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REVIEW

Graphene-Based Photodynamic Therapy and Overcoming Cancer Resistance Mechanisms: A Comprehensive Review

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Abstract: Photodynamic therapy (PDT) is a non-invasive therapy that has made significant progress in treating different diseases, including cancer, by utilizing new nanotechnology products such as graphene and its derivatives. Graphene-based materials have large surface area and photothermal effects thereby making them suitable candidates for PDT or photo-active drug carriers. The remarkable photophysical properties of graphene derivates facilitate the efficient generation of reactive oxygen species (ROS) upon light irradiation, which destroys cancer cells. Surface functionalization of graphene and its materials can also enhance their biocompatibility and anticancer activity. The paper delves into the distinct roles played by graphene-based materials in PDT such as photosensitizers (PS) and drug carriers while at the same time considers how these materials could be used to circumvent cancer resistance. This will provide readers with an extensive discussion of various pathways contributing to PDT inefficiency. Consequently, this comprehensive review underscores the vital roles that graphene and its derivatives may play in emerging PDT strategies for cancer treatment and other medical purposes. With a better comprehension of the current state of research and the existing challenges, the integration of graphene-based materials in PDT holds great promise for developing targeted, effective, and personalized cancer treatments.

Keywords: graphene quantum dots, graphene oxide, cancer research, photosensitizers, drug delivery

Introduction to Cancer Therapy

Cancer has been one of the leading causes of death in various countries, genders, and age groups in the last two decades, with an estimated total of 10 million deaths in 2020. The major types of cancer leading to fatal outcomes are lung cancer, breast cancer, and prostate cancer.[1–5] Cancer is a multifactorial genetic disease, and mutations in the cellular genetic material are necessary for its development. These mutations can gradually accumulate over a lifetime, starting from a precancerous condition and developing into a malignant tumor. Malignant diseases can be divided into acquired mutations and hereditary ones, such as the familial form of retinoblastoma.[3,6] External agents that trigger malignant transformation can be divided into physical carcinogens (eg, ultraviolet and ionizing radiation), chemical carcinogens (such as asbestos) and biological carcinogens (bacteria and viruses, such as human papillomavirus, hepatitis B virus), human herpesvirus-8 and H. pylori).[3,6–8]

The disadvantages of conventional cancer treatments, such as chemotherapy, radiation therapy, and surgery must also be taken into account when discussing cancer (Figure 1). Treatment may not only lead to many harmful side effects, but it can also cause cancer resistance. As a rule, side effects occur when healthy cells and the malignant ones are affected. Side effects usually vary according to a given type of malignancy, person and treatment used.[9] These topics will be covered in more detail later in this review.

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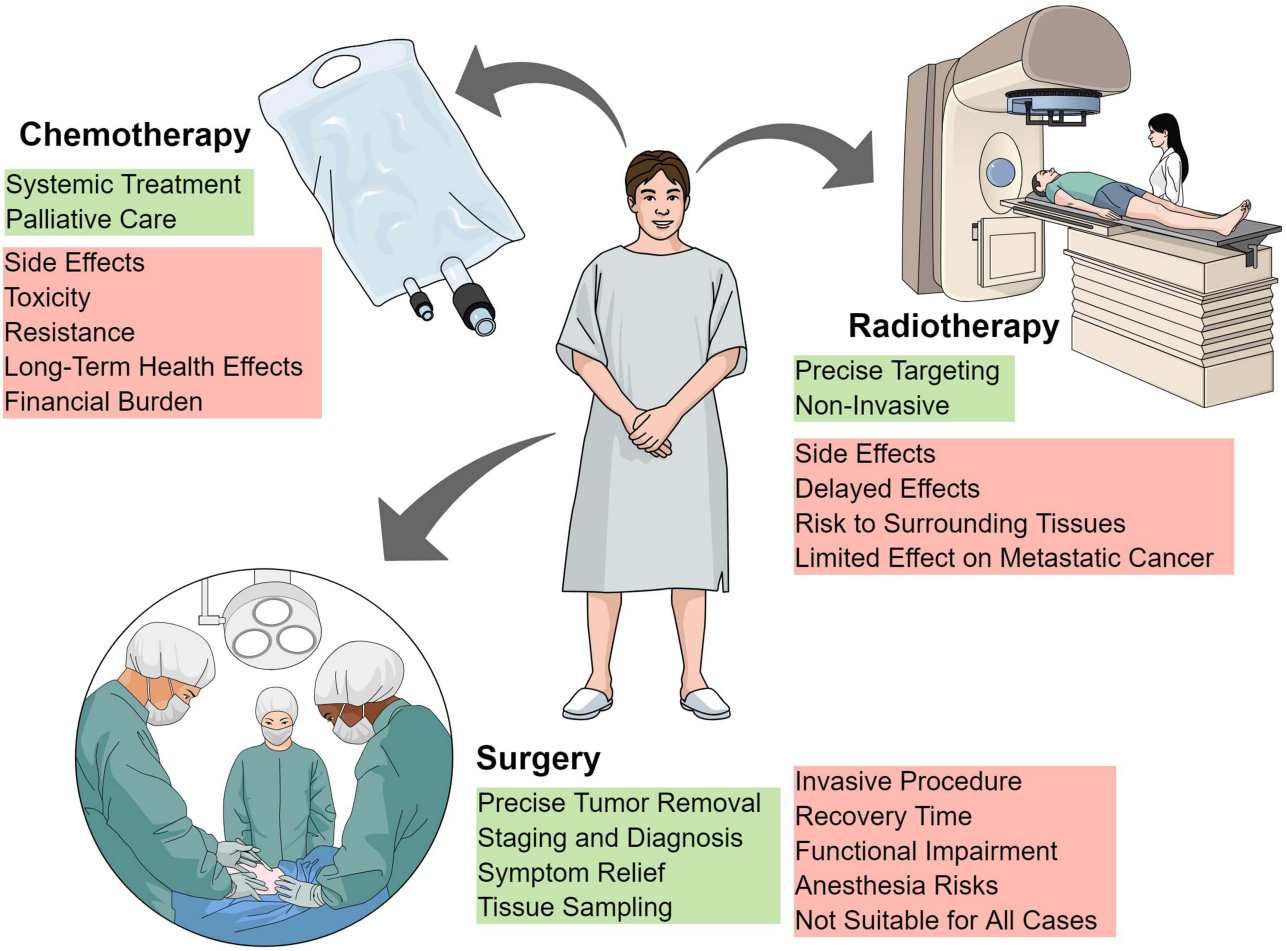

Figure 1 Advantages and disadvantages of traditional cancer treatment techniques. Green boxes represent advantages and red boxes represent disadvantages.

Chemotherapy

One of the classic types of cancer treatment is chemotherapy, the main task of which is to eliminate tumor cells without significantly damaging healthy tissues, which is obviously impossible with classic chemotherapy agents because they are not tumor cell-specific. The history of chemotherapy began in 1940 with the use of nitrogen mustard.[10,11] It is usually administered through the mouth or intravenously in regular intervals called cycles so that the organism can recover after the toxic effect.[11,12] Different types of drugs are administered for chemotherapy and include alkylating agents that bind to proteins and nucleic acids, antitumor antibiotics that are produced by bacteria and generate free radicals, antimetabolites (disrupt purine or pyrimidine synthesis), topoisomerase inhibitors that are responsible for disrupting the process of DNA replication and many others.[11]

Radiotherapy

Radiotherapy started in 1895 after the discovery of X-ray and is used in more than a half of cancer treatment regimens.[13] Over the years, huge achievements have been reported in the field with the development of 3D conformal radiation methods such as stereotactic (body) radiotherapy (SBRT) and intensity-modulated radiation therapy (IMRT). In addition, accomplishments in imaging systems have minimized radiation exposure to healthy tissue.[13,14] This removes some limitations imposed by the maximum tolerated dose.[13] Radiation therapy is also associated with ROS production inside the cells via water radiolysis and cytosolic Rac1/NADPH oxidase system.[13,15–17] The other mechanism to influence cancer via radiotherapy is through tumor hypoxia.[13]

Surgery

Surgery is the oldest cancer treatment and the most effective in the case of localized primary tumors.[18,19] It can be used to achieve goals such as removing the entire tumor mass, debulking a tumor in case when removing the entire tumor is impossible, or easing cancer symptoms.[19] Compared to both chemotherapy and radiotherapy, surgery makes it possible to eliminate all malignant cells.[18]

Resistance

As was written above, cancers can also outsmart therapy efforts, and the triggered therapeutic resistance will significantly contribute to cancer mortality.[20] Unsuccessful treatment will result from combined factors of pharmacokinetics, TME and the resistance mentioned above.[21] The vast majority of cancer therapies are chemotherapy, and, in most cases, tumor recurrence and treatment resistance are observed.[20,22–25]

Non-genetic/epigenetic changes that occur independently of DNA changes play an important role in cancer development.[24–27] Many studies have failed to prove the genetic evolution of the disease in a large number of patients with resistance to therapy.[24,28] Non-genetic resistance can occur as drug persistence, unstable non-genetic resistance and stable non-genetic resistance.[24] Drug persistence for cell culture is similar to antibiotic-resistant bacteria. It occurs in the population of malignant cells with low frequency and exhibits reduced growth and altered metabolism.[24] Remarkably, they are genetically identical to the entire tumor mass which proves that epigenetic mechanisms have a curtail part in them. These cells are not mitotically active but can allow other cancer cells to adapt via genetic mutations or epigenetic changes.[24,29–31]

Epigenetic heterogeneity refers to the variability of the epigenetic state within a cell population as a result of stimulus.[24] Two different theories have been proposed for the emergence of acquired resistance to the treatment: Darwinian theory and Lamarckian theory of cancer cell evolution (Figure 2). Darwinian theory of acquired resistance says that natural selection plays the leading role in resistance and there is always a small population of tumor cells that already have therapy-resistant potential. Darwinian theory acts via heritable variability from accidental changes in the genetic material for which positive selection is necessary. It works either by gradually increasing the number of resistant cells or by gradually increasing the stability of resistance. However, in this case, the frequency of advantageous mutations in the cell population is extremely low, and adaptations are limited by these mutations.[23,24,32]

The second widely known theory is Lamarckian theory which postulates that the environment plays a crucial role in developing therapy resistance. During the therapy, epigenetic changes force the drug-refractory phenotype, and selection is not involved in the spread of adaptive changes.[23,32–36]

Nevertheless, recent research showed us that these two theories do not exclude each other and can co-exist in the same cancer cell population, what leads to the existing cancer cell plasticity theory which is very different from healthy tissue plasticity and stem cell plasticity.[23]

Also, the new theory “use-it or lose-it” by Catania et al combined different driving factors like environment, phenotypic plasticity, mutations, genetic drift, and others. In this theory, positive selection is not necessary and evolved adaptations stem from existing genetic features that are activated in the specific environment, while genes that are not used are being silenced or even possibly physically lost.[32]

Also, Charles C. Bell suggested that cancer cells adapt via “the path of most resistance”, which includes a mix of both non-genetic changes and genetic changes.[24] In addition to these theories, it has been established that information between cancer cells and TME is transferred by tumor-derived exosomes which are vesicles ranging from 30 nm to 150 nm. They contain the noncoding RNA (ncRNA) which is responsible for treatment resistance and metastasis phenotypes.[37,38] The cytochrome P450 enzymes could be associated with drug resistance as well, and they are usually overexpressed in some solid tumors.[39] It should also be noted that during radiotherapy, immunosuppressive pathways are activated, which can lead to accumulation of tumor-associated macrophages (TAMs), myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs), which are all radioresistant.[40,41]

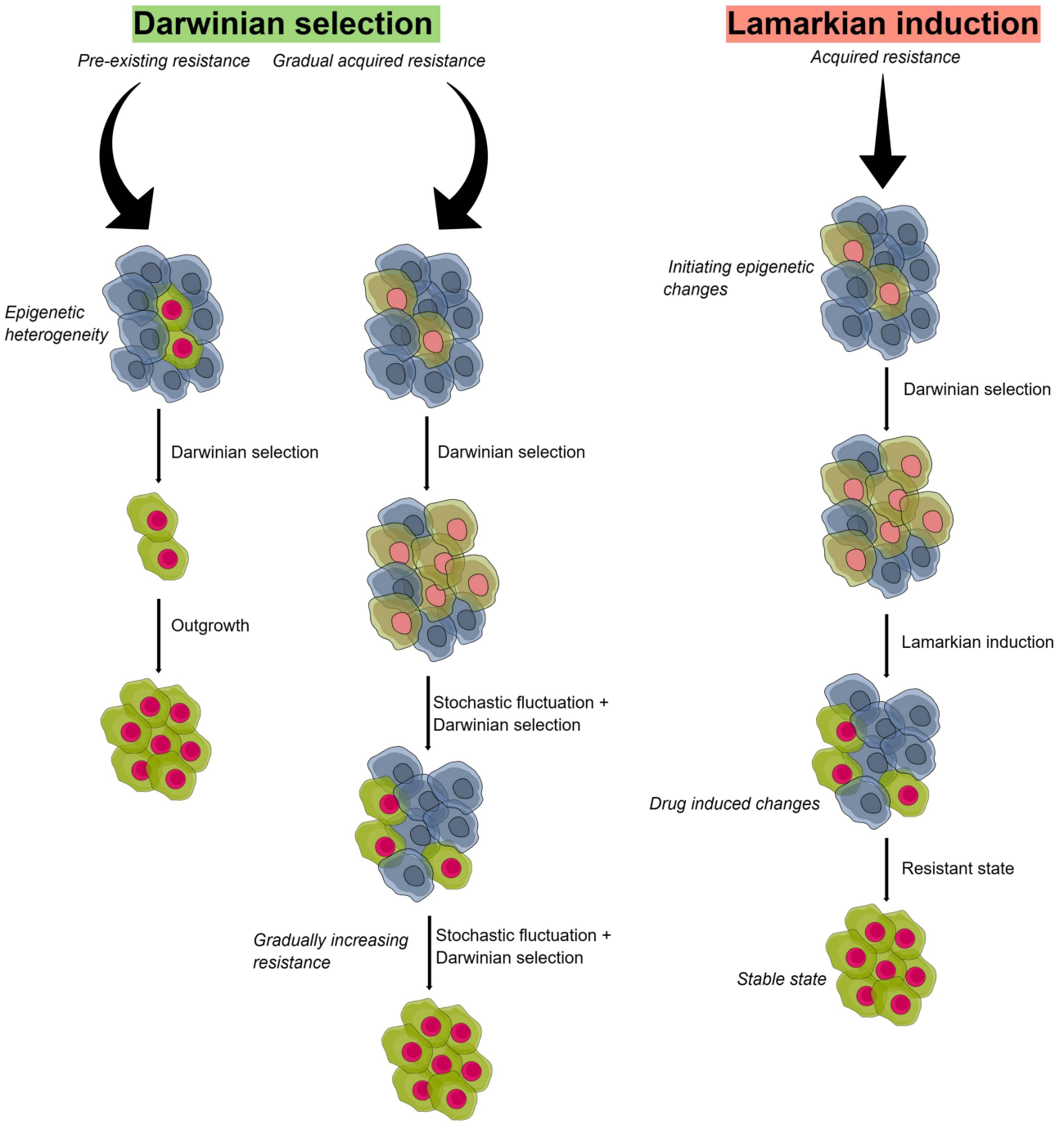

Figure 2 Models of cancer resistance include Darwinian cancer resistance theory and Lamarckian cancer resistance theory. The Darwinian theory of cancer resistance is based on principles of natural selection, survival advantage and genetic diversity, resulting in highly resistant population. The Lamarckian theory, proposed by Jean-Baptiste Lamarck, suggests that cancer cells can acquire traits during their lifetime and pass them on to their offspring.[24–27]

Photodynamic Therapy in Cancer

On the contrary, photodynamic therapy (PDT) is one of the contemporary non-conventional methods for cancer treatment. In this field, PSs are used along with light of a specific wavelength which will activate them (Figure 3). It focuses on retention of these specific drugs at the tumor site after local or systemic administration.[42,43] The antineoplastic effect of PDT originates from three different effects on the human body which area direct cytotoxic effect, damage to tumor blood vessels, and activation of both innate and adaptive immunity.[44]

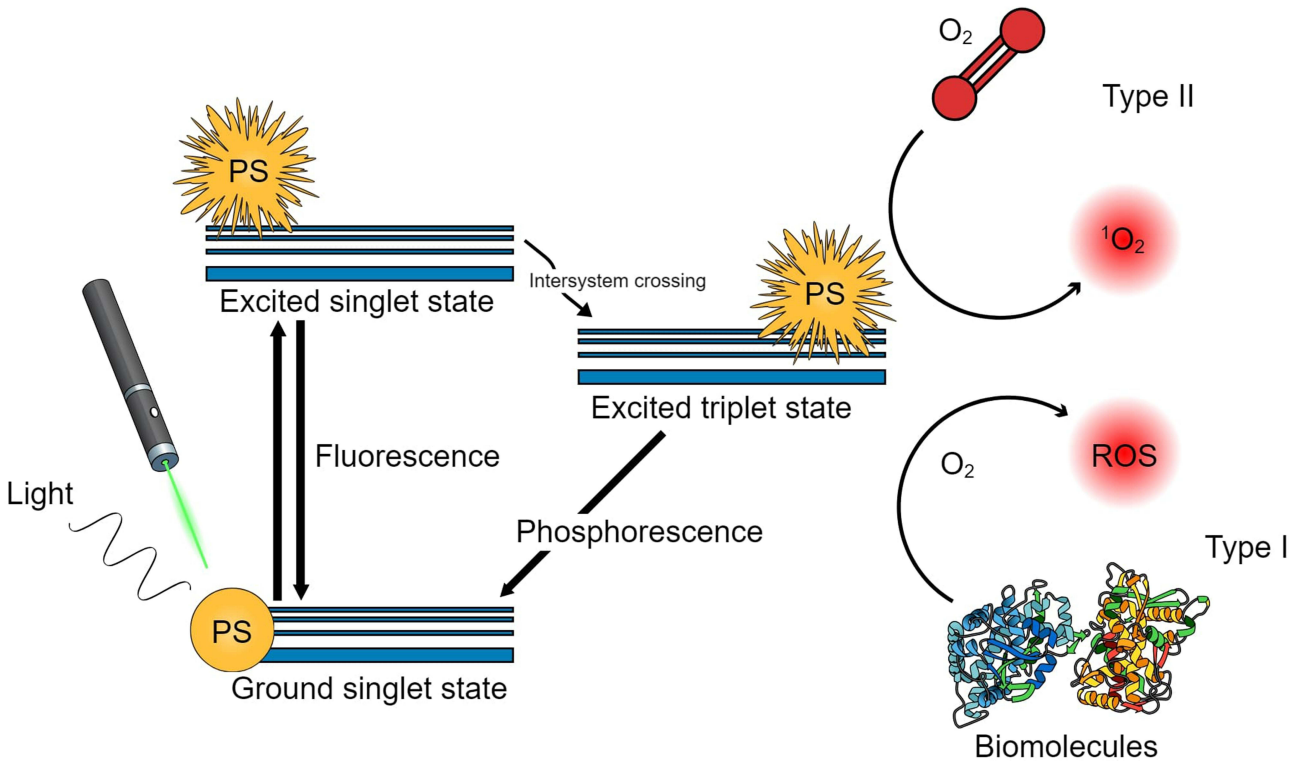

Figure 3 PDT is a treatment method that uses a photosensitizing agent and light to destroy abnormal cells. PDT can be divided into two main types of reactions: Type I and Type II reactions which describe the mechanisms through which the ROS are generated to induce cell damage. In Type I reaction, the PS, after absorbing light, transfers an electron to a substrate molecule without participation of molecular oxygen. This creates a highly reactive radical species, often mentioned as a superoxide anion radical which leads to cell damage. It can react with cellular components, triggering oxidative stress and damage to proteins and DNA. This type of reaction is typically non-specific and can damage numerous cellular components. In Type II reaction, after light activation, the PS transfers its energy to molecular oxygen directly producing singlet oxygen, a highly reactive and cytotoxic species. Unlike Type I reactions, Type II reactions are highly specific and primarily target cells containing the PS. The balance between these two reaction types can be influenced by the type of PS used, the presence of oxygen in the target tissue, and the local environment. It is important to consider the generation of singlet as it is mainly responsible for the therapeutic effects of PDT.[42]

PDT is a promising cancer treatment. However, it is not without limitations as cancer tissue may develop resistance to PDT due to factors such as multiple treatment sessions, changes in protein expression, and alterations in gene expression after irradiation.[45–47] PDT can also enhance many intrinsic survival pathways, such as NF-κB, autophagy, anti-apoptotic signals, p53 and many others.[46] Also, tumor hypoxia contributes to resistance to oxygen-dependent treatments such as PDT.[48,49]

Nuclear factor-kappa B (NF-κB) is a transcription factor that plays an important role in both inflammatory and immune responses and cannot be easily considered a target to fight PDT inhibition as it can educate the immune system to fight neoplastic cells but can also help these neoplastic cells to survive the stress arisen by ROS.[44,50]

It is worth noting that PDT can also trigger autophagy that can add to either resistance or susceptibility to the cancer treatment. It is not a homogeneous process and consists of macroautophagy, microautophagy and chaperone-mediated autophagy.[51,52] Autophagy can increase resistance to apoptosis by reusing dysfunctional organelles and cellular components damaged by PDT-induced ROS (Figure 4). This would maintain cellular homeostasis by providing enough energy for cellular vital functions and suppressing anticancer immune effector mechanisms.[53]

PDT can also increase cell resistance to treatment in terms of autophagy by enhancing signaling interactions between cells and microenvironment or by protecting cells from anoikis and promoting metastasis.[51] As several studies clearly show, autophagy has cytoprotective and prosurvival features, and depending on a variety of factors such as the cancer type, PS type and tumor stage, it can range from an antitumor effect to a protumor one.[54]

In accordance with everything written above, there are also different targets to overcome PDT resistance and enhance its therapeutic effect, mainly GRP78-targeting, survivin targeting, PS modification, two-photon absorption and use of NPs.[55–57]

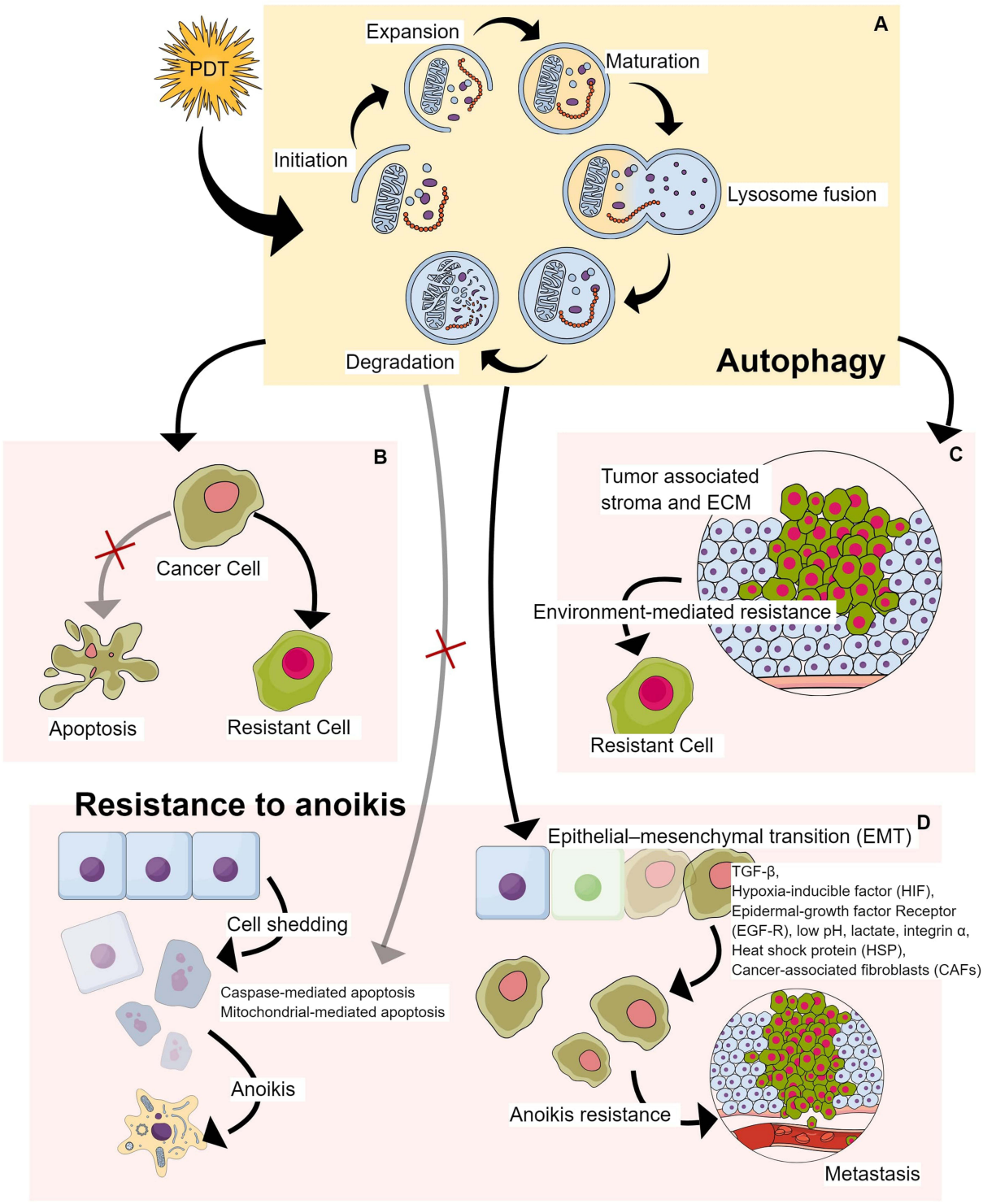

Figure 4 How PDT affects autophagy and cancer evolution. (**A**) Autophagy is an essential biological process that includes degrading and recycling cellular components. Through this process, cells undergo self-digestion, breaking down their organelles, proteins and other components. Throughout autophagy, a double-membrane structure (autophagosome) forms in stages such as initiation, expansion and maturation around the cellular material subjected to degradation. The autophagosome eventually fuses with lysosomes which leads to formation of autolysosomes and degradation of its contents for future recycling. There are different types of autophagy, including macroautophagy (the most common type), microautophagy and chaperone-mediated autophagy. This allows cells to remove damaged or redundant cellular materials, crucial for sustaining homeostasis. (**B**) As mentioned before, autophagy is responsible for degradation of dysfunctional or damaged cellular components and organelles, thereby providing cells with both energy and building blocks. Cells without proper autophagy mechanisms are vulnerable to PDT which causes apoptosis or cell death. However, in cancer, this can result in forming resistant cell population. (**C**) Signaling between tumor cells and their microenvironment can induce a temporary, drug-resistant state in malignant cells. Moreover, in cancer-associated fibroblasts, autophagy facilitates proliferation of adjacent cancer cells. (**D**) Autophagy also triggers the process of epithelial–mesenchymal transition, leading to more stem-like features in cells. In this case, anoikis, which is a form of cell death occurring after cell detachment, is less likely to happen. Additionally, by providing energy to disseminating cells, autophagy also assists with cancer cell dormancy and metastasis.[51]

Glucose-regulated protein 78 (GRP78) is a heat shock protein that is upregulated in tumor cells after PDT, and it was shown that GRP78 could be overexpressed in cancer cells (especially cells in malignant gliomas that are resistant to conventional chemotherapy and radiotherapy) and contribute to metastasis. Reduction of GRP78 concentration sequentially reduces metastasis development in xenograft models.[55,58–60] Targeting via subtilase cytotoxin (SubAB) is the most selective targeting as it cleaves and subsequently inactivates GRP78.[55] However, GRP78 suppression is under consideration as SubAB could be the reason for the hemolytic uremic syndrome as it is originally derived from Shiga toxigenic Escherichia coli (STEC) strains.[55,61,62]

The next target could be survivin which is an inhibitor of an apoptosis protein family, and usually the application of PDT results in an upregulation of survivin in a tumor. It plays an important role in stabilizing mitosis and cell adaptation; thus, the suppression of survival may enhance PDT treatment.[57] The first antagonist of survivin is a phosphorothioate antisense oligonucleotide which provides a strong anticancer activity.[57,63]

It should also be noted that one of the limitations and drawbacks of PDT is a limited light penetration to the tissue, as only NIR light can penetrate deeper into the tissue and most of the PS absorbs light at a shorter wavelength than 700 nm. Therefore, one solution can be using two-photon absorption (TPA)-induced excitation as it uses fewer energy photons but a higher wavelength.[56]

Another drawback of the most commercially used PS is their poor solubility as most of them are hydrophobic and would aggregate in the aqueous environment (cellular cytoplasm and extracellular environment) which would limit their properties for PDT and could harm normal tissue. Nanoparticles could serve as an essential platform for enhancing PTD and drugs in general.[56,64,65]

Nanoparticles can be different metal NPs (GNPs), super-paramagnetic iron oxide NPs (SPIONs) or even quantum dots (QDs), and they are capable of carrying a large load of PS on their surface, changing their water solubility and its kinetics and also securing them from early degradation.[56,66–69] Changes in kinetics usually occur through a specific mechanism, enhanced permeability and retention (EPR) effect.[56,70] NP can be functionalized in many different ways, for instance, Master et al worked on PEG-PCL (Poly (Ethylene Glycol)-block-Poly (ε-CaproLactone) methyl ether, with Phtalo- cyanine-4 (Pc4) which further were functionalized with peptide GE11 specific from the epidermal growth factor (EGR) receptor which results in enhanced uptake in an SCC-15 head and neck cell line.[56,71] Meanwhile, Gary-Bobo et al noticed the enhanced uptake of mesoporous silica NPs functionalized with galactose-carrying fluorescein by colorectal cancer cells.[56,72]

Introduction to Graphene

Graphene is a relatively new nanomaterial, discovered in 2004, which has attracted considerable attention in the scientific community due to its unique physical and chemical characteristics and which plays a vital role in various fields of science.[73] Graphene has properties such as high specific surface area, good electrical conductivity, zero bandgap, biocompatibility, and high drug-loading efficiency.[74–77] Graphene material is also used for lithium-ion batteries (LIB) due to its electrochemical properties.[74,78,79]

Graphene is a flat sheet one carbon atom thick (a monolayer). The atoms in its composition are sp^2 hybridized and arranged in a honeycomb lattice.[80–86] These atoms have four valence bonds, among which one is s and three other p orbitals.[87] It can be obtained in various ways, in particular, mechanical exfoliation, chemical vapor deposition (CVD), chemical reduction of graphite oxide, epitaxial growth on SiC, liquid-phase separation, and unzipping of carbon nanotubes (Figure 5).[80,86,88,89] CVD method is considered one of the most efficient methods for obtaining monolayer graphene or graphene films with only a few defects. However, this method requires a large number of high-purity gases and high energy costs.[74]

Graphene-based materials are often developed as smart platforms for nanocarriers and targeted drug delivery (Figure 6). Such carriers may be sensitive to the tumor microenvironment (TME), in particular, acidic pH and elevated levels of glutathione. In addition, the carriers can be activated by light, magnetic, or ultrasonic stimuli ("exogenous stimuli"). It was also shown that graphene can serve as a heat-conducting basis for increasing local temperature.[87] Electricity can also be an exogenous stimulus. Servant et al developed electrosensitive scaffolds based on graphene for polymer implants for drug delivery.[91]

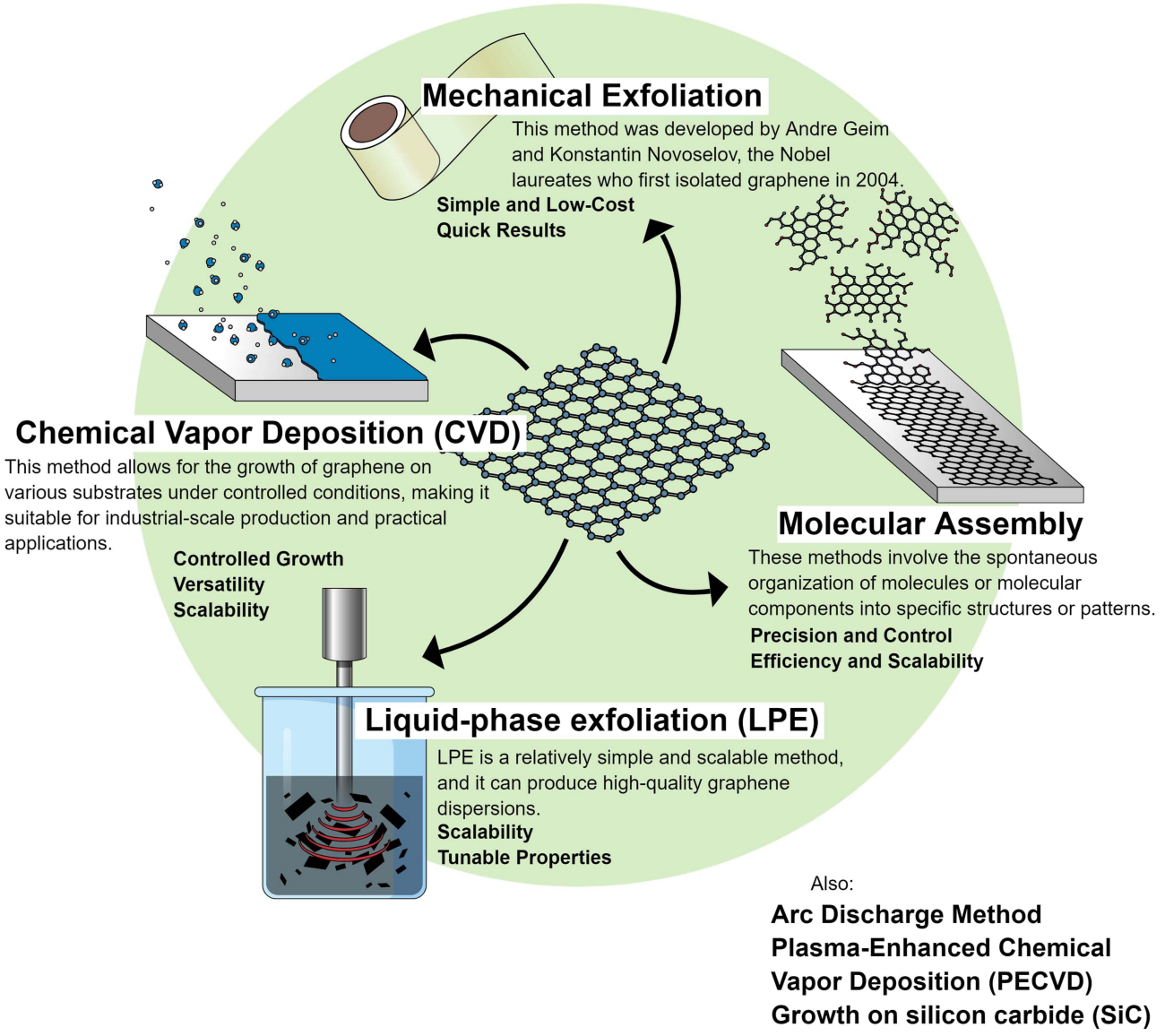

Figure 5 The example of graphene preparation methods.[22,80,88,89,291]

Graphene is also selectively absorbed by a tumor. In addition, a high yield of ROS products is characteristic.[81] This material has delocalized π bonds responsible for the unique electronic properties that give graphene the ability to heat under NIR (near-infrared) irradiation photothermally. This property is used to ablate tumors.[81] Furthermore, graphene is able to adsorb aromatic compounds on its surface due to π-π-electron interaction.[81,87,92] Graphene nanomaterials can penetrate the skin, get into the lungs when inhaled and overcome the hemato-tissue barriers when injected, and accumulate in the tissues. Graphene itself accumulates in the kidneys, lungs, and liver when injected intravenously. Nanoparticles are also easily absorbed by mitochondria and cell nuclei. One of the most severe toxic effects of graphene is DNA fragmentation by cellular endonucleases. Moreover, elevated concentrations of heme oxygenase 1 (HO-1), heat shock protein 90 (HSP90), active caspase-3, and endonucleases such as deoxyribonuclease I and endonuclease G are observed.[93,94] In addition to cytotoxicity, it is noteworthy that graphene particles can induce stem cell osteogenesis.[93]

Imperfections such as hydrophobicity and high cost had to be overcome, thus many graphene derivatives have been created. Such derivatives are graphene oxide (GO), reduced graphene oxide (rGO), graphene quantum dots (GQD), graphene nanoribbons (GNR), graphene nanoplates, and many more (Figure 7).[80,81,95]

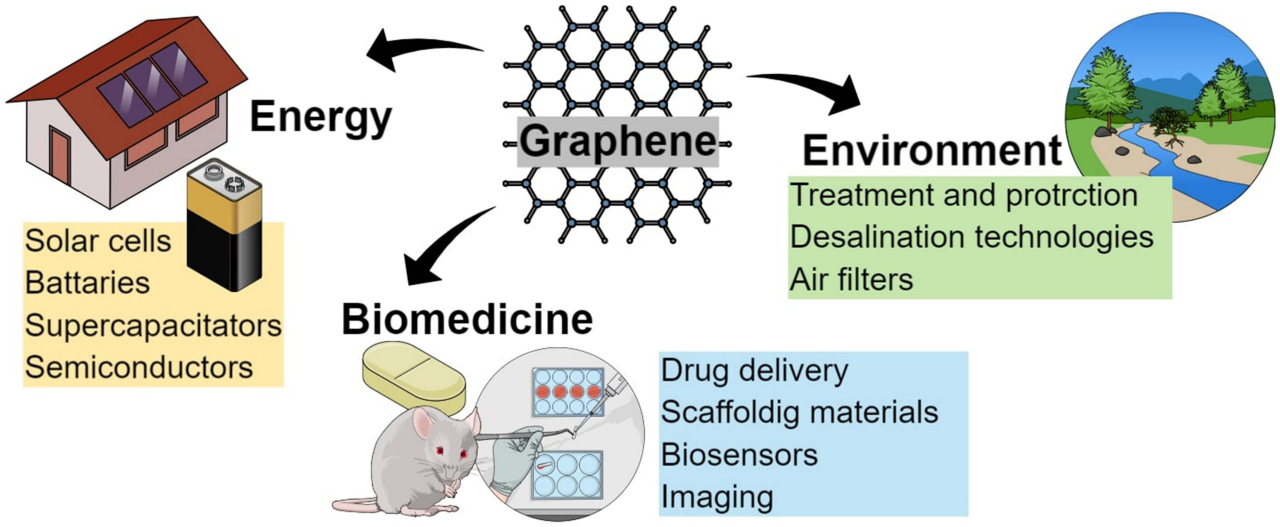

Figure 6 The versatility of graphene use. As a highly sought-after material, it is used for a wide range of applications in electronics, energy storage, water filtration, biomedicine, and composites.[73,74,78,79]

Graphene-based materials can also be used for visualization. Single-Wall Carbon Nanotubes (SWNTs), for example, have NIR photoluminescence and low autofluorescence, making SWNTs promising new NIR fluorophores.[98,99] This review describes graphene derivatives such as GO, rGO, GA, and quantum dots in more detail.

Graphene Derivatives

Graphene Oxide and Reduced Graphene Oxide

Graphene Oxide

GO is a budget material with a lattice of carbon atoms bound by sp^2 bonds with sp^3 defects, well dispersed in water and other solvents due to functional groups on its surface. GO contains functional groups such as hydroxyl, epoxy, carboxyl, carbonyl, phenol, lactone, and quinone groups. These functional groups increase the hydrophilicity of the surface, which means that biochemical reactions and bioconjugation reactions can occur on its basal plane as well as on its edges.[26,81,96,100] These functional groups create active sites for covalent or non-covalent modifications, which makes it easy to functionalize GO further using polymers, drugs, and other molecules. GO also showed a high adsorption capacity for proteins. The adsorption mechanism depends on GO morphology, oxidation state, and hydrophobicity. Polypeptides can be adsorbed on the surface of GO by the following interactions: hydrophobic–hydrophobic interaction, van der Waals interactions, electrostatic interactions, and also π–π stacking due to the large number of π-electrons on the basal plane of the GO surface.[100] It also exhibits photoluminescence, the wavelength of which varies from near-UV to NIR.[101]

Such materials have found their way into many areas of science, including drug delivery, corrosion protection, sensors, and water treatment.[82,102–104] GO also finds its application in electrochemistry and energy storage: super-capacitors, solid-state electrolytes, and GO in fuel cells.[105,106] Moreover, GO can be used to fabricate composites in various forms, such as nanoparticles, hydrogels, films, and fibers.[107]

This material is easily obtained by oxidizing graphite with concentrated acids and strong oxidizing agents such as H_2SO_4, HNO_3, or $KMnO_4$.[82,108,109] This method of obtaining GO was introduced in 1859 by Brodie who oxidized graphite in the presence of potassium chlorate $KClO_3$ and fumed $HNO_3 + NO_2$ (Figure 8).[109] Then, in 1937 Hofmann and Koenig made several improvements, as well as Hummers and Offeman.[110] Marcano et al improved the Hummers' method by eliminating sodium nitrate (Figure 8).[110–113] This change eliminated the formation of toxic nitrous gases. Since these methods use potent oxidizing agents, the resulting GO sheets have significant defects in their crystal network.[114] In addition, industrial waste can be utilized as a source of GO. It is possible to extract graphene from industrial waste, namely, the synthesis of GO from waste containing graphene precursors. Such waste may include Li batteries, biowaste (food, grass, insects), charcoal, soot, and others.[115–118]

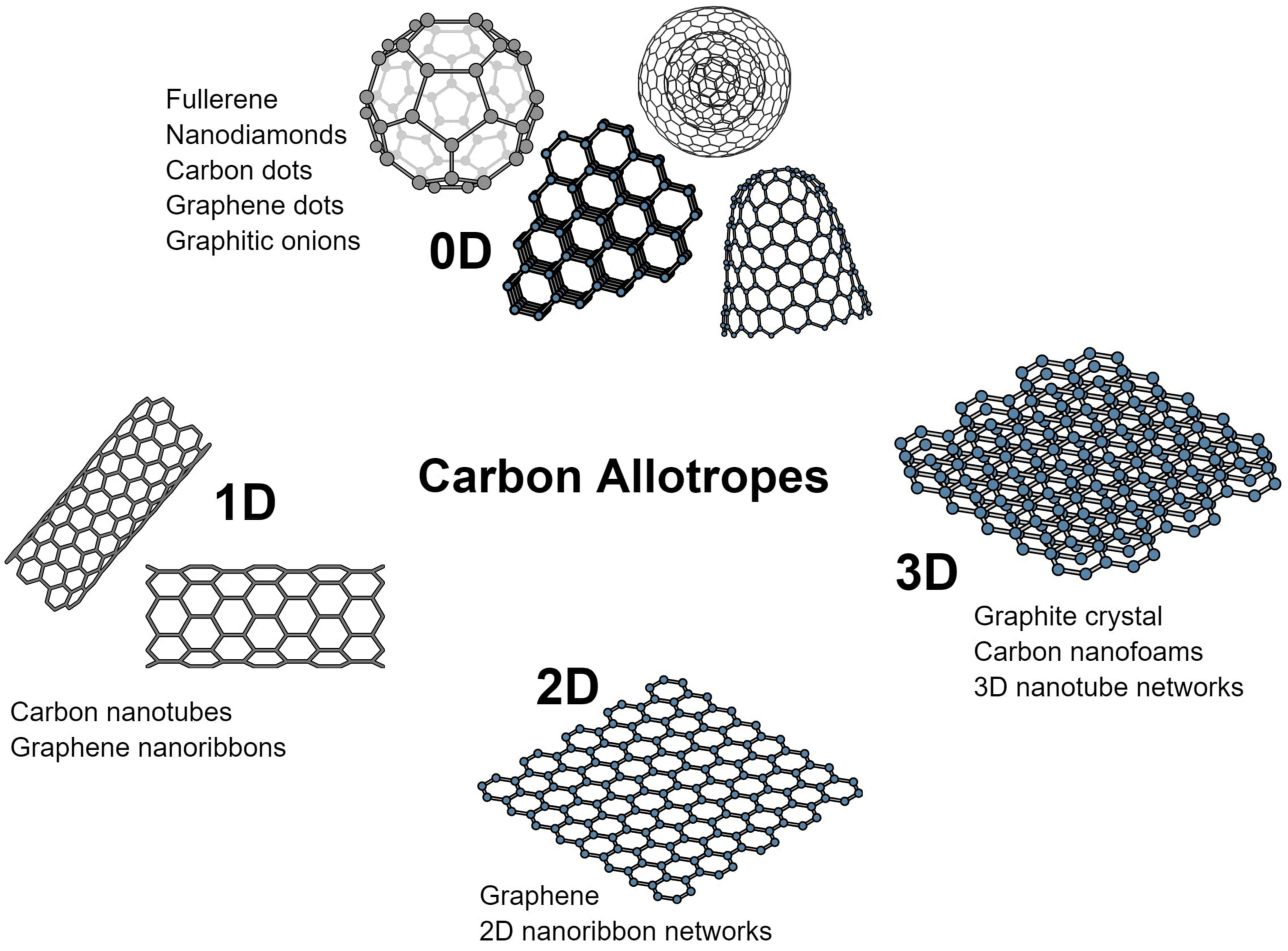

Figure 7 The classification of carbon allotropes encompasses several distinct forms, including carbon dots, fullerenes, carbon nanotubes, graphene (a single layer of graphite), graphite (two-dimensional layers), diamonds, and other related variants.[96,128]

Mechanical characteristics of GO include internal strength, ductility, brittleness, and others. However, destroying sp^2 bonds also decreases internal strength and Young's modulus compared with graphene. To analyze the mechanical properties of GO, various methods can be used, such as tensile atomic force microscopy.[81] The thermal conductivity is also relatively low, and it can be increased by imposing a polymer on the GO surface or by combining GO with metal oxide nanoparticles (for example, TiO_2 or ZnO).[81]

Reduced Graphene Oxide

rGO is a sheet of sp^2 carbon atoms with a restored π-electron graphene network and a minimum number of oxygen-containing groups.[114,119] Thanks to π conjugation, improved optical absorption, and conductivity, rGO is even more suitable for PTT than GO. GO is reduced using chemical agents or physical methods, during which the carboxyl (-COOH), hydroxyl (-OH), and epoxy (-O-) groups are removed by the reducing agent, which in turn reduces the solubility in water.[96] The properties of rGO are similar to those of graphene, and it is possible to change them depending on the reduction method and reduction degree. The most effective and simplest method is chemical reduction.[119,120] Reductants such as hydrazine, hydrazine hydrate, dimethylhydrazine, or strong alkalis can be used, as well as green reductants such as honey, tulsi (Ocimum sanctum) leaf extract, cinnamon extract, and green tea extract.[114,121,122] The following methods are available: photoreduction, solvothermal reduction, and microwave reduction (Figure 9).[114,123]

Biological Properties and Bio Applications

The data on the biocompatibility of GO are rather contradictory. More and more studies show that GO has a small cytotoxicity, but its manifestation depends on the method of obtaining GO, as well as on the form of GO.[81,100,124] For

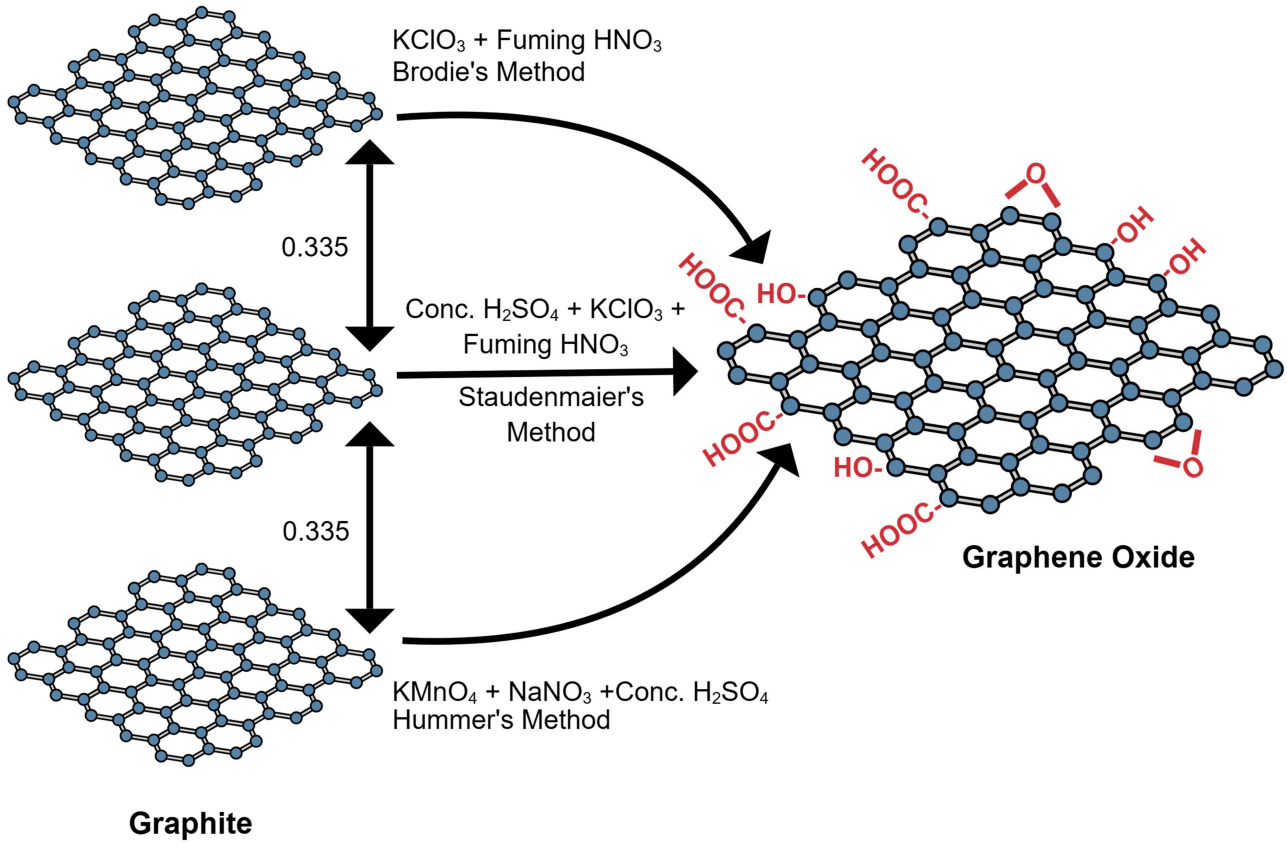

Figure 8 Methods of preparation of GO.[82,108,109]

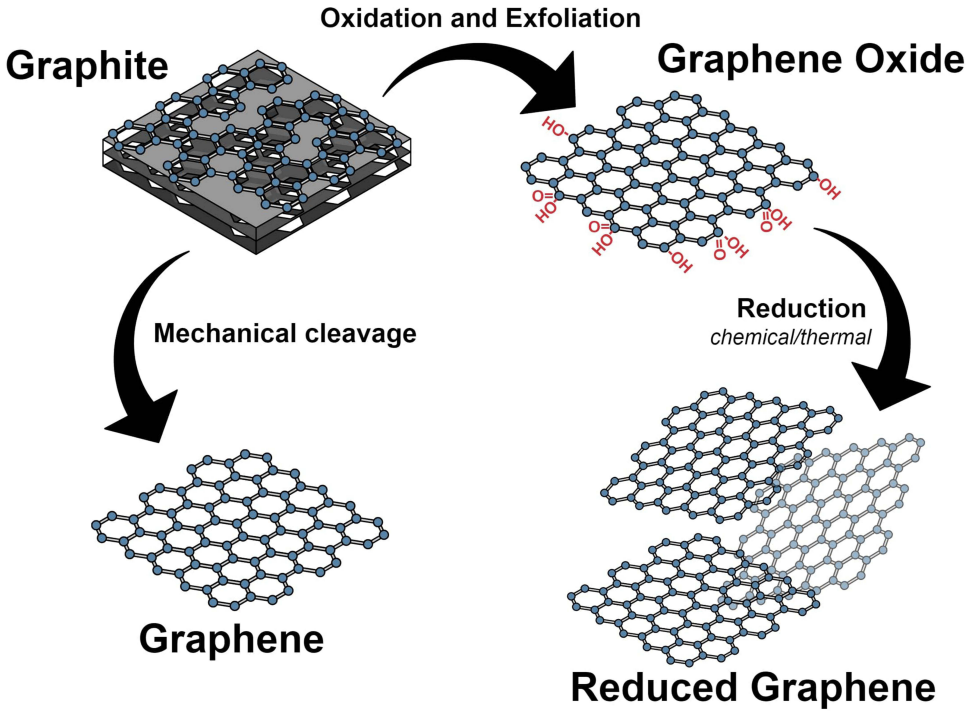

Figure 9 Connections between Graphite, Graphene, GO, and rGO.

example, GO flakes have rough and sharp edges, which allow them to disrupt the integrity of a bilipid layer of a membrane, disrupt the membrane potential, and are widely distributed in the whole volume of tumors (in particular, tumors of the nervous system such as glioblastoma). These data demonstrate the potential of graphene as a delivery vector for both drugs and various proteins.[100,119,125] This is especially important for potent aromatics that are insoluble in water. Modification of GO with polyethylene glycol (polyethylene glycol) makes it possible to create a biocompatible GO-PEG conjugate, stable in biological solutions, which can add hydrophobic aromatic molecules like SN38 (analogous to camptothecin) via π-π-stacking.[126] GO-PEG can also be loaded via π-π stacking with doxorubicin (DOX), which is hydrophobic. Thus, altered GO exhibits more potent cellular toxicity.[97,127] The release of imposed drugs is possible with the help of various stimuli, as discussed above. One of these incentives can be electricity. In their work, Weaver et al showed that it is possible to release the anti-inflammatory molecule, dexamethasone, in response to voltage stimulation with a linear release profile.[128]

Graphene itself and rGO, on the other hand, exhibit high cytotoxicity, which can also be explained by their geometry and spatial structure. rGO also has a large number of delocalized electrons due to low oxygen content, which leads to disruption of signaling pathways in the cell.[81] Wang et al showed in their work that exposure to GO below 20 μg/mL on cells (Human Fibroblast Cells, HDF) exhibits low cytotoxicity with cell survival over 80%.[76] At concentrations above 50 μg/mL, GO exhibits obvious cytotoxicity.[76] It has been shown that GO is internalized by cells and is mainly localized within endoplasm and organelles, such as lysosomes, and mitochondria. The adhesiveness of HDF cells treated with GO was also analyzed. Western blot results showed that cells cultured with GO have markedly reduced expression levels of laminin, fibronectin, focal adhesion kinase, and the cell cycle protein cyclin D3 compared to untreated cells.[76] Regarding the effects of GO on living organisms, namely mice, the injection dose of 0.1 and 0.25 mg GO per mouse did not cause death in the exposed animals and showed no clinical signs of toxicity. However, Wang et al also showed that in the group of mice treated with 0.4 mg per mouse, 4 out of 9 died, and their death was usually preceded by lethargy, inactivity, and weight loss.[76]

GO can also be used for work in the field of regeneration and tissue engineering, especially to restore bone tissue in severe lesions.[129,130] One of the modern materials to be applied in this field is GO aerogels. These aerogels are strong, have a porous structure, and can imitate bone tissue. Another advantage is their ability to absorb growth factors on the surface.[129,130]

Moreover, GO and rGO show high antibacterial activity. As already mentioned, these materials mainly affect bacteria through direct contact with sharp and superoxide anion-independent oxidation.[131–133] Lipid peroxidation plays an important role as well; GO nanosheets can also trap bacteria and are able to extract phospholipids from cell membranes due to dispersion interactions between GO and lipids.[134,135] Also, when modifying GO and rGO with silver nanoparticles, it is possible to achieve a synergistic effect.[120,134]

Graphene Acid

Graphene acid (GA) is a graphene derivative that contains evenly spaced carboxylic acid groups directly bonded to the sp^2 carbon backbone and has several advantages over the commonly used GO. Such advantages are aromaticity and a large number of homogeneously distributed COOH groups on the basal plane. GA luminescence has a maximum of 500nm. This product has excellent conductivity and biocompatibility and can be used as a catalyst and an electrocatalyst.[136–139] By oxidation with permanganate, GA can be obtained according to Tour's method. During the first oxidation, GO is obtained, and during the second one graphene acid. The total volume of the sample decreases by about three times, which indicates the oxidation of GO to CO_2.[137]

Further, one of the most important applications of GA is environmental cleaning, in particular removing heavy metals, since this plays a key role in the global issue of drinking water availability. In this case, GA with 33% by weight carboxyl groups is one of the solutions to this problem, as it has proved to be able to remove highly toxic metals such as Cd^{2+} and Pb^{2+}.[139]

It is also possible to modify GA via carboxylic acid groups. One option is covalent functionalization.[136,140] For instance, Mosconi et al functionalized GA surface with ferrocene (Fc) moieties through carbodiimide chemistry.[140] It allowed the introduction of up to 3.6% at. of iron as Fe^{2+} ions.[140] The next options are non-covalent functionalization, nanoparticles, and single metal atom immobilization on GA.[141,142] Bioinspired nickel bis-diphosphine HOR catalyst was

grafted on GA by Reuillard et al.[141] The immobilization of Sm_2O_3 particles by Sanad et al could be an example of functionalization with nanoparticles.[143]

Carbon Quantum Dots (CQDs), Graphene Quantum Dots (GQDs), and Graphene Oxide Quantum Dots (GOQDs)

Carbon Quantum Dots (CQDs)

CQDs were mentioned and obtained during the isolation and purification of single-walled carbon nanotubes for the first time by Xu et al[144,145] Later, Sun et al named these fluorescent carbon nanoparticles "carbon quantum dots".[144,146] This novel material solved several problems the conventional graphene had, as CQDs have good solubility and strong luminescence, for which they are referred to as carbon nanolights.[147,148]

CQDs are a mixture of sp^2 and sp^3 carbons in a quasi-spherical crystalline structure with their properties being directly linked to the π-electron state of the sp^2 carbons.[149] Their size is up to 10 nm.[147] The photoluminescence is size dependent, the size of the conjugated π-domains influences photoluminescence, with changes either promoting or inhibiting the direct transition of electrons from the conduction band to the valence band. This transition is responsible for generating band gap fluorescence.[149–151] CQDs also show a clear dependence of photoluminescence on the excitation wavelength.[147] When photoexcited, CQDs demonstrate outstanding capabilities as both electron donors and acceptors.[147,152] As well, CQDs exhibit optical absorption in the UV region, with a tail extending into the visible range.[147]

There are various methods of CQD synthesis that are classified into top-down and bottom-up routes. Top-down methods involve the reduction and fragmentation of large sp^2 carbon domains into smaller components. These techniques include arc discharge, chemical oxidation, sonication, hydrothermal methods, and others (Figure 10).[144,146,153–155] Bottom-up approaches for synthesizing CQDs mean constructing the material from precursor molecules, yielding particles with consistent sizes and

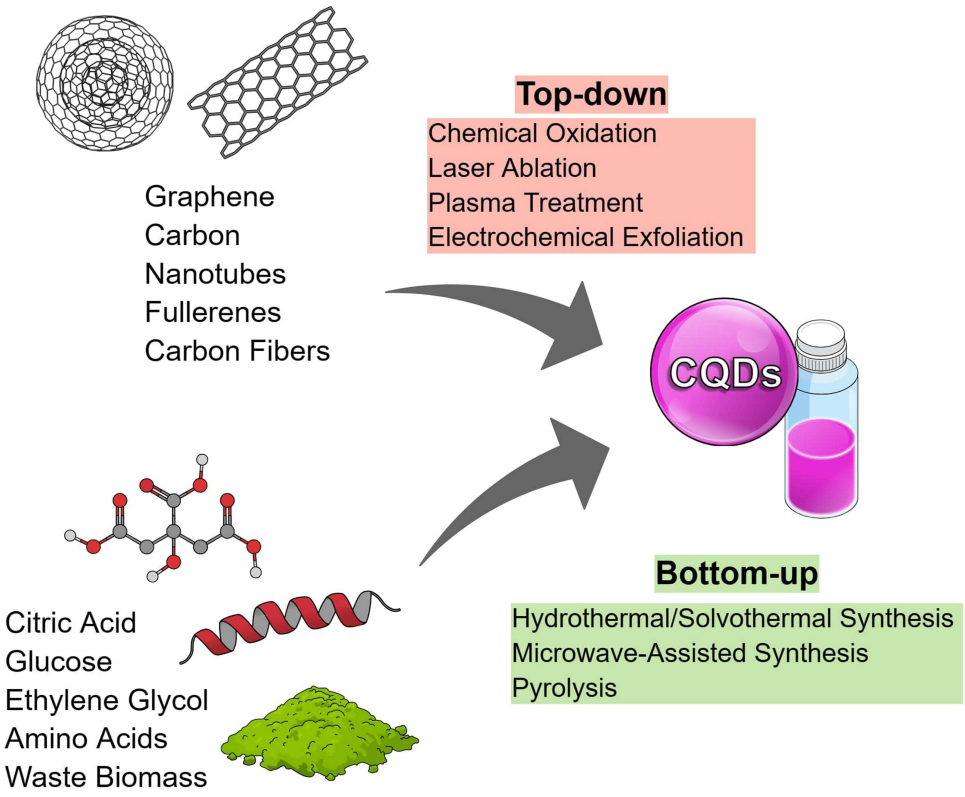

Figure 10 Various preparation methods can be employed to obtain CQDs, utilizing different carbon sources and synthesis procedures. The most usual division of preparation methods are top/down and bottom-up methods. Commonly used carbon sources include citric acid, glucose, and carbon black, while synthesis procedures range from hydrothermal and microwave-assisted methods to electrochemical and pyrolysis techniques.[156–158]

control over size distribution. These methods cover hydrothermal treatment, ultrasonic treatment, thermal decomposition, pyrolysis, carbonization, microwave synthesis, and the electrochemical method (Figure 10).[156–158]

Graphene Quantum Dots (GQDs)

GQDs are a new zero-dimensional material with lateral sizes up to 100 nm, most often 3–20 nm, single nanosheets of sp^2 carbons with luminescence properties, exceptional optoelectronic properties, and excellent biocompatibility.[159–163] Also, GQDs are low-cost, optically and chemically inert, and easy to fabricate. GQDs have applications in areas such as drug delivery, bioimaging, sensors, photovoltaic devices, and catalysis.[161,164–166]

GQDs have negatively charged carboxyl groups, which can provide good electrostatic properties for further functionalization. Conjugated π–π bonds also contribute to it.[167] GQDs are considered non-toxic, particularly to human cell lines. However, cytotoxicity can increase due to the nonspecific adhesion of dots to the cell membrane.[166,168]

There are various methods for synthesizing GQDs, which are classically divided into top-down or bottom-up ones. The top-down method involves destroying the graphene sheet, CNTs, the graphite using arc discharge, chemical or laser ablation, chemical or electrochemical oxidation, and ultrasound.[162,169,170] The bottom-up methods include carbonizing organic precursors such as citric acid, amino acids, carbohydrates, and some aromatic organic compounds using microwave treatment, hydrothermal treatment, solvothermal treatment, or other methods.[166,169–171] GQDs were first synthesized by Pan et al in 2010.[162] They had a crystalline structure of single or a few layered graphene and had an elliptical or circular shape. However, there may also be quadrate, hexagonal, as well as triangular GQDs.[162,169]

Graphene Oxide Quantum Dots (GOQDs)

As it was mentioned earlier, GO attracted attention among researchers due to its minimal toxicity, biocompatibility and hydrophilicity. GOQDs are nanoscale carbon-based materials that are derived from GO. These quantum dots possess unique optical and electronic properties due to their small size up to 30 nm and quantum confinement effects.[160,172–174]

On their basal plane and at the edges, GOQD have oxygen-rich functional groups such as epoxy, carbonyl, hydroxyl, and carboxyl groups, which facilitate further functionalization through electrostatic interaction, π–π stacking and chemical reactions.[175]

Preparation of GOQDs includes oxidizing, exfoliating, and cutting carbon precursors into nano-sized particles using chemical oxidation, hydrothermal, or solvothermal treatments under harsh conditions, often requiring concentrated acids like HNO_3 or H_2SO_4 for prolonged time.[172,176,177]

GOQDs have applications in diverse fields, regarding their distinct characteristics. They find utility in removal water pollutants, biological imaging, optoelectronic sensors, LEDs, fluorescent agents, lithium-ion batteries, and many others.[160] GOQDs hold promise for biomedical applications due to their non-toxicity, hydrophilicity, and high light-emitting efficiency, which originate from quantum confinement and edge effects associated with their oxygen-functional groups.[156,177]

Biological Properties and Bio Applications

Due to their properties, CQDs and GQDs can be widely used in various fields, including drug and gene delivery, biological imaging, electrochemiluminescence sensors, electrochemical sensors, and more (Figure 11). Numerous studies have confirmed the DNA fragmentation activity of therapeutic drugs when used in conjunction with GQDs.[178] For example, Fang et al developed a multifunctional GQD complex of hollow carbon nanoparticles to encapsulate DOX at the average size of 120 nm. They were also able to generate heat when irradiated with an NIR laser for synergistic photothermal therapy (PTT).[169,179] When functionalized with an antibody, selective destruction of cancer cells in vitro is possible.[91]

It has also been reported that GQDs are a promising potential treatment and a way to relieve the symptoms of amyloidosis, the essence of which is the aggregation and deposition of amyloid proteins in plaques around cells, which subsequently causes organ and tissue failure. Misfolded amyloid proteins are also the cause of brain tumors, Alzheimer's disease, Parkinson's disease, and stroke. GQDs can act as inhibitors of aggregation and, consequently, toxicity of amyloid proteins.[181,182]

Moreover, the fluorescence of CQDs and GQDs can be used to visualize living cells in the NIR range and to selectively recognize and bind to cancer cells, such as B-cell lymphoma.[91] They are also characterized by their resistance to photobleaching due to their crystal structure. From this point of view, GQDs are superior to CQDs.[183,184] GQD could

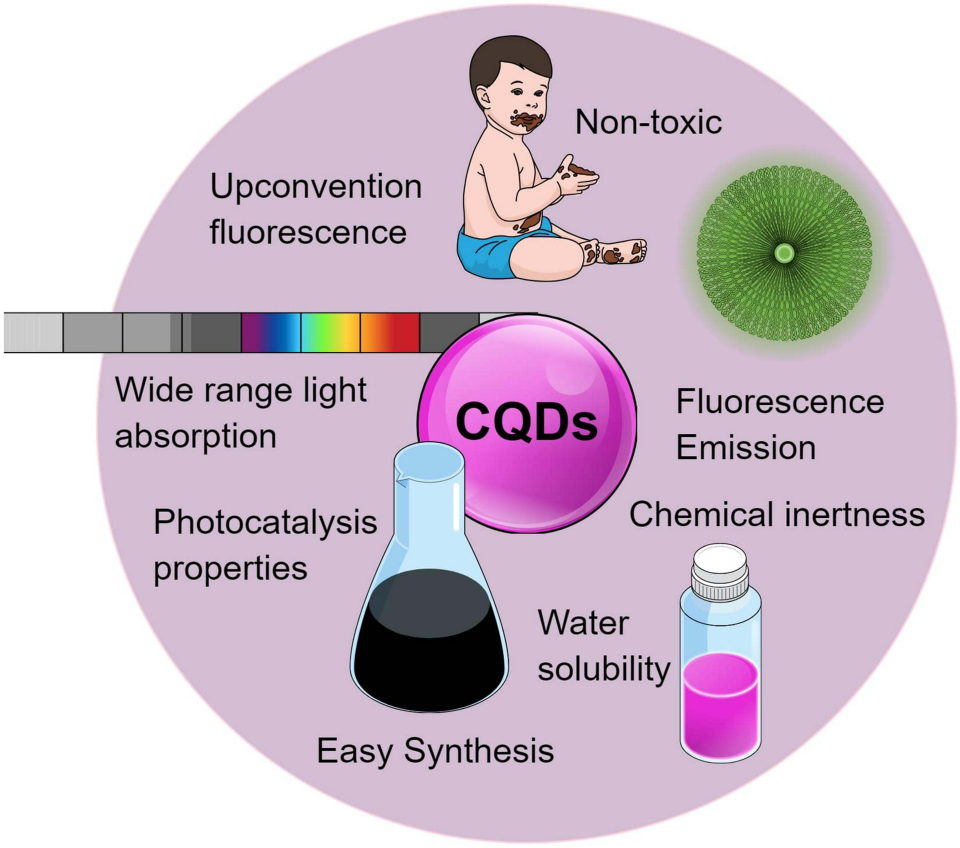

Figure 11 The features of CQDs.[159,160,162,163,169,180]

be further functionalized with PEG and can selectively accumulate in the tumor after being injected as an agent for tumor fluorescence imaging.[185]

Shi et al developed coated GOQD magnetic nanocomplexes with high fluorescence, which can improve the diagnosis of cancer in infected blood using multiphoton luminescence.[176] Pramanik et al reported short sequences of artificial RNA conjugated graphene oxide-based for improved two-photon selective imaging of breast tumor cells.[186] Also, GOQD can be used as a two-photon fluorescence probe for imaging multiple drug-resistant bacteria (like Methicillin-resistant Staphylococcus aureus).[187]

Nanotubes and Nanohorns

Single-Walled Nanotubes and Multi-Walled Nanotubes

Carbon nanotubes can be divided into two groups: single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). They are rather different in terms of their physical properties due to their structural differences, namely the number of carbon layers. SWCNTs, respectively, consist of a single layer of graphene with a diameter of 0.4 to 2 nm. MWCNTs, on the other hand, consist of two or more sheets of graphene with a distance between layers of 0.34 nm that form cylinders, so their diameter is from 1 to 3 nm.[188] SWCNTs can be further divided into the following three groups: armchair, zigzag, and chiral (Figure 12).[189] Carbon nanotubes have properties such as high rigidity (Young's modulus 1 TPa) and strength with a tensile strength of 60 GPa for SWCNTs and 150 GPa for MWCNTs and stability at high temperatures (in vacuum and air, the limiting temperatures are 2800 °C and 750 °C, respectively). They also exhibit high electrical conductivity and high heat transfer coefficient.[189–192] Their application is possible in areas such as electronics, sensors, and biomedicine, including the delivery of drugs to target organs.[193–195] They have a large surface area, which enables the conjugation of various molecules on the walls in large quantities. Molecules containing aromatic groups can also be noncovalently bonded due to strong π–π interactions.[195]

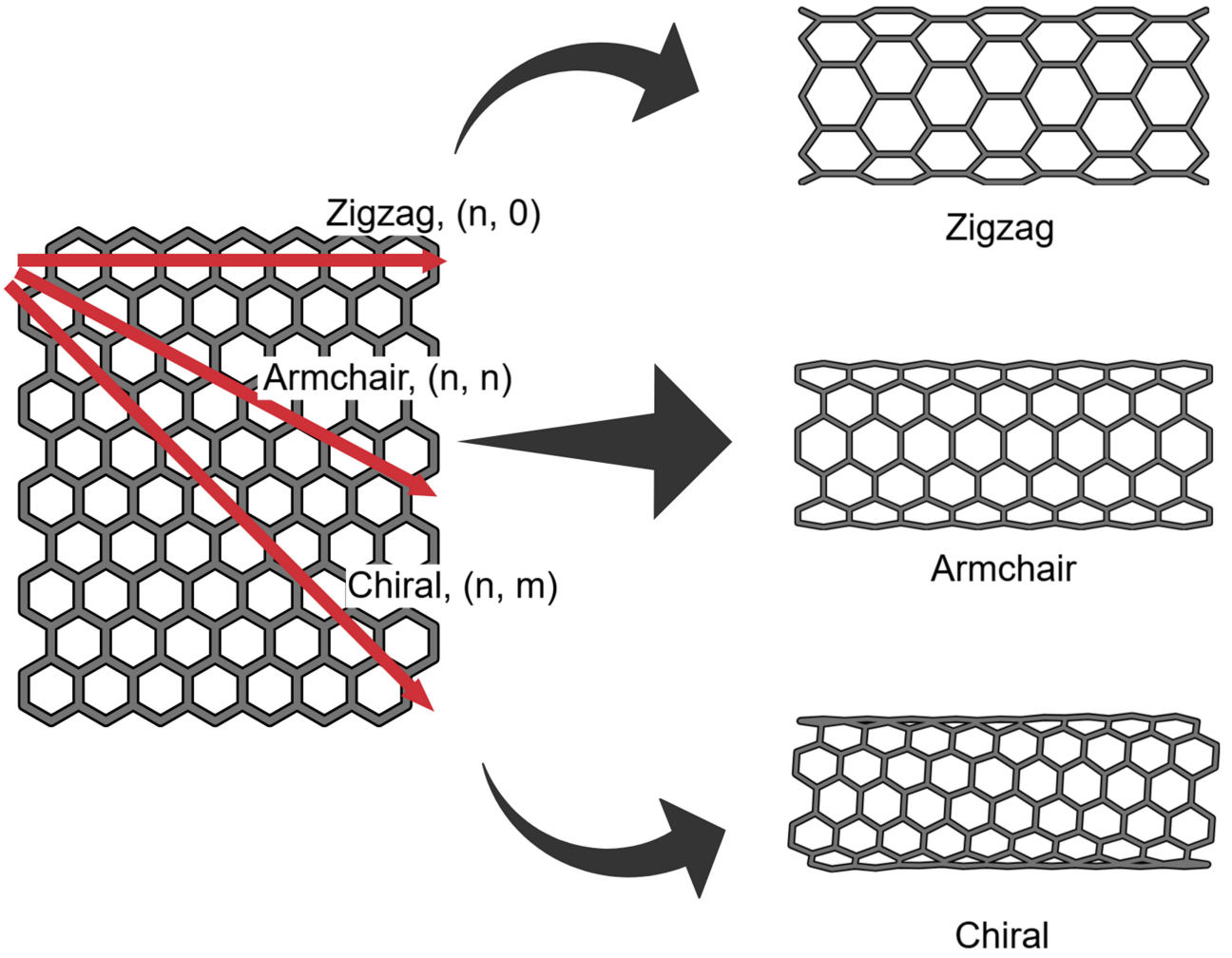

Figure 12 Carbon nanotubes are nanostructures that take the form of cylindrical tubes by rolling up a sheet of graphene. They can be divided into the following three types: zigzag, armchair, and chiral. Zigzag nanotubes have chirality (n,0), hexagons at the tube end with edges resembling a zigzag pattern, and are typically metallic, with no band gap, affecting their electronic properties. Armchair nanotubes have chirality (n,n), and hexagons at the tube ends, with edges running parallel to the tube axis, resulting in a flat, open-ended structure. Depending on the tube's diameter, they can either be metallic or semiconducting. The tunability of the electronic properties of chiral nanotubes makes them versatile for various applications.[189,196]

CNTs can typically be synthesized by the following methods: arc discharge, laser ablation, and chemical vapor deposition. The synthesis of individual SWNTs requires catalysts such as cobalt, nickel, iron, and others. In the synthesis by the arc discharge method, a high temperature of more than 3000°C is required, which mediates the evaporation of carbon atoms into the plasma to form various CNTs. Iijima used this method to synthesize MWCNTs. The next synthesis method, chemical vapor deposition, uses such precursors as methane, ethylene, and similar. The laser ablation method uses the evaporation of graphite in an electric furnace heated to 1200°C.[188]

Carbon nanotubes also have significant antimicrobial activity, which may be due to the synergy of physical and chemical effects. The intracellular content of bacterial cells is released through physical damage to the membrane, as described above. This process, however, depends on the size of the CNTs. Small CNTs can be internalized by bacteria and disrupt the metabolic processes in cells through oxidative stress.[89]

CNTs have several drawbacks, as well. Firstly, CNTs are inherently hydrophobic and insoluble in most biological media, making them difficult to use as a material for drug delivery or biomolecules. To overcome this problem, CNTs are functionalized for improved solubility and biocompatibility, allowing further drug modification with growth factors, antibodies, and so on. The methods of such functionalization can be noncovalent functionalization outside CNTs, functionalization of defects, covalent functionalization, and encapsulation of bioactive molecules inside CNTs.[195,197]

Also, functionalization methods can be divided into chemical and physical. The surface of CNTs can be chemically modified by oxidation, cycloaddition, and addition of functional groups such as carbenes, nitrenes, and similar. Physical modification can include methods such as the π–π stacking described above, coating with polymer chains, using surfactants, and adsorption via hydrophobic interactions.[190]

Secondly, CNTs may exhibit toxicity, which may be caused by their spatial conformation. Thus, carbon nanotubes and other fibrous materials will have an impact on living cells due to their jagged and flat edges.[86]

Nanohorns

Single-Walled Carbon Nanohorns (SWNHs) were first presented by Iijima in 1999. As a rule, SWNHs do not exist separately; they exist in a spherical aggregate of 80–100 nm in size in the amount of about a hundred.[198–200] The cones are formed by cutting a graphene wedge and seamlessly joining open edges, and individual SWNHs are 1–2 nm in diameter at the ends and 4–5 nm at the base.[199,201] They also have many advantages over nanotubes, they are widely used as drug delivery structures, do not require additional treatment with strong acids, and can be mass-produced with a high disassembly yield at a room temperature under Argon atmosphere at a high purity of about 95%.[202–204]

All production methods for SWNHs are based on disassembling and reorganizing carbon products.[204] Various operating parameters optimized during synthesis, such as pressure and temperature, result in different forms of SWCNH with different purities and morphologies.[202,205]

The closest structural analog of SWNHs is nanotubes due to the similarity in the atom arrangement. Due to this, SWNHs acquire similar physicochemical characteristics and hold promise as catalysts, as well as fuel source and basis for electronic cells. However, there are also differences between SWNHs and carbon nanotubes when interacting with living cells, including apoptosis, protein expression, membrane disruption, and interaction with membrane proteins.[130] Nanohorns are superior to na notubes due to the absence of a metal catalyst during synthesis and the possibility of their mass production at ambient temperature. Currently, SWNHs are a platform for drug delivery and can be applied to PTT.[198,206,207]

Fullerenes

Fullerenes, like Buckminsterfullerenes, were discovered in 1985.[208,209] The most extensive group of this family consists of C60 fullerenes with 60 carbon atoms in a spherical structure, which is a truncated icosahedron containing twelve pentagonal rings separated by twenty hexagonal rings, with sp^2 hybridization and resembling a soccer ball.[208,210] However, sp^2-hybridized carbon atoms in fullerenes have a pseudo sp^3-character since the arrangement is not flat but pyramidal.[199,211] Subsequently, C20, C70, C80 and even larger molecules were found.[210] Upon functionalization of C60, spectrum absorption expands to the near-IR region.[208]

The main disadvantage of fullerenes is their low solubility in polar solvents, which complicates their use.[208] In biological systems, the hydrophilicity of materials is more important than hydrophobicity, and methods such as preparation of two-phase colloidal solutions, synthesis of fullerene derivatives, encapsulation in cyclodextrins, polyvinylpyrrolidone, micelles and liposomes, and chemical modification are used to increase hydrophilicity of fullerenes and solubility in water. Chemical modification can be carried out by adding hydrophilic substances such as amino acids, carboxylic acids, and amphiphilic polymers.[212] On the other hand, the apolar character of fullerenes allows their use by penetrating cell membranes and being used in lipid-like systems.[212,213]

Fullerenes also have extended π-conjugation of molecular orbitals, which causes the absorption of UV–visible light. Due to this property, as well as the long lifetime of the excited triplet state, fullerenes are effective PSs.[208] This accounts for their significant antimicrobial activity.[214] Therefore, irradiation of fullerenes and their derivatives with white light produces ROS.[215] Oxidation of vital cellular structures or components without ROS formation is also possible.[89,216] Several methods for synthesizing C60 are available, such as arc discharge, chemical vapor deposition, laser irradiation, combustion, and evaporation of carbon sources.[217] Fields of fullerenes application include nucleic acid delivery, topical drug delivery, biosensors, and many others (Figure 13). [218–222]

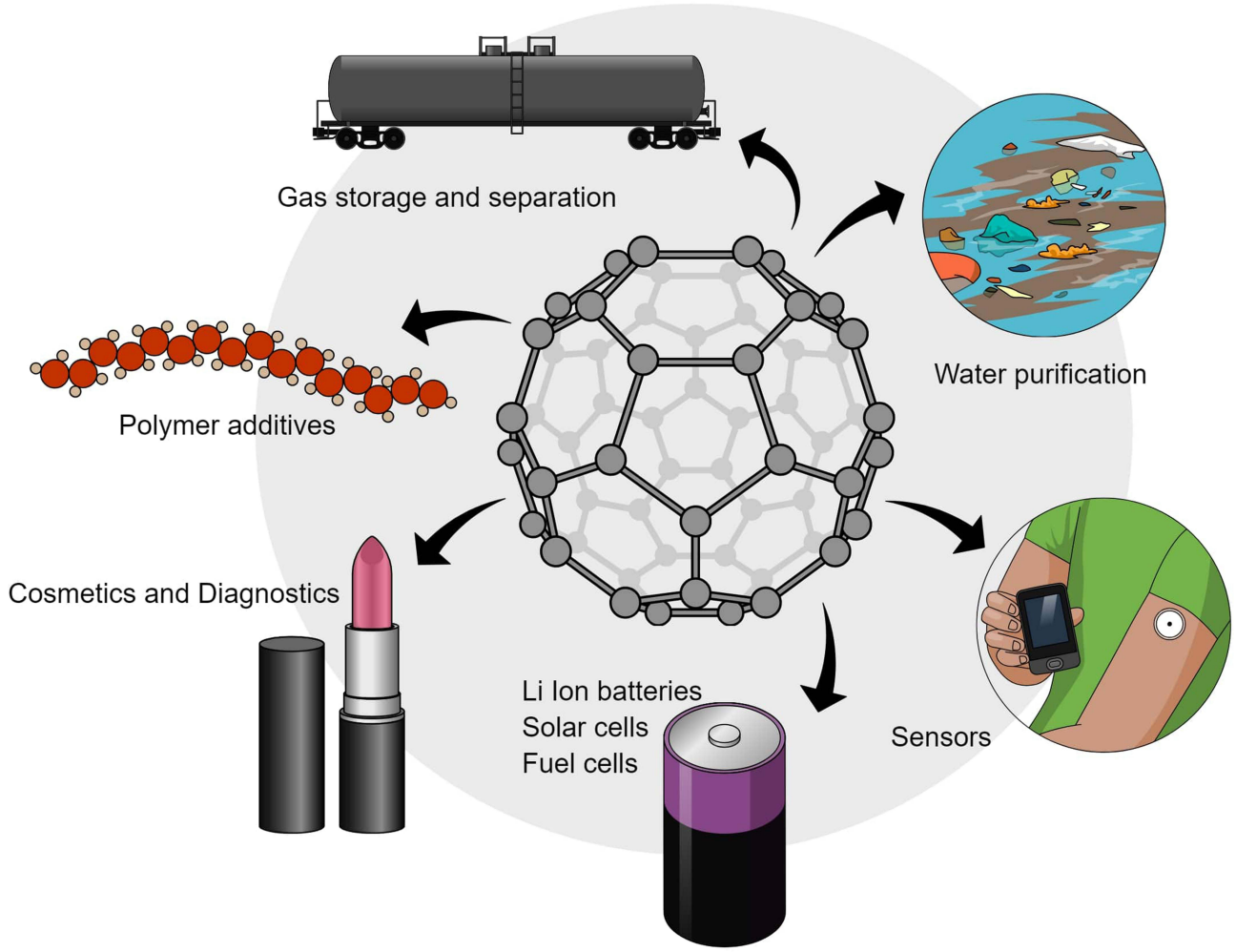

Figure 13 Fields of fullerenes application.[218–222]

Biological Properties and Bio Applications

With the help of the antioxidant activity of fullerenes described above and the ability to penetrate the skin, fullerenes can be a promising material in transdermal delivery and cosmetic applications.[223] It is also possible to eliminate the side effects of chemotherapy by imposing the medicinal substance on a fullerene and its subsequent targeted delivery. For example, it is possible to eliminate the side effects of DOX associated with cardiomyopathy.[223,224]

The possibility of binding fullerenes and other medicinal substances was also described above. Lysozyme can serve as an example; the C60-lysozyme complex showed effective endogenous activity of ROS after the exogenous formation of H_2O_2 in HeLa cells.[213,225] In some cases, suppression of ROS production is possible, which allows the use of fullerenes as neuroprotective agents.[226]

There are also reports on the ability of fullerenes to inhibit the activity of HIV-1 protease. The antiviral activity is due to the fullerenes attaching to the active center via van der Waals bonds.[213,227,228]

HIV-1 maturation is disrupted by altering protease activity and molecular interactions of structural proteins. New cationic derivatives of N, N-dimethyl fulleropyrrolidinium iodide inhibit more than 99% of HIV-1 infectivity at low concentrations.[229]

Nanoribbons

Nanoribbons were described in 1996 by Fujita et al and first mentioned in 1990 by Murayama and Maeda.[230–232] GNR are characterized by remarkable electrical and mechanical properties, due to their ultra-large surface area and their

structure. They can be considered unfolded CNTs with a high length-to-width ratio.[230,233,234] Chemically, they are sp^2-hybrid carbon networks with a crystalline structure and a honeycomb lattice shape which readily aggregate in solid or dissolved form. Their oxygenated derivatives attract attention in the field of biomedicine due to the presence of oxygen functional groups (hydroxyl, carbonyl, and carboxyl groups) at the edge and on the base plane, with the help of which subsequent functionalization is possible.[233,234] Their photoluminescent nature originates from the reduction of the π-electron network.[235] The three most common types of structures are "armchair" or AGNRs, "zigzag" or GNRs with zigzag edges (ZGNRs), and "cove".[230]

Nanoribbons can be used in areas such as sensor fabrication (mechanical, chemical, photo, and acoustic sensors), gene and drug delivery, and tissue engineering.[230,236] They are considered excellent candidates for drug and gene delivery.[237,238] In addition, they have high adsorption and synergistic effects when combined materials are used.[236] It is possible to create electrochemical biosensors to detect drugs such as nimesulide, dobutamine, nifedipine, and imatinib.[236,239–241] Moreover, there are biosensors for detection of insecticides, pesticides, and toxins, as well as further optical biosensors, luminescent biosensors and colorimetric biosensors.[236] Semiconductor nanoribbons on insulating substrates may also be useful for digital circuits.[242] They also stimulate the production of ROS in the cell and inhibit proliferation, apoptosis, and DNA fragmentation. They may have toxic effects due to mechanical damage to the cell membrane, as well.[230]

Regarding the functionalization mentioned above, it is possible to functionalize the GNR with the help of metals. Liu et al successfully created graphene nanoribbons in conjunction with Au (111) through a stepwise reaction using two precursor molecules co-adsorbed on surfaces.[243] To determine biomarkers, the GNR surface is functionalized by antigen immobilization.[236,244]

GNR synthesis includes the following methods: cutting graphene, electron beam lithography, plasma etching, nanoparticle etching, epitaxial growth on silicon carbide, and others.[230,245–248] Graphene and its derivatives present a widely used method for preparing GNR, as cutting from graphene sheets is readily available.[248] The process consisted mainly of exfoliating graphite by annealing at 1000 °C, followed by sonicating in a dichloroethane solution and centrifuging following suspension.[232] Electron beam lithography consists of etching carbon atoms with the help of a scanning tunneling microscope tip.[232]

Chowdhury et al reported oxidized GNRs (O-GNRs) as delivery vectors for gene therapy.[249] Efficient loading of double-stranded DNA was carried out on O-GNRs which were synthesized by longitudinal unzipping of multi-walled carbon nanotubes (MWCNTs). The bond between O-GNR and DNA is stable when ionic strength is reduced or treated with surfactants. O-GNR or DNA-O-GNR complexes <100 μg/mL were not cytotoxic.[250]

Biocompatibility and Toxicity

Derivatives such as nitrogen-doped graphene nanoribbon aerogels (N-GNRA) can be a worthy scaffold for various cell-line cultures. Superhydrophilicity and three-dimensional structure make N-GNRA a potential material in biomedicine. Liu et al reported human medulloblastoma cells (DAOY) cultured on the surface of N-GNRA for cytotoxicity analysis. Within 24 hours, most DAOY cells were found to adhere to the N-GNRA scaffold and after 3 days, DAOY cells proliferated and migrated along the skeleton and into the porous structure of N-GNRA.[251]

Another derivative of O-GNR, coated by amphiphilic polymer (1, 2-distearoyl-sn-glycero-3-phosphoethanolamine-N [amino (polyethylene glycol)]) (O-GNR-PEG-DSPE), also does not show a toxic effect in the case of MCF-7 and rat glial progenitor cells (CG-4) and similar. On the other hand, its complex with the antitumor drug Lucanthone (Luc-O-GNR-PEG-DSPE) was significantly toxic to malignant glioblastoma tumor cell-line U251.[252,253]

According to Mbeh et al, O-GNRs synthesized by oxidative decompression of MWCNT and functionalized with albumin at various concentrations may exhibit cytotoxicity.[254] The loss of viability of the human epithelial cells on which the material was tested is dose-dependent. Concentrations of ≤50 μg/mL did not exhibit significant cytotoxicity on the cells, while the concentration of 100 μg/mL exhibited significant cytotoxicity, causing proliferation, inhibition, and apoptosis.[254] The toxic effect of sonicating GNRs due to structural disruption is also an interesting feature.[255]

Use of Graphene-Based Materials to Enhance PDT

Functionalization of Graphene and Graphene Derivates

As stated before, a huge variety of NPs can be used for PDT but carbon-based and graphene-based materials stand out among them due to their properties.[256,257] Such materials as graphene, its oxide, GA, carbon nanotubes, CNR, fullerenes, CQDs and many others could be used as therapeutic agents, drug carriers, photoactive sensors and diagnostic platforms in cancer and other diseases.[256,258,259] Graphene nanostructures in many cases should be further functionalized for therapeutic purposes covalently or noncovalently, so their exceptional properties would be increased in biocompatibility, water solubility and many others.[256,260,261]

Noncovalent functionalization of graphene means functionalization via weak interactions such as π-π stacking, van der Waals forces, hydrogen bonding, electrostatic interactions, or coordination bonding, without breaking the carbon–carbon bonds of graphene. This type of functionalization offers preserving the structural integrity and its unique properties via a relatively simple process where materials and graphene interact without a chemical reaction.[262] However, the noncovalent functionalization of graphene does not significantly change the electronic transport which is crucial for sensing applications.[263,264] For example, molecules with π-conjugated systems can interact with the π-electron system of graphene through π-π stacking or polymers with functional groups like hydroxyl, carboxyl, or amine can interact with graphene via hydrogen or electrostatic interactions.[262,265–267] Another option is the adhesion of molecules to graphene surfaces through van der Waals forces or coordination bonding.[262,268]

Functionalizing graphene with PEG typically also involves noncovalent functionalization. PEG is a hydrophilic polymer with terminal hydroxyl groups, which can form hydrogen bonds with the oxygen-containing functional groups on the graphene surface.[269] PEGylation can increase stability of graphene materials, inhibit aggregation, reduce toxicity, and prolong blood circulation half-life improving pharmacokinetics of graphene-based materials.[269,270] For PEGylation, simple mixing of both graphene material and PEG with incubation under ultrasonication for 30 min at room temperature is enough in order to initiate physical adsorption, as Mendonça et al stated.[269] Graphene materials can also be functionalized with further polymers such as polystyrene sulfonate (PSS).[271] Du et al incorporated GQDs into poly3,4-ethylene-dioxythiophene:polystyrenesulphonate (PEDOT:PSS) conducting polymer mixture. This incorporation was possible due to the electrostatic interaction between oxygen-containing group of GQDs and PSS and also becouse of π-π conjugation between PEDOT and GQDs.[271] Another example introduced Hong et al, when PSS-rGO complex was prepared by simple mixture of GO and PSS in deionized water under 30 min sonication.[272] Alternative polymer that could be coupled with graphene-based materials is dextran. Jin et al reported preparation of GO hybrids functionalized with hematin-conjugated dextran. Preparation included a mixture of dextran and GO solutions with further addition of ammonia solution and 50% hydrazine solution and stirring under nitrogen at 60 °C for 3.5 h.[273] Polyvinyl alcohol (PVA) is the next important polymer that can be used for graphene functionalization.[274–276] Ma et al reported a simple mixing of 10% (w/v) PVA and GO solutions at 40 °C for 3 h and further sonication treatment for 30 min to obtain a GO/PVA complex.[274] A similar process was also reported by Morimune et al.[275] Use of other polymers via electrostatic interactions like polyethyleneimine (PEI), polypropylene imine (PPI), and poly-(amidoamine) (PAMAM) is also possible.[267,277,278]

It is also possible to functionalize graphene with such macromolecules as DNA. Thiolated DNA was shown to bind noncovalently to both graphene and GO surfaces.[279,280] It is also possible to create a 3D hydrogel through a self-assembly process of GO/DNA material.[279,281] Xu et al fabricated GO/DNA hydrogel by mixing equal volumes of the GO aqueous solution and the aqueous solution of double-stranded DNA followed by heating at 90 °C for 5 min.[281] However, EDC/NHS chemistry is the most common method of attaching antibodies and ssDNA onto graphene and its derivatives. Enzymes are typically immobilized using physisorption.[282] Lu et al successfully fabricated rGO sheets noncovalently functionalized with β-lactoglobulin. This hybrid material was characterized with pH-dependent water solubility and was an efficient platform for further Au nanoparticles self-assembly.[279,283]

Covalent bonds are much stronger than noncovalent and can be achieved through various chemical reactions, such as oxidation, reduction, diazonium chemistry, cycloaddition reactions, cross-linking, and doping. This can enhance properties like solubility, stability, and reactivity, making graphene more versatile for further applications.[262] Covalent functionalization improves the water dispersibility and stability of graphene derivates.[262,284,285] Carboxylic acids or

hydrophilic polymers are used the most. Carboxylic treatment is simple, and attachment of carboxyl, epoxy, and hydroxyl side groups on graphene leads to its increased dispersibility in the aqueous phase.[262] However, carboxylic acids can introduce other active molecules, and this may result in the creation of additional defects in graphene sheets.[262] It can also be challenging to realize the covalent functionalization of pristine graphene due to its lack of conjugatable functional groups.[286]

Doping is a prevalent method that is used to modify the electronic characteristics of semiconductor materials. Carbon nanotubes can undergo doping with nitrogen or boron atoms to achieve n-type or p-type materials, respectively.[286,287] Yalcin et al reported fabrication of GO-doped LaB6 composite for photodiode base.[288] For this purpose, LaB_6 was stirred into deionized water for 30 min. Gradually, GO solution was added to the mixture, and then homogenized via ultrasonication for 30 min. Subsequently, hydrothermal processing was applied on the homogenized mixture for 24 h at 120 °C with the following drying at 60 °C for 24 h in a vacuum oven.[288] Zhai et al reported fabrication method for N-doped CQDs from garlic skins without any additional organic reagents that had a potential application as a fluorescent ink or smart fluorescent sensor.[289] Rishabh et al reported another green synthesis of N-CQDs from Aegle Marmelos.[290] Aegle Marmelos leaves were crushed with a household mixer. For nitrogen doping, a suspension solution was made with solid urea in deionized water, which was later added to the leaf paste. The mixture was further irradiated with microwave waves, filtered, and dialyzed.[290]

Numerous polymers are capable of serving as both covalent and noncovalent modifiers for graphene and its derivatives. Liu et al achieved successful modification of GO for delivering water-insoluble cancer drugs. They utilized PEG conjugated to the carboxylic acid groups on GO via carbodiimide-catalyzed amide formation.[286,291] Kim et al reported rGO-PEI complex via covalent conjugation.[277] Branched polyethyleneimine (BPEI) was linked to the carboxylic groups of graphene oxide (GO) utilizing EDC/NHS chemistry. Following this, BPEI-GO underwent reduction by hydrazine monohydrate.[277]

Another successful method for functionalization involves the electrophilic substitution of aryl diazonium salt onto the surface of graphene sheets.[90,284,292] Aryl diazonium salt molecules have been effectively utilized to alter carbon materials, such as SWCNTs, graphite, and many others.[286,293–296] This modification process can be done under mild conditions, either through simple agitation or electrochemical reduction adsorption, often accompanied by the release of N_2. The use of aryl diazonium salt functionalization chemistry on nano-carbon materials was pioneered by Bahr et al.[293]

Covalent functionalization also represents a viable approach for the conjugation of graphene and its derivatives with biomolecules such as enzymes, antibodies, and others. Ganji Arjenaki et al fabricated an antibody-conjugated GQD complex for in vivo breast cancer imaging and biodistribution.[297] For that GQDs were dissolved in a mixture of DMF and water and then, via EDC/NHS chemistry pembrolizumab, which is a humanized antibody used in cancer immunotherapy, was conjugated to GQDs.[297] Kaushal et al reported the preparation of a complex system of AuNPs coated with PEGylated GO and antibody conjugated to GO for rapid visible detection of food-borne bacteria.[298] Before the addition of antibody, PEG-GO -AuNPs were activated by EDC/NHS.[298] As to enzyme immobilization, Royvaran et al fabricated GO nanosheets that were further decorated with superparamagnetic iron oxide nanoparticles on which xylanase was later immobilized. Both covalent and noncovalent immobilizations were utilized.[299]

Mechanisms of Graphene-Based Materials in PDT

There are several ways in which graphene-based materials can improve PDT efficacy. This could happen via light absorption, energy transfer, electron transfer, enhanced ROS production, synergistic effects with photosensitizers, and enhanced photothermal effect.[300–304] In many ways each process cannot be separated from one another and usually, it is a combination of the abovementioned factors.

When irradiated with light, graphene can absorb photons and transfer the absorbed energy to nearby molecules, including oxygen and PSs. This energy transfer process promotes the generation of ROS, such as singlet oxygen and free radicals. However, it has been found that the light absorption of graphene is quite low, with only 2.3% of the incident light being absorbed by a single layer of graphene. This limitation affects the efficiency of graphene-based materials and calls to find ways to enhance their optical absorption, especially for the optoelectronic field.[300–302,305,306] GO and rGO have been used in the synthesis of p-n heterojunction photocatalysts, which can enhance the separation of electron–hole pairs and improve photocatalytic activity. rGO has also been used as a p-type coupling semiconductor to n-type copper

phosphate for high visible light photocatalytic activity.[307] On the other hand, fullerenes have a capacity for visible light absorption, appealing triplet yield, and ability to ROS. With superior bioactivity and outstanding electronic properties, C60 garners the most attention as an efficient PS, boasting a near 100% quantum yield in generating singlet oxygen.[303,308] The other aspect that needs to be noted is that the optical properties of graphene and its derivates rely on distance-dependent interactions and the design and fabrication of layered structures.[302]

Additionally, the distinctiveness of graphene as an energy acceptor strongly backs the excitation wavelength. This observation opens up new insights into the dynamics of excitation and energy transfer in systems where the characteristics of either acceptors or donors can be further controlled independently through light.[302]

Graphene and its derivates exhibit high electron conductivity and can act as an electron mediator in redox reactions. In the presence of light, it can transfer electrons to molecular oxygen leading to the formation of superoxide radicals.[309–313] Graphene materials serve as electron sinks, boosting visible-light photodynamic capabilities, and synergistically integrating photodynamic and photothermal hyperthermia, maximizing therapeutic effect.[304] For instance, GQDs function as effective Förster Resonance Energy Transfer (FRET) donors with tunable optical properties.[303,314,315] In GQDs, the ROS generation mechanism is also different from the traditional one, when singlet oxygen is produced via energy transfer originating from the excited triplet state. ROS can occur from both the excited singlet (S1) and triplet (T1) states.[316,317]

The synergistic effect of graphene and its materials with photosensitizers is based on excellent electrical conductivity, high surface area, and efficient charge transfer.[318,319] Also, novel hyaluronic acid (HA)–GO conjugate systems were reported for the switchable photoactivity of PSs.[304,320] It was found that hyaluronic acid increases the stability and biocompatibility of the GO nanosheets. Cellular uptake of PS was also improved by targeting the cancer cells with overexpressed HA receptors. The loading efficiency of PS was as high as 115% via both π–π stacking and hydrophobic interactions. The photodynamic activity of Ce6, when adsorbed on HA-GO nanocarriers, was largely suppressed in aqueous solution to ensure biocompatibility. However, this suppression was recovered upon the release of Ce6 following cellular uptake. Consequently, the photodynamic therapy (PDT) efficiency of the HA-GO/Ce6 was enhanced compared to free Ce6.[304,321] Other examples will be discussed further for each graphene material.

Graphene Oxide and Reduced Graphene Oxide

GO and rGO could be modified in a lot of different ways, such as through PEGylation and combination with other polymers, combination with different PS and addition of anticancer chemotherapeutic agents. Majority of the studies, however, combine several approaches. PEGylated GO co-loaded with PS to improve their hydrophilicity could be used for both PDT and PTT and it can be activated by 980 nm laser for achieving two-photon PDT, as noted by Liu et al.[322] By combining these two types of therapy, it was possible to achieve improved anticancer efficacy against breast cancer while preventing damage to normal tissue.[322] Similarly, Zaharie-Butucel et al successfully combined rGO, IR820 dye and DOX to prepare platforms for NIR-triggered therapy for both PTT and PDT activity under 785 nm laser irradiation.[323]

As mentioned before, not only PEG could be used as a sufficient modification of NP to combine it with different PS. The other widely used polymer is Pluronic (PF127) which was used by Ma et al to prepare a composite with GO and methylene blue by a thin-film hydration method.[324] This platform can be used for both PDT and PTT which is beneficial as PTT is still effective when oxygen-dependent PDT is limited during hypoxia.[324]

As to methylene blue, several researchers show its efficiency against different cancers when combined with GO.[325–327] It has pH-responsive properties and PS release could be even more efficient at acidic pH.[327] In addition, a combination of PDT and PTT could provide a synergistic effect, preventing tumor regrowth and metastasis with low systemic toxicity.[325,326]

For both PTT and PDT, GO can also be combined with indocyanine green (ICG). In complex with sgc8 aptamer, cancer cells were efficiently killed even though GO loaded with ICG produced less singlet oxygen compared to free ICG.[328,329] Also, not only PS can be loaded on the GO surface; chemotherapeutic agents and other drugs through π–π stacking interaction like wedelolactone can be as well.[329]

After binding rGO with hyaluronic acid, it is also possible to create an enhanced intracellular uptake and prepare a trimodal platform for cancer treatment via IR780 and DOX conjugation. IC_{50} of DOX was reduced by 86% in vitro as reported by Dash et al.[330]

Carbon Quantum Dots (CQDs), Graphene Quantum Dots (GQDs) and Graphene Oxide Quantum Dots (GOQDs)

CQDs, GQDs and GOQDs have a lot of beneficial properties according to several scientists. Remarkably, Pillar-Little et al noticed the connection between the preparation method of CQDs and its PDT-toxicity. Top-down synthesized CQDs show much stronger light-activated toxicity.[331,332] Thakur et al claimed, in their research with an 808 nm laser, that GQDs are not photo-bleachable-like organic dyes and do not lose their fluorescence despite continuous irradiation.[333] Also, producing such complexes of QDs as conjugation of rare-earth elements doped upconversion, nanoparticles with GQDs could produce ROS efficiently under NIR light dealing with low ROS yields with conventional PSs. As Li et al stated, such functionalized GQDs show biocompatibility and concentration-dependent PDT efficiency.[334] It is also possible to use other lasers, like the one with micro-watt power (290 μW) 365 nm UV tube light, as Ahirwar et al reported.[315] Ahirwar et al also showed that GQDs and GOQDs both have strong absorbance in the UV region and ROS generation. B16-F10 cells and MCF-7 cells were used in their PDT experiment, and the viability dropped dramatically after a brief 5-minute exposure.[315]

Fan et al also showed that doping GQDs with heteroatoms can modify their optical properties and nitrogen (N) doped GQDs (N-GQDs) for PDT are broadly researched now.[335] They can be synthesized using various methods like hydrothermal method and solvothermal method.[335–337] Shi et al were able to fabricate samarium doped carbon dots (Sm/CDs) via a one-step hydrothermal method. Sm/CDs exhibited noteworthy biocompatibility and remarkable absorption properties in the near-infrared spectrum. The incorporation of Sm^{3+} significantly enhances the production of ROS and photothermal conversion efficiencies when exposed to 808 nm and 1060 nm wavelengths.[338]

It is also possible to prepare PEGylated material, similar to GO and rGO particles. Zhang et al obtained GQDs-PEG material displaying a low cytotoxicity and efficient endocytosis.[339] It was also demonstrated that host-immunity-related CD8+ T cells and proinflammatory cytokines significantly increased after photoactivation of GQDs-PEG material which means that this material has immunostimulatory activity. It makes them not only PDT agents but also promising immunotherapy candidates.[339,340] Not only PEG but other polymers can be used. Juzenas et al also noticed that propionyl ethylenimine-co-ethylenimine coated CQDs when exposed to UV irradiation destroy malignant human prostate cancer cells, as tested on Du145 and PC3 cell lines.[332,341]

There is a possibility to combine GQDs with other NPs as evident from the synthesis of N-doped GQDs/titanium dioxide nanocomposites (N-GQDs/TiO2 NCs).[342] Some studies also report the conjugation of GQDs and GOQDs with upconversion nanoparticles (UCNPs), as already mentioned.

Choi et al reported that UCNP-like ytterbium and erbium ions-doped sodium yttrium fluoride NPs (NaYF4:Yb3+, Er3+) were bound to the QDs by coupling chemistry with EDC and afterwards, it was possible to conjugate newly prepared material with PSs by π-π stacking interaction.[343] This product was also shown to be a candidate as a photosensitizing agent and in cancer cell imaging.[343]

As to PSs, a lot of them can be coupled to the GQDs surface; among them are BODIPY, chlorin e6 (Ce6) and hypocrellin A (HA), curcumin, methylene blue and others.[335,340,344,345] Mangalath et al described boron dipyrromethene dye derivatives in conjugation with GQDs (GQDs-BDPA) for PDT purposes.[344] GQDs-BDPA exhibited a higher ROS generation yield than the free BDPA.[344] Li et al reported that GQDs with disulfide-linked PEG and conjugated with Ce6 caused efficient suppression of tumor growth.[340] When using methylene blue as PSs in conjugation with sulfur-doped GQDs, improved ROS generation and even antimicrobial activity were reported.[346]

One of the promising PS used with GQDs is curcumin, which has a low water solubility on its own, therefore further adjustments are needed.[347] It is possible to dissolve curcumin in methanol or DMSO and just add curcumin solution to the solution of GQDs.[348,349] Methanol or other solvents can be evaporated later via rotary evaporation.[348] Another way is to add curcumin through tryptophan. Ghanbari et al reported enhanced curcumin loading capacity on the tryptophan-conjugated GQDs where π–π stacking and hydrophobic interaction played a crucial role in conjugation with an aromatic of curcumin.[350] Changes in the absorbance spectra and ζ-potential were observed in the conjugated materials.[349,350]

Nanohorns

Moreno-Lanceta et al stated that single-walled carbon Nanohorns (SWNHs) are promising PTT agents and PDT PS carriers as they exhibit excellent photothermal features in NIR light.[202] As carriers, they can be coupled with other PSs such as indocyanine green (ICG), chlorin e6, fabricated zinc phthalocyanine (ZnPc), tetrasodium salt copper phthalocyanine (TSCuPc) or IR808 covalently grafted to hyaluronic acid.[207,351–357] ICG is possible to couple via the above-mentioned hydrophobic π–π stacking; Gao et al tested SWNHs coupled with ICG as a PDT agent on 4T1 triple-negative breast cancer cells and reported that ROS formation increased within activation by 808 nm wavelength and temperature increase.[354] Yang et al reported the preparation of Gd^{3+} and chlorin e6 loaded SWNHs, which stimulated dendritic cells to secrete IL-6 and TNF-α by PTT, while PDT upregulated IFN-γ and CD80.[355] As a result of this immune response, migration of Gd-Ce6@SWNHs to the tumor-draining lymph, it eliminates the distant metastases and prevents cancer reoccurrences.[355] To improve its solubility in water, it was also coated first with poly(lactide-co-glycolide)-b-poly (ethylene glycol)-maleimide and maleic anhydride-alt-1-octadecene before drug loading.[355]

Nanotubes

CNTs have also been evaluated as candidate materials in PTT and PDT on their own or in combination with PSs.[358] Single-wall CNTs in combination with polyethyleneimine and polyvinylpyrrolidone can form stable complexes, like SWNT-PEI and SWNT-PVPk30, that can act as a promising PDT agent, as Wang et al stated.[359] Again, number of PSs are possible for conjugation. Among others, we can mainly note Chlorin e6, m-tetrahydroxyphenylchlorin (mTHPC), curcumin, palladium(ii) porphyrin (PdP), platinum(ii)porphyrin (PtP) and tris(triphenylamino)porphyrin palladium(ii) (Pd(TPA)3P).[360–364] Chlorin e6 (Ce6) could be coupled with SWCNTs by noncovalent π–π interactions, and the resulting complex induces the significant ROS production. Optionally, this complex can also be wrapped by chitosan to improve biocompatibility and solubility in water.[360,364] Li et al in their work used curcumin as the PSs of choice for PDT and it showed enhanced antitumor efficacy, cell uptake, and blood concentration compared to pure curcumin. In that case, curcumin was complexed with SWCNT in methanol.[360] Arellano et al successfully linked tris(triphenylamino)porphyrin palladium(ii), Pd(TPA)3P covalently to single-walled carbon nanotubes via Sonogashira cross-coupling with the use of microwave irradiation.[363]

Fullerenes

Fullerenes have some unique features that make them candidates for PDT even though they have some unfavorable optical absorption properties, such as high absorption at the UVA and blue spectral region. However, poor light absorption in the range of 600–700 nm is a drawback of C60 above all, which means that we should use C70. Nevertheless, functionalization can overcome those difficulties; for instance, a light-harvesting antenna molecule could be introduced to the fullerene molecule. It is known that both pristine and functionalized fullerenes can catalyze the formation of ROS.[365–369] Two widely known reactions will lead to covalent functionalization; these are the Bingel and the Prato reactions.[365,370] Gündüz et al also reported the preparation of glucose-BODIPY-fullerene dyads and the same related nano micelles in the presence of Tween 80.[371] These systems were tested in the K562 cell line, and sufficient ROS generation was reported, as well as absorption of the red spectrum.[371] Tokuyama et al published the first report on using fullerenes in cancer cells, namely in 1993. Fullerenes functionalized with carboxylic acid and white light were used.[372] Burlaka et al similarly used a mercury lamp to produce phototoxicity in cancer cells.[373] It is noted that cell death was mainly caused by membrane damage.[373,374]

To overcome the water insolubility of fullerenes, for instance, C60 can be coupled with PEG to form conjugate C60-PEG. It is also noted that such a complex performed better than Photofrin as a PDT agent.[367,375,376] It is also possible to introduce Tween 80 and PVP to enhance the solubility of the fullerenes.[377] Liu et al mentioned another complex; C60-PEG was mixed with diethylenetriaminepentaacetic acid and further introduced to gadolinium which then demonstrated the significant antitumor effect after light irradiation of the spectral range from 400 to 500 nm.[378]

Another way to prepare an efficient complex for PDT is to complex fullerenes with porphyrins. This kind of complex can be more efficient in terms of cell penetration and ROS generation. Milanesio et al compared the PDT effect of

porphyrin-C60 and its metal complex with Zn(II) to the pure porphyrin (5-(4-acetamidophenyl)-10,15,20-tris(4-methoxyphenyl)-porphyrin) in Hep-2 cell line and concluded that the porphyrin-C60 complex had the greatest impact on cells.[379]

Miki et al reported the preparation of amphiphilic γ-cyclodextrin-fullerene complexes and Sugikawa et al described ROS generation.[375,380] With such molecules, it is also possible to prepare hybrid complexes of C60 and hydrophobic porphyrin by mixing in water in the presence of PEG. The resulting C60-porphyrin NPs are negatively charged and can be dispersed in water.[375,381–383] As reported, the singlet oxygen generation ability of C60-porphyrin NPs under light radiation of 620 nm wavelength is improved compared to C60 NPs.[375]

Li et al also described the enhancement of Type I photoreactions using antennae-fullerene complexes and NIR irradiation.[384] Type I photoreactions are considered important as they have higher oxidizing ability than Type II, and they also lead to lesser oxygen dependency. Rare-earth UCNPs can act as antennae for various PDT agents, as well as fullerenes.[384]

Nanoribbons

Carbon nanoribbons and their application in the biomedical field and PDT fields are still to be investigated. A small number of research papers are available, but all of them show promising properties of carbon nanoribbon materials. There is evidence of using it in the field of PTT and other cancer research areas. Nanoribbons could be modified for use in cancer research with some already mentioned chemicals, such as polyethylene glycol and DOX for synergistic effects.[385,386] They were shown as an effective PTT agent under 808 nm NIR laser irradiation. This material was also tested by Lu et al in vitro on the U87 cell line and mice with no cytotoxicity.[386]

Recent Approaches, Future of PDT, and Conclusion

Nowadays, cancer resistance is one of the main challenges for cancer patients. Addressing this problem requires a multifaceted and complex approach, and graphene-based materials have the potential to provide a promising solution.

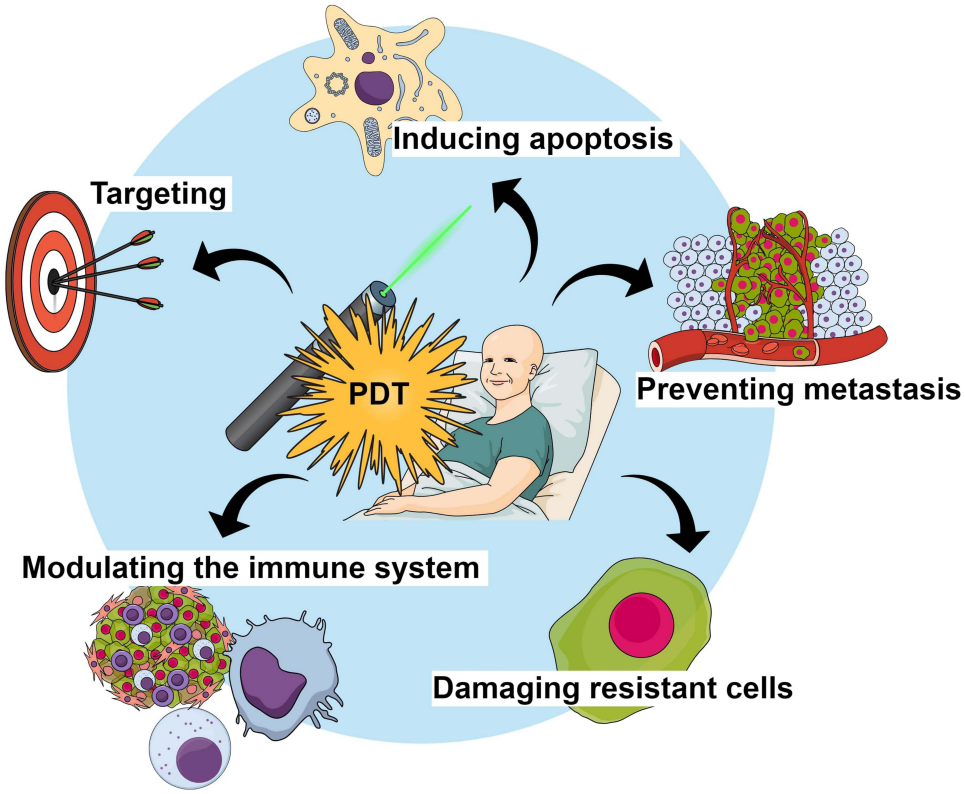

Figure 14 The modalities through which PDT can affect cancer resistance.

There are several methods through which these materials can be utilized to overcome cancer resistance, like targeted drug delivery bypassing resistance mechanisms, immunotherapy; graphene-based materials can be used to modulate the immune response, gene therapy with graphene materials as gene delivery vector, hyperthermia therapy as graphene materials have outstanding photothermal and photodynamic properties.

The PDT treatment method has a distinctive approach that functions through various modalities. These modalities include targeting specific cells, causing damage to resistant cells, inducing apoptosis, modulating the immune system, preventing metastasis and reducing resistance development (Figure 14).

One of the most exciting future aspects of PDT is its potential for multimodal therapy. This tactic combines PDT with other therapies such as PTT, immunotherapy, chemotherapy, and targeted therapy. Multimodal therapy can strengthen different treatment modalities to achieve better therapeutic outcomes.

For some researchers, it seems to be interesting and promising approach to combine PDT with traditional specific and non-specific immunotherapies.[387,388] This would include administration of antibodies and cytokines or targeting of immune checkpoints.[387,388] One of the most promising methods is a combination of PDT with programmed cell death protein 1 (PD-1) and its ligand, programmed death ligand 1 (PD-L1) immune checkpoint inhibitors. PD-1 is expressed by activated T cells, B cells, dendritic cells, and natural killer cells. On the other hand, PD-L1 is expressed in several types of tumor cells.[387–389] Nagaya et al demonstrated that NIR photoimmunotherapy induced tumor cell death aiming for cell-surface CD44 and PD-1 blockade in multiple tumor models.[390] This could be a target for the use of graphene materials and PDT. Wang et al reported a fabrication method of a PEGylated rGO hybridized with Fe_3O_4 nanoparticles for photothermal immunotherapy of cancer.[391] These modifications were possible through electrostatic interactions and showed PTT effectiveness under irradiation by an 805 nm laser.[391] Application of this nanocomplex resulted in PTT-induced ICD, release of danger-associated molecular patterns, and activation of dendritic cells (DCs) in lymph nodes under irradiation. Median survival time was also increased in 4T1 tumor-bearing animals after NIR irradiation. Wang et al also proposed that this novel nanosystem could be used for magnetic resonance imaging, which could potentially pave the way for MRI-guided photothermal immunotherapy for metastatic cancers.[391] Wu et al synthesized hybrid nanosystems containing polydopamine stabilized GQD-photosensitizer composites (GCpD), immunostimulatory poly-cationic polymer nanoparticles, and Gd3+/Cy3 imaging probes for both magnetic resonance and fluorescence imaging-guided photoimmunotherapy.[392] This material was denoted as PC@GCpD(Gd), was reported to act via photothermal and photodynamic effects mediated by GCpD, and was targetedly delivered to endosomal Toll-like receptor 9 (TLR9) to enhance the secretion of proinflammatory cytokines and the maturation of dendritic cells and to activate T lymphocytes. PC@GCpD(Gd) was also shown to successfully suppress the EMT6 murine mammary cancer model under laser irradiation.[392] Zhao et al also stated that clinically approved carbon nanoparticle suspension injection (CNSI) inhibits the growth of primary tumors, distal tumors, and metastasis via PTT and anti-PD-1.[393]

Other modalities like chemotherapy and targeted therapy can also complement PDT by targeting cancer cells that may be resistant to PDT alone. Zhou et al fabricated a nanosystem that was loaded with mitoxantrone and SB-431542, which is a specific inhibitor of transforming growth factor-beta, onto reduced graphene oxide (rGO).[394] The administration of this nanocomplex was followed by irradiation of a near-infrared laser and as a result, it destroyed local primary tumors and inhibited distant metastases in the 4T1 mouse tumor model, which is highly tumorigenic and invasive.[394] It was also clear that mitoxantrone, SB-431542, and rGO together induced an effective tumor vaccination by the increased infiltration of tumor-specific cytotoxic CD8+ T lymphocytes and decreased infiltration of regulatory T cells in distal tumors.[394] Sawy et al reported different types of carbon nanomaterials that were further employed as nanocarriers for DOX. GO with the highest surface negative charge exhibited the highest loading capacity and GQDs with the lowest surface negative charge showed the highest release effectiveness.[395]

The next step to further advance the use of PDT and graphene in PDT is to target cancer stem cells (CSCs). They are difficult to eradicate with conventional chemotherapy or radiation. The survival of residual CSCs can result in tumor recurrence, metastasis, and drug resistance. Fiorillo et al showed that GO hinders tumor-sphere formation in multiple cell lines such as breast cancer, ovarian cancer, and lung cancer as well as many others. GO inhibits key pathways such as Wnt signaling pathways, notch signaling and STAT signaling (Signal Transducer and Activator of Transcription) and thus inducing CSC differentiation.[396] Their research was focused specifically on the influence of GO on CSCs, which can

contribute to tumor recurrence, distant metastasis and drug resistance. GO was able to inhibit tumor growth of cancers such as breast, prostate, lung, ovarian, and pancreatic cancer, as well as glioblastoma (brain cancer).[396] The results obtained from the Fiorillo et al study also indicate that GO specifically targets a global phenotypic property of CSCs.[396] Prior research has also demonstrated the potential of GO in targeted cancer therapy, tumor growth prevention, and tumor cell migration inhibition.[91,397–399] It was also shown by Burke et al that carbon nanotube-mediated thermal treatment sensitizes breast CSCs and limits their long-term proliferative capacity.[400] Another research also suggested the possibility to target cancer cells with GQDs, especially GQDs that are combined with Cu^{2+}, Zn^{2+}, or Ni^{2+} ions as they are possible to target ABC transporters of multiple multidrug-resistant genes.[401,402] There is also the ability to target different organelles, such as mitochondria, selectively.[403]

Selective targeting of malignant cells is closely related to targeting, damaging resistant cells, and modulating immune response. PDT can also work through immunogenic cell death (ICD) by inducing damage-associated molecular patterns (DAMPs), although only a few PSs can trigger that. Yu et al noted that induced immune response after PDT application can be caused by damage to cancer cells. PDT activates dendritic cells, and as a result, CD8+ infiltration will increase in the tumor site. In addition, Yu's et al research reported that lung metastatic growth could significantly decrease after PDT treatment. It is also possible to enhance anti-metastasis response with the oxygen-boosted PDT via ICD and DAMPs release. Wang et al suggested to use nanoplatforms synthesized with polyethylene glycol altered $Cu_{2-x}Se$ nanoparticles, β-cyclodextrin, and chlorin e6 as Fenton-like-Haber–Weiss catalyst for this purpose.[404,405]

It is also possible for PDT to trigger more than one cell death type, and this could be a prominent strategy to overcome cancer resistance (Figure 15).[46,406–409] There are cell death types such as necroptosis, ferroptosis, pyroptosis, parthanatos, and mitotic catastrophe. Mishchenko et al suggested that there is an "ideal protocol" for PDT which should include different irradiation regimens and a combination of PSs for successful overcoming of cancer resistance.[410,411]

Mitotic catastrophe (MC) is one of the onco-suppressive mechanisms that hinder the proliferation of cells with excessive DNA damage that cannot complete mitosis and generally defective mitosis. Thus, in case of triggering this cell death form, cytoskeletal components will be the most sensitive organelles and a subject for PDT treatment.[410,411,413] Although some cancer cells are also reported to be able to bypass MC, some cancers will be more resistant and aggressive via aneuploidy and genomic instability as a result.[409]

Paraptosis is a different non-conventional cell death type that does not show chromatin condensation and cell fragmentation contrary to apoptosis.[410] This cell death type should mainly occur in the cells that exhibit diminished apoptosis and are unaffected by autophagy. In case of triggering paraptosis, the endoplasmic reticulum is a key aim as paraptosis is associated with misfolded proteins. Hypericin and Verteporfin are two PSs primarily located in the ER which, after PDT, have demonstrated the induction of paraptosis.[410,414–416] Decreasing the level of thiol-containing antioxidants can also facilitate the induction of paraptosis and its application in cancer therapy.[417]

Pyroptosis could be considered a double-edged sword as well, as on the one hand, it shows several ICD hallmarks, such as the production of DAMPs, but, on the other hand, it can provide an appropriate microenvironment for tumor development and metastasis.[410,418–422] During the pyroptosis formation of pyroptotic bubbles, activation of caspase-1 and production of the cytokines IL-1β and IL-18 are typically noticed. Zhu et al reported that curcumin-loaded poly (L-lactide-co-glycolide) could be effective against liver cancer under PDT conditions, as it enhances apoptosis and pyroptosis rates.[423,424] Pyruvate kinase M2 and ROS induced by chemotherapeutic drugs are also considered to be important players in PDT-induced pyroptotic cell death.[425,426]

There is limited evidence to support the occurrence of parthanatos during PDT, as Soriano's research provided the only available evidence thus far.[427] Parthanatos relies on the hyperactivation of the DNA damage response. It is, namely, dependent on the activation of Poly(ADP-ribose) polymerase (PARP1), which can happen after stimuli like ultraviolet irradiation and ROS generation.[410,411,428,429]

Necroptosis is one of the cell death modalities that resembles necrosis and includes swelling, rapid plasma membrane permeabilization and moderate chromatin condensation, although nuclear fragmentation and caspase activation are not present.[410,430,431]

Ferroptosis is one of the most important non-conventional cell death modalities associated with mitochondria shrinkage, mitochondrial cristae reduction or disappearance and outer mitochondrial membrane rupture. It relies on iron-

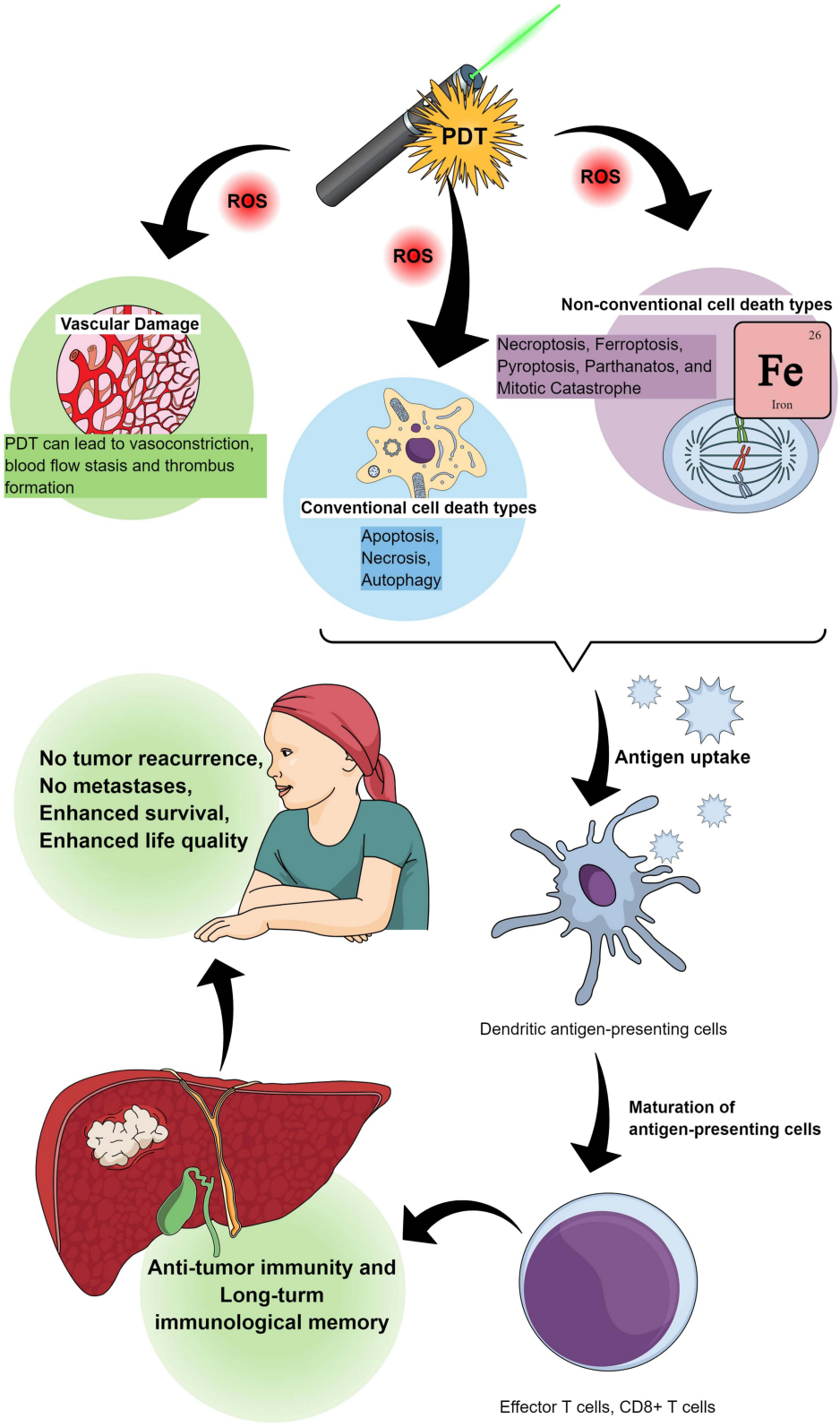

Figure 15 PDT effects on the cell, cell death types and immune boost scheme.[410,412]

dependent oxidative modification of phospholipid membranes.[410,432] It is a promising perspective for apoptosis and/or necroptosis-resistant tumors.[432,433] Shishido et al reported that 5-aminolevulinic acid can trigger ferroptosis through the regulation of glutathione peroxidase 4 (GPX4) and heme oxygenase 1 (HMOX1) and showed antitumor effects in esophageal squamous cell carcinoma cell lines. There are also inhibitors of ferroptosis reported: ferrostatin-1, liproxstatin-1, the iron chelator, deferoxamine, and some others.[410,434] Quantum Dots are reported to be effective in ferroptosis triggering. It could be triggered by disrupting calcium homeostasis in microglia or via mitochondrial oxidative stress in microglia, as reported by Wu et al, N-GQDs are described to activate two calcium channels in the hippocampus of mice that lead to ferroptosis. Also, N-GQDs application could cause ferroptosis in the BV2 cell line via accumulation in mitochondria resulting in mitochondrial iron overload and redox imbalance.[435,436]

Apoptosis itself can occur through different modalities after PDT application. Mitochondrial membrane damage permeability leads to cytochrome c release into the cytoplasm with caspase activation afterward.[437–440]

Increasing the cellular uptake of PSs is crucial to expand the scope and efficacy of PDT. Graphene-based nanocarriers have emerged as a promising solution to enhance the absorption of PSs, as it was already mentioned before. Although further research is needed, the use of graphene materials for delivering non-water soluble photoactive agents shows great potential. This approach can overcome the challenge of limited solubility of PSs in aqueous environments, making it possible to deliver them efficiently to targeted sites. Aguilar Cosme et al reported CQDs to improve protoporphyrin IX cellular uptake and solubility.[441] Klimenko et al also showed that graphene prevents the agglomeration of the aluminum phthalocyanine chloride (AlClPc).[442]

The application of graphene-based PDT holds promise in advancing personalized medicine methods. By using the unique properties of graphene nanomaterials, patient-specific treatment approaches can be developed to overcome specific resistance mechanisms. Functionalized graphene nanomaterials can be tailored to target genetic mutations and specific molecules associated with resistance, resulting in precise and effective delivery of treatment. This novel approach has the potential to revolutionize the field of medicine and pave the way for improved patient outcomes through individualized therapy.[443] One of the techniques for achieving personalized therapy is the utilization of biosensors that are based on graphene. These biosensors can be highly sensitive and specific in detecting various biomarkers. Graphene-based biosensors have potential in early disease detection, monitoring disease progression, and assessing treatment response. Biosensors that target patient-specific biomarkers can be designed and therefore will help healthcare workers in obtaining real-time information about an individual's health status. Graphene-based nanosystems can also be utilized for genomic analysis and genetic testing. Graphene biosensors and sequencing platforms can detect DNA mutations, gene expression patterns, and epigenetic modifications. Thus, disease risk, prognosis, and treatment response can be assessed. By integrating genomic information with clinical data, medical interventions can be customized to minimize adverse effects.[444–446]

Zhang et al proposed a disposable nano-biosensor for glucose monitoring using saliva. The working electrode in this biosensor was functionalized with SWNT and layers of chitosan, gold nanoparticles and glucose oxidase. It also demonstrates excellent clinical accuracy.[447] Li et al also reported highly sensitive biosensor for the detection of microRNA and adenosine based on graphene oxide-gold nanoparticles (AuNPs) composites.[448] GO-AuNPs composite worked as both a sensing substrate and signal amplification element. The developer surface plasmon resonance biosensor successfully detected miRNA-141 in cancer cell extractions.[448] Khalil et al reported a surface-enhanced Raman scattering platform with a short DNA probe for DNA biosensing. It was based on the abovementioned GO-AuNPs.[449] As to CQDs and GQDs, one of the most important biosensing mechanisms are fluorescent interactions.[450] Kong et al showed that N-doped CQDs can act as α-glucosidase inhibitors based on the inner filter effect of N-doped CQDs, when CQDs absorb both the excitation light and the emitted fluorescence light, leading to a reduction in the measured fluorescence intensity.[451]

Graphene-based materials can also act as contrast agents to enhance the sensitivity and resolution of magnetic resonance imaging (MRI) or computed tomography (CT).[443,452,453] Zhang et al fabricated PEGylated ultrasmall GO with a chelating agent DOTA and gadolinium(III) to form GO-DOTA-Gd complexes, which showed improved T1 relaxivity.[453] Antoine et al reported that that GQDs are able to decrease the intensity of X-rays and form contrast images in both X-ray and computed tomography.[454]

Graphene-based materials also have the potential to enable real-time monitoring of treatment response and resistance development. By incorporating imaging agents or biosensors into graphene nanomaterials, it becomes possible to non-invasively observe tumor dynamics. This allows for timely adjustments to treatment strategies based on feedback, which can help improve the effectiveness of PDT or other treatment modalities. Zhang et al reviewed graphene and its derivatives as prominent materials for wearable sensors aimed at monitoring biophysical signals for healthcare applications.[455] Maity et al fabricated sensors that were able to execute a real-time detection of heavy-metal ions and E. coli bacteria in flowing tap water.[456] This calls for extended research and application in humans.

In conclusion, applying graphene materials in PDT holds massive potential in transforming and revolutionizing cancer treatment strategies. With their unique properties, such as high surface area, excellent conductivity and biocompatibility, graphene-based PSs have the potential to enhance PDT efficiency. Additionally, graphene-based nanomaterials present a promising potential to overcome multidrug resistance, which is a significant challenge in cancer therapy.

The synergy between graphene materials and PDT not only upgrades and optimizes the targeting and destruction of cancer cells but also improves the immune response against tumors. By triggering immunogenic cell death and changing and modulating the TME, graphene-based PDT strategies again contribute to overcoming cancer resistance mechanisms, pioneering the way for more efficient and personalized cancer treatments.

As the study of cancer biology develops and advances in huge steps, the utilization of graphene materials in PDT serves to broaden our understanding of this complex field and gives us a promising solution for patients in their fight against cancer.

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Disclosure

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