, and toxicological profiles [38].

Without reducing biological activity, surface modification and composite formation seem to be a good existing method to solve biological toxicity. In one study, the more biocompatible nitrogen-doped graphene quantum dots (N-GQDs) were successfully incorporated onto the surface of the TiO₂ NPs resulting in a N-GQDs/TiO₂ nanocomposites (NCs), the cytotoxicity of which was significantly lower compared to pure TiO₂ [124]. A nanoplateform coated with silver nanoparticles and GO composite showed limited immunological stimulation and significantly reduced cytotoxicity towards fibroblasts in comparison to the nanoplateform coated only with silver nanoparticles [125]. A uniform, thin-film of chitosan/polyvinyl alcohol/graphene oxide (CS/PVA/GO), which with ultra-low cytotoxicity (<29.08%) against human hepatocellular carcinoma (HepG2) and peripheral blood mononuclear cells [126].

Constructing composite scaffolds with spatial structure, controlled release function of growth factors, or combined with bioactive substances is an effective strategy for achieving gradient regeneration at the TBI. Researchers have synthesized a composite material of structural titanium scaffolds, thermosensitive collagen hydrogels and TGF- β 3 as a bioactive implant, which has shown great application potential in the integration of the TBI. This composite scaffold promotes the repair of the fibrocartilage layer and mineralized bone layer at the TBI [127]. This kind of approach that combines bioactive molecules, drugs, etc., with biological materials is currently a research hotspot in the field of regenerative medicine [128,129]. In the future, on the basis of improving the toxic effects of graphene materials, the relevant advantages of graphene materials can be fully utilized to design graphene composite materials loaded with drugs and bioactive molecules, which can be applied in the field of TBI integration [82]. Recently, there have been reports on the application of multi-layer nanomaterial functional scaffolds in TBI healing. This is a design strategy based on functional zoning, material synergy, and biomimetic regeneration, aiming to simultaneously address the three major challenges of mechanical fixation, cell guidance, and osteogenic induction in tendon-bone healing. It has shown great potential in promoting biological integration and enhancing mechanical properties in preclinical models [130]. In the future, it is expected that by combining the high spe-

cific surface area, porous structure, and mechanical properties of graphene materials, as well as the advantages of promoting cell adhesion, proliferation and differentiation [30,33,34], multi-layer nanomaterial functional scaffolds based on graphene can be designed to promote the repair of the TBI.

Conclusions

TBI represents a longstanding challenge in orthopedic sports medicine owing to its unique gradient fibrocartilaginous transition zone, and overcoming its regenerative bottleneck is critical for improving clinical outcomes. This review summarizes the advances of graphene materials in TBI healing and highlights their core advantages: high specific surface area for bioactive loading, superior mechanical properties to compensate for the drawbacks of traditional biomaterials, biomimetic topology resembling native microenvironments, and multimodal regulatory effects on key cells such as macrophages, MSCs, and fibroblasts. These multifunctional features endow Graphene materials with broad translational potential in PRP composites, hybrid hydrogels, 3D-printed scaffolds, and functionalized internal fixation devices. Nevertheless, critical issues remain for clinical translation, including dosedependent biosafety risks, undefined *in vivo* safety standards, and inadequate matching of gradient structures and growth factor release to the dynamic TBI healing process. Future research should focus on standardized safety evaluation, smart gradient scaffolds, and integration with 3D bioprinting and functional components for personalized repair. This review clarifies the value of Graphene materials in TBI healing, identifies key scientific gaps, and provides guidance for laboratory-to-clinical translation.

List of Abbreviations

3D, three-dimensional; ADSC, adipose-derived mesenchymal stromal cell; ADSC-Exos, adipose-derived stromal cell exosomes; ALP, alkaline phosphatase; BFP-1, bone-forming peptide-1; BMP-2, bone morphogenetic protein-2; BMSC-Exos, bone marrow-derived stromal cell exosomes; BMSCs, bone marrow mesenchymal stem cells; BMSCS-PLGA, PLGA scaffolds loaded with bone Marrow mesenchymal stem cells; Ce/rGO, Cerium/reduced graphene oxide; C-F, Carbon-fluorine; CFR-PEEK, carbon fiber-reinforced polyether ether ketone; CMC, carboxymethyl chitosan; CS/PVA/GO, chitosan/polyvinyl alcohol/graphene oxide; COL-I, Collagen type I; CTAG, Ca²⁺-TArGO; ECM, extracellular matrix; ES, electrical stimulation; FG, fluorinated graphene; FGO, fluorinated graphene oxide; GBNS, graphene-based nanomaterials; GelMA, gelatin methacrylate; GO, graphene oxide; GO/PDLLA, graphene oxide nanosheets within a photopolymerizable poly-D, l-lactic acid; GO-GelMA, graphene oxide-gelatin methacrylate; GO-HA, graphene oxide-hydroxyapatite; GO-PEI, graphene oxide-

polyethylenimine; GO-SPEEK, sulfonation of PEEK using a porous structure of adsorbing GO; GQDs, graphene quantum dots; hMSCs, human mesenchymal stromal cells; hucMSCs, human umbilical cord mesenchymal stem cells; IL-10, Interleukin-10; IL-4, Interleukin-4; mBM-SCs, mouse bone marrow stem cells; MSCs, mesenchymal stem cells; Nano-GO, Nanochain GO; N-GQDs, Nitrogen-doped graphene quantum dots; OEC, outgrowth endothelial cells; PDLLA, photopolymerizable poly-D, l-lactic acid/polyethylene glycol; PEEK, poly-ether-ether-ketone; PEGDA, poly (ethylene glycol) diacrylate; PLA/GO/TCP, poly (lactic acid)/graphene oxide/ β -tricalcium phosphate; PLC/GO/CaP, Calcium phosphate (CaP) coating to polycaprolactone; PLGA, poly (lactic-co-glycolic acid); PRP, platelet-rich plasma; PVA, polyvinyl alcohol; PI3K, Phosphatidyl Inositol 3-Kinase; RBMSCs, rat BMSCs; rGO, reduced graphene oxide; ROS, reactive oxygen species; SOD, superoxide dismutase; TBI, tendon-bone interface; TGF- β , transforming growth factor; Ti-GO, GO-coated titanium; TLR, Toll-like receptor; TNF- α , Tumor necrosis factor-alpha; TNT, Titanium dioxide nanotubes; TSPCs, tendon stem progenitor cells; VEGF, vascular endothelial growth factor.

Availability of Data and Materials

Not applicable.

Author Contributions

JX, LMS, HYY, WZB and BG contributed to the design of this work; YKK, YCJ, GPJ, YNG and LF contributed to the collection of references; JX, LMS, YCJ, GPJ, YNG and LF analyzed references; JX, LMS and YKK drafted the work; WZB, BG and HYY revised critically for important intellectual content. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics Approval and Consent to Participate

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Conflict of Interest

The authors declare no conflict of interest.

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