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Mutual influence of malignant cells and cellular microenvironment: prospects for manipulating tumour microenvironment with nanomaterials

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Summary

Development and progression of neoplasia occurs in parallel with changes in the surrounding stroma. Cancer cells may functionally reshape their microenvironment by secreting various cytokines, chemokines and generation of acidic medium. These factors contribute to differentiation of immune cells into immunosuppressive phenotype, stimulate the synthesis of a number of amino acid metabolism enzymes, growth factors, adhesion molecules, which promote invasion, angiogenesis and metastasis, and also reduce efficiency of anticancer drugs and radiation therapy. To increase effectiveness of the chemotherapy, multitargeted carbon nanomaterials may be applied. In particular, nanomaterials based on modified graphene make it possible to create multicomponent therapeutic constructs, including macromolecules, polymers, and effector agents. Initial experiments with unmodified graphenes demonstrated their toxicity associated with their accumulation in parenchymal organs and initiation of inflammatory processes. In the past few years, a series of works has been published in which the possibility of reducing the toxicity of graphene oxide through functionalisation has been demonstrated. This review summarises the experimental data on the creation of covalent and non-covalent conjugates based on graphene oxide and demonstrates their *in vitro* efficacy on various tumour cell lines. Separately, there are few data on the effect of nanomaterials based on graphene oxide on the tumour microenvironment.

Keywords

Tumour, microenvironment, progression, cytokines, acidosis, immune system, carbon nanomaterials.

Introduction

During the development of malignant neoplasia, a specific cellular environment is formed in the chronic inflammation site termed "inflammatory microenvironment of the tumour" (TME). This cell community consists of tumour-associated macrophages (MF), dendritic cells (DC), myeloid suppressor cells (MSC), neutrophils (NF), mast cells, natural killer cells (NK), T- and B-lymphocytes, cancer-associated fibroblasts (CAF) and endothelial cells. The interaction between tumour cells, myeloid cells and lymphocytes is a dynamic, bidirectional process and includes intercellular contacts, constant exchange of secreted soluble molecules, factors, vesicles, due to which an autonomous system is established that regulates tumour growth [1-5].

Neoplastic progression is associated with lack of oxygen, deficiency of nutrients causing hypoxia and development of metabolic acidosis in the tumour microenvironment. These factors promote selection of tumour cells with the gene mutations that allow them to survive under more severe microenvironmental conditions. Such adaptation of tumour cells is accompanied by increased production of various growth factors, cytokines, chemokines, which together present a triggering factor for enhancement of angiogenesis, metastases, and inhibition of local immune response. In turn, the normal TME cells also begin to secrete factors promoting tumour progression. As a result, a closed-circuit regulatory system is formed [6]. E.g., the content of IL-4 increases in TME, thus inducing differentiation of macrophages to the second-type (M2) resident cells. The M2 subpopulation may account for up to 50 % of the tumour mass and contribute to activation of pro-tumourigenic processes accompanied by the synthesis of IL-1, IL-1RA, IL-4, IL-6, IL-10, IL-12, L-arginine, prostaglandin E2, TNF-α, TGF-β, VEGF-A, and a variety of chemokines and their receptors CCL1, CCL5, CCL17, CCL22, CCL24, CCR2, CXCL10, CXCL16 [7-9]. These mediators are involved in angiogenesis, immunosuppression, and metastasis.

In tumour cells, increased production of some amino acid metabolism enzymes is revealed, e.g., of indolamine 2,3-dioxygenase, arginase-1. Activation of iNOS, as well as STAT3 transcription factor is noted, thereby initiating the differentiation of dendritic cells into tolerogenic tumour-associated dendritic cells (TADC) [10]. These cells produce TGF-β which promotes immunosuppression by stimulating Th2, Th17 and T regulatory cells [11].

Of interest, differentiation of neutrophils in the TME structures depends on the stage of the disease. Thus, the normally pro-inflammatory neutrophils differentiate at later phase to an immunosuppressive phenotype under the influence of TGF-β and angiotensin II [12]. The tumour-associated neutrophils synthesise collagenase IV, heparanase, elastase and matrix metalloproteinases (MMPs) which contribute to extracellular matrix degradation, tumour cell invasion and metastasis. The secreted proteinases destroy extracellular matrix, and degrade the pro-inflammatory cytokines, thus causing anti-inflammatory effects [13]. Neutrophils also produce oncostatin M, which enhances angiogenesis, as well as CXCL1, CXCL8, CCL-3, CXCL6, TGF-β, and prostaglandin E2 synthesis, thus supporting the neoplastic progression [14].

The CSF-1, HIF-1α, CCL2, CCL7, CXCL1 peptide factors synthesised by the TME cell populations are able to alter the metabolism of myeloid cells, leading to transition to MSC [15]. MSC enhance the synthesis of reactive oxygen species, arginase-1, prostaglandin E2, IL-4, IL-6, inhibit the function of T-lymphocytes [16], support the stemness of tumour cells [17], increase angiogenesis and metastasis [18]. It should be noted that MSC create background for spreading the tumour not only locally, but also to the target organ, inducing expression of adhesion molecules on the surface of endotheliocytes, e.g., E-selectin, intercellular adhesion molecules 1 (ICAM-1), and vascular cell adhesion molecules 1 (VCAM-1), promoting residence of tumour cells in the target organ [19].

M2 macrophages and MSCs are the main producers of IL-1β, which initiates a whole spectrum of procarcinogenic effects [20–23]. IL-1β provides both direct and indirect effects upon angiogenesis, by inducing the synthesis of various cytokines and angiogenesis factors [24]. Direct effects of IL-1β include activation of FGF-β expression in endothelial cells [24], VEGF-A and its receptors [25], regulation of endothelial progenitor cells, thus contributing to neovascularisation [25]. IL-1β also affects Bv8, CCL2, and CCL3 secretion, leading to (*i*) enhanced synthesis of VEGF-A, PLGF, bFGF by endothelial cells, (*ii*) VEGF-A secretion by myeloid cells (CD34+ or Flk-1+) [26], (*iii*) FGF1 secretion by mononuclear cells [27], (iv) IL-8 secretion by macrophages [28]. In general, IL-1β may affect cell differentiation, causing synthesis of either pro-inflammatory, or angiogenetic factors [28]. Immunosuppressive effect of IL-1β proceeds via stimulated synthesis of anti-inflammatory factors (IL-10, TGF-β, arginase-1) by tumour-associated macrophages and MSCs. This effect results into suppression of T cell and M1 activities [28], and the non-canonical signalling pathway of the NF-κB transcription factor is triggered, thus, in turn, suppressing antitumour immunity of T-regulatory cells [29]. The effect of IL-1β was shown to be associated with PD-L1 overexpression, an additional factor of immunity inhibition [29].

The role of immune cells in TME may be either to suppress tumour growth (antitumour TME), or to promote tumour growth (immunosuppressive TME). Thus, depending on the TME factors and type of malignancy, the immune cells may exert pro- or antitumour effects (Fig. 1) [30].

Cancer-associated fibroblasts (CAF) synthesise factor(s) inducing differentiation of macrophages to M2 and depletion of CD8+ T cells, which also stimulates proliferation, invasion and metastasis of tumour cells [31]. Along with cytokine production, tumour cells may activate pro-tumourigenic processes, due to metabolic acidosis in the extracellular matrix. E.g., acidification of extracellular matrix triggers p53-dependent apoptosis of surrounding cells and degradation of the basement membrane [32], along with increased secretion of cathepsin B, metalloproteinases, urokinase plasminogen activator, hydrolysing components of the extracellular matrix [33]. Also, acidification of extracellular matrix alters the lysosomal distribution, thus further enhancing secretion of proteinases causing destruction of extracellular matrix [34] and disruption of intercellular adhesion contacts by degradation of E-cadherin [35].

Several studies suggest acidosis to be a factor of immune therapy efficiency, as shown in murine models of melanoma and pancreatic adenocarcinoma, where the increased TME acidity correlated with inhibited antitumour T cell-mediated immunity, associated with lower efficacy of immune drugs [36, 37].

Increased acidity of TME leads to decreased efficiency of anticancer drugs, due to decreased transfer of drugs into the cells. For example, anthracyclines (doxorubicin), anthraquinones and alkaloids are weak bases and require optimal pH range (7.5-9.5) for their transmembrane transport [38-40]. Under these conditions, activity of a well-known glycoprotein transporter (pGP) is enhanced, thus promoting efflux of anticancer drugs from malignant cells. This effect was

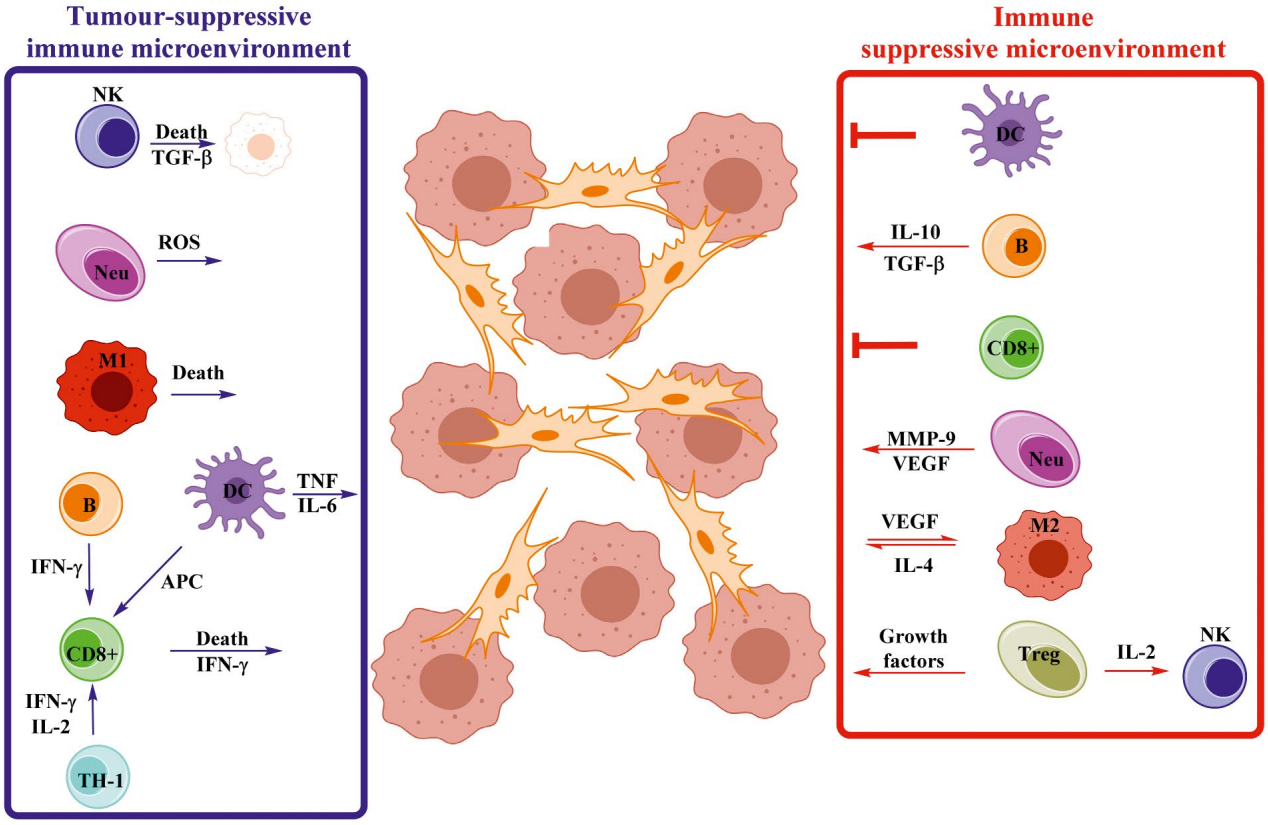

Figure 1. Influence of various immune cell populations upon TME

Abbreviations: *NK, natural killers; Neu, neutrophils; MI, type I macrophages; DC, dendritic cells.*

observed in tumour cells adapted for low extracellular pH, with acquired TP53 gene mutations [41–43]. These adaptive processes cause multidrug resistance and limit the choice of therapeutic options.

Hence, malignant cells may stimulate differentiation of tumour-associated immune cells to immunosuppressive phenotypes by synthesising a wide range of signalling molecules. In turn, these immune cells produce anti-inflammatory factors, growth factors, proteinases, enhance expression of adhesion molecules, causing invasion and metastasis of tumours, activation of angiogenesis. TME acidification is not only a factor leading to selection of the most resistant and aggressive tumour phenotypes, but it also induces destruction of intercellular contacts and extracellular matrix, which ultimately triggers the processes of invasion and metastasis.

Mutual influence of tumour cells and normal TME populations promotes development of cell associations, and their extracellular milieu protects from external impacts, e.g., anticancer therapy, immune surveillance. Even a small number of tumour cells forms a microenvironment resistant to antitumour therapy, especially if they are represented by stem or 'dormant' cells. Hence, a prevalence of the distinct component of the cellular microenvironment presumes differentiated approach to treatment. The strategic purpose in oncology is to transform cancer into a long-term chronic disease which is well controlled by the low-toxicity approaches. To implement this task, three areas of research could be highlighted: (*i*) a search for specific key target molecules, in order to create targeted drugs; (*ii*) personalisation of treatment programs based on molecular and cellular characteristics of the tumour, and individual clinical prognosis; (*iii*) use of nanomaterials when creating novel drugs, thus providing higher efficiency of treatment. The latter approach may increase concentrations of active substances in the tumour foci and reduce the drug toxicity. Long-term studies provide convincing evidence that carcinogenesis is a multistage multicomponent process, including disturbances of apoptosis, proliferation, angiogenesis and cell metabolism leading to the formation of altered pathological microenvironment.

Multimodality of carcinogenesis requires usage of combined treatment methods aimed at different molecular targets. In the past ten years, a series of nanomaterials has been developed in various laboratories around the world that have great potential for therapeutic use in oncology, e.g., liposomes, polymer carriers, carbon nanoparticles, iron oxide and gold nanoparticles. Currently, there is a technical opportunity of creating structures that would deliver active substances to the target cells and undergo biodegradation. However, the mentioned nanocarriers have a number of disadvantages. Liposomes, polymers, dendrimers can provide a significant decrease in overall toxicity of cytotoxic drugs, but they have a low potential in terms of targeted delivery. Carbon nanomaterials make it possible to create multicomponent and multitarget therapeutic constructs. Graphene and its derivatives are considered the most promising carbon nanomaterials for these purposes.

Current experience with graphene carriers

Initial experiments with unmodified graphene demonstrated its systemic toxicity [44,45] associated with accumulation in lungs [46], reticuloendothelial system including liver and spleen [47, 48] and provoking an inflammatory response [49]. Recent studies have shown that modified graphene oxide is promising for manipulating the tumour microenvironment; however, an analysis of the literature suggests that research in this area has just begun. For example, the use of graphene oxide functionalised with polyethylene glycol (GO-PEG) in photodynamic therapy led to a decrease in the interleukin-4-dependent polarisation of M2 in macrophages of the tumour microenvironment. The antitumour action of GO-PEG was to reduce the migration and invasion of subcutaneous osteosarcoma cells in mice [50]. In [51], the combined effect of low-frequency ultrasound therapy and graphene oxide-doxorubicin (GO-DOX) conjugate on local damage to endothelial cells lining the neovascular network was shown. This effect increased the penetration of the GO-DOX conjugate into the interstitial space of mouse liver carcinoma through damaged capillaries. Over past few years, a series of works was published at the Department of General and Bioorganic Chemistry (Pavlov University, St. Petersburg) which demonstrated an opportunity of reducing toxicity to acceptable level, due to functionalisation of the graphene carrier [52-54]. Moreover, the graphene-based nanomaterials (GBN) have been shown to have a number of advantages: stimulation of immune response, inhibition of tumour stem cells, regulation of angiogenesis and hypoxia [55]. In particular, it should be noted that the GBNs exhibit photodynamic and photothermal activity, and can be effectively used as nanoplatforms for targeted delivery of cytostatic drugs.

Graphene is known to consist of sp^2-hybridised carbon atoms forming two-dimensional nanolayers, while graphene oxide (GO) contains various oxygen-containing oxygen functional groups: (*i*) carboxyl, carbonyl, and lactol, located at the edges of GO layers; (*ii*) epoxy and hydroxyl groups distributed on the surface of the GO plane [56-61] (Fig. 2). Reduced GO (rGO) is a variant of GO in which most of the oxygen-containing functional groups are reduced by means of hydrazine hydrate or biomolecules [54, 62].

A graphene monolayer was obtained in 2004 by A. Geim and K. Novoselov [63], while GO was first synthesised in 1859 by B. Brodie by oxidising graphite using a mixture of oxidising agents (potassium chlorate and fuming nitric acid) [64]. However, the most effective method was developed by W. Hammers and R. Offeman in 1957, with a mixture of sulphuric acid, sodium nitrate and potassium permanganate [65]. GO functionalisation can be carried out using various reactions (Fig. 3): amidation, esterification, 1,3-dipolar cycloaddition, halogenation, as well as through non-covalent functionalisation through the formation of hydrogen bonds, π-π stacking and hydrophobic interactions. These reactions make it possible to obtain unique nanomaterials having a medical potential in cancer treatment [66], delivery of drugs and biomolecules [67, 68], development of biosensors [69], as well as substances with antiviral [70], antibacterial [71]

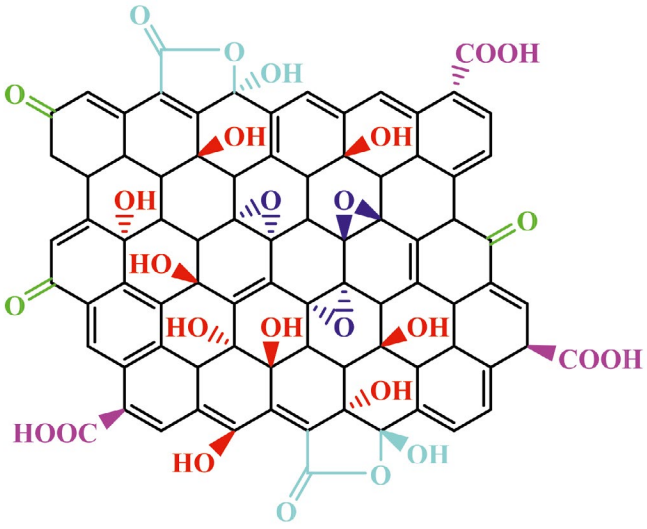

Figure 2. General structure of graphene oxide

and antifungal activity [72]. Among GBN, GO has the greatest potential for use in medicine for the following reasons: (*i*) GO contains various functional groups that allow further surface functionalisation; (*ii*) functionalisation of GO increases its biocompatibility; (*iii*) the presence of oxygen-containing functional groups ensures stability of aqueous GO dispersions.

Analysis of the literature revealed a number of research works devoted to synthesis and biological activity of GBN-based conjugates. Zhang *et al.* [73] reported that covalent GO functionalisation with sulphonic acid and folic acid (GO-SO_3H-FA) groups increased the specific cytotoxicity for MCF-7 cells (breast cancer-derived strain). Conjugation of doxorubicin (DOX) and camptothecin (CPT) with GO through its non-covalent functionalisation (due to π-π stacking and hydrophobic interactions) significantly increases therapeutic efficacy as compared to individual drugs. The CPT and DOX loading in the mixed GO-SO_3H-FA-CPT-DOX conjugate was 4.5% and 400%, respectively.

Wang *et al.* [67] demonstrated that covalent functionalisation of GO with chlorotoxin (CTX) increases the efficiency of drug delivery to C6 glioma cells. At the same time, non-covalent DOX attachment with a loading of 570 mg DOX per gram of CTX-GO significantly increases efficiency of the conjugate (the release of the cytostatic drug was pH-dependent). Fan *et al.* [74] synthesised a covalent GO-based conjugate with adipic acid dihydrazide and sodium alginate (SA). Then, DOX·HCl was attached non-covalently to GO-SA. The maximum DOX loading was 1.8 mg *per* 1 mg GO-SA. The highest drug release rate was observed at pH 5.0. Cytotoxicity testing with HeLa (cervical carcinoma) cell line showed that the GO-SA conjugate is not cytotoxic, while GO-SA/DOX exhibits cytotoxicity due to the specific effect on CD44 receptors.

Qin *et al.* [75] synthesised GO non-covalently conjugated with polyvinylpyrrolidone (PVP, M=30 kDa), and then folic acid (FA) was covalently attached through the formation of an amide bond (carboxyl groups of GO and amino groups of FA). Next, the authors performed non-covalent DOX loading (due to π-π stacking and hydrophobic interactions).

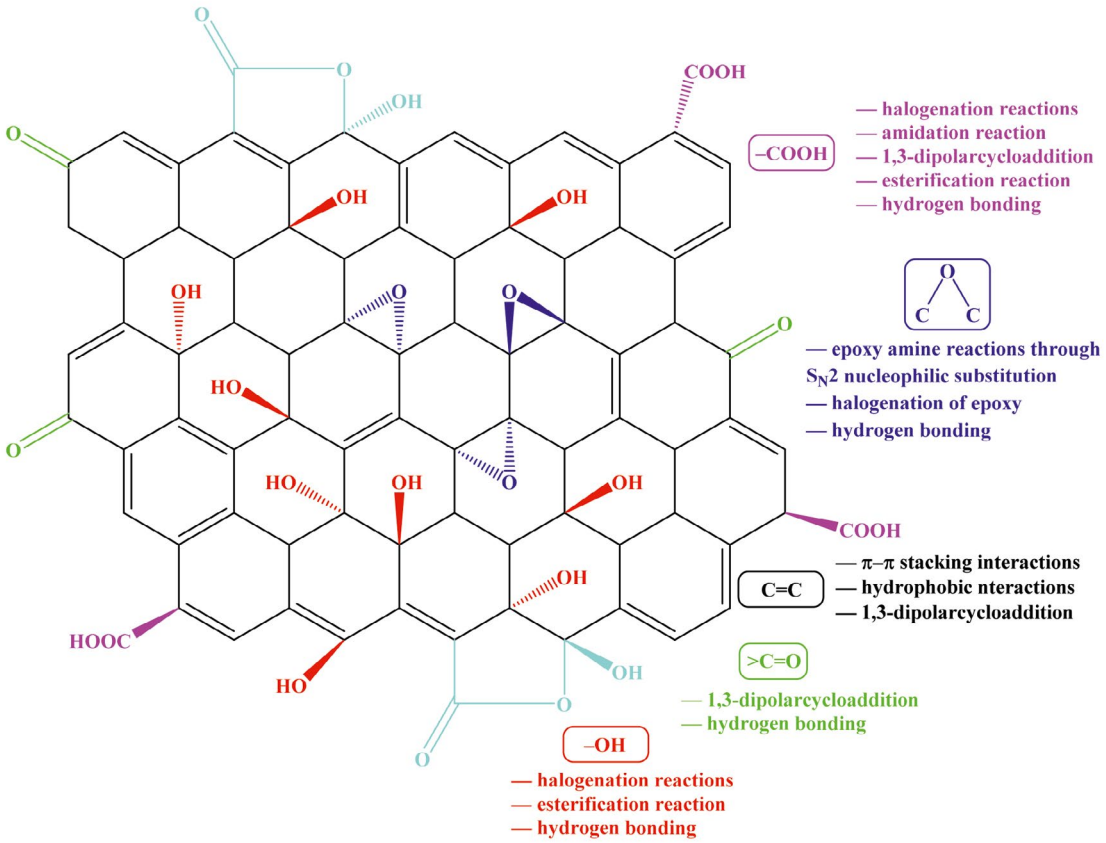

Figure 3. Basic ways to functionalise graphene oxide

The calculated value of the DOX loading on the FA-GO-PVP was 107.5 wt. %. The resulting conjugate demonstrated high antitumour efficacy against HeLa cells. Huang *et al.* [76] described the ability of FA-functionalised GO to efficiently bind the chlorine e_6 photosensitiser for photodynamic therapy. Tiwari *et al.* [77] used the GO-PVP noncovalent conjugate for double noncovalent addition of quercetin (QS) and gefitinib (GF) and compared it with the GO-PVP-QS and GO-PVP-GF conjugates. The authors found that the combined loading of the drugs showed higher cytotoxicity against PA-1 (ovarian cancer) cell line compared to individual drugs. The amount of QS and GF in GO-PVP-QS-GF was 20% and 46%, respectively.

Deb *et al.* [78] functionalised GO with polyethylene glycol (PEG), FA, and CPT via non-covalent π-π stacking interactions (CPT loading was 45%). The resulting conjugate (*C*=100 μg·ml^{-1}) caused the death of 76% of cells compared with the control when using the MCF-7 cell line [78]. The same group functionalised GO with the natural polymer chitosan (CS) and FA, to deliver CPT and 3,3'-diindolylmethane (DIM). The resulting conjugate (GO-CS-FA-CPT-DIM) demonstrated high cytotoxicity against the MCF-7 cell line (95.7% decrease in cell viability), which was significantly higher compared to individual DIM preparations (42.4%) and CPT (52.6%) [79]. Pei *et al.* [80] showed that simultaneous functionalisation of the GO surface with PEG (pGO) (pGO-CP-DOX, mass ratio: 1: 0.376: 0.376) with cisplatin (CP) and DOX leads to increased cytotoxicity towards Cal-27 (human squamous carcinoma) and MCF-7 cell lines. The authors observed higher inhibition of cell proliferation for the pGO-CP-DOX conjugate compared to individual preparations: IC_{50} (MCF-7)=14.5 μg·ml^{-1} for pGO-CP-DOX, 22.5 μg·ml^{-1} for pGO-DOX, and 22 μg·ml^{-1} for pGO-CP [80]. Bullo *et al.* [81] demonstrated the ability of GO functionalisation using PEG, FA, and anticancer drugs: protocatechuic acid (23.5% PCA) and chlorogenic acid (18.3% CA). The authors investigated the effect of the GO-PEG-FA-PCA-CA conjugate on the HT29 (colon cancer) and HepG2 (liver cancer) cell lines. Cytotoxicity trials showed the following results: IC_{50} (HT29)=50.7 μg·ml^{-1}, IC_{50} (HepG2)=40.4 μg·ml^{-1} [81]. Gong *et al.* [82] demonstrated that fluorinated graphene (FG) can be used to load a mixture of DOX and CPT after CS covalent functionalisation; DOX and CPT loading were 110% and 25%, respectively. The resulting FG-CS-DOX-CPT conjugate demonstrated a 60% and 75% decrease in the viability of HeLa cells with simultaneous laser irradiation (wavelength 808 nm) [82]. Gong *et al.* [83] evaluated the ability of non-covalent FG conjugation with a cytostatic DOX loading as high as 200%. The FG-DOX conjugate at 30 μg·ml^{-1} drug content reduced HeLa cell line viability to 94% after 48 h of incubation [83].

In an *in vivo* study, Shim *et al.* [84] showed that rGO functionalised with low-molecular weight heparin (LHT7) acts as a targeted drug for the delivery of DOX. The rGO-LHT7-DOX conjugate with rGO: DOX mass ratios of 2, 1, 0.5, 0.1 demonstrated a high antitumour effect at the KB human carcinoma cell line (cell viability was decreased by 61.1%), along with significant decrease in tumour size by (92.5±3.1)% [84]. Table 1 shows the results of studying cytotoxic conjugates based on GBN and cytostatic drugs.

Table 1. Cytotoxicity of GBN and non-covalently linked cytostatic drugs

GBN type	Cytostatic loading	Cell lines or type of cancer	Applied method	Conjugate concentrations and IC_{50} or cytotoxic effect (%) compared to control at highest concentration	Reference
GO-sulphonic acid groups-folic acid (GO-SO_3H-FA); GO-FA	Dual drug loading: camptothecin (CPT) (4.5%) and DOX (400%).	MCF-7 (human breast adenocarcinoma)	WST-8	C = 2 and 20 μg·ml^{-1} for (GO-SO_3H-DOX-FA), cytotoxicity = 20% and for GO-FA-DOX (% cytotoxicity = 67%) C = 0.002, 0.02 and 0.2 μg·ml^{-1} for (GO-FA-DOX-CPT) of % cytotoxicity = 22% and (GO-FA-CPT) % cytotoxicity = 26%	[73]
GO-chlorotoxin (GO-CTX)	DOX loading is 570 mg *per* g GO-CTX	C6 (glioma cells)	CCK-8	C = 1–5 μg·ml^{-1} % of cytotoxicity = 60%	[67]
GO-sodium alginate (GO-SA)	DOX loading is 1.8 mg *per* mg GO-SA	HeLa cells	MTT	C = 5–20 μg·ml^{-1} % of cytotoxicity = 69%	[74]
GO nanoparticles sized 50 × 50 nm^2	Cisplatin (CP) loading not determined	A549 (lung adenocarcinoma)	WST-8	C = 2.5–30 μg·ml^{-1} % of cytotoxicity = 90%	[85]
GO-polyethylene glycol-folic acid (GO-PEG-FA)	Camptothecin (CPT) loading is 45%	MCF-7	MTT	C = 20–100 μg·ml^{-1} % of cytotoxicity = 76%	[78]
GO-Fe_3O_4-β-cyclodextrin	DOX loading is 37.4%; MTX loading is 23.4%	K562 (leukaemia)	MTT	C = 2–16 μg·ml^{-1} % of cytotoxicity (DOX) = 65% % of cytotoxicity (MTX) = 55%	[86]
GO-PEG-FA	Loading of protocatechuic acid (PCA) is 23.47% and chlorogenic acid (CA) loading is 18.33%	HT29 (colon cancer), HepG2 (hepatocellular carcinoma)	MTT	C = 1.56–100 μg·ml^{-1} % of cytotoxicity (HT29) = 58% IC_{50} (HT29) = 50.69 μg·ml^{-1}; % of cytotoxicity (HepG2) = 61% IC_{50} (HepG2) = 40.39 μg·ml^{-1}	[81]
GO-FA-bovine serum albumin (GO-FA-BSA)	DOX loading is 437.43 μg *per* 1 mg GO-FA-BSA	MCF-7 (FA-receptor-positive) A549 (FA-receptor-negative)	MTT	C = 0.01–20 μg·ml^{-1} IC_{50} (MCF-7, 24 h) = 8.9 ± 0.7 μg·ml^{-1} IC_{50} (MCF-7, 48 h) = 0.048 ± 0.010 μg·ml^{-1} (% of cytotoxicity = 83%) IC_{50} (A549, 24 h) = 5.3 ± 0.7 μg·ml^{-1} IC_{50} (A549, 48 h) = 0.279 ± 0.037 μg·ml^{-1} (% of cytotoxicity = 78%)	[87]
FA-GO-PVP (folic acid-GO-polyvinyl pyrrolidone, M = 30 kDa)	DOX loading is 107.5%	HeLa cells	MTT	2 μg·ml^{-1}; 20 μg·ml^{-1} (% of cytotoxicity = 71%)	[75]
Fluorinated GO (FGO)	DOX loading is ~200%	HeLa cells	MTT	C = 1.11–30 μg·ml^{-1} (% of cytotoxicity (24 h) = 70%) (% of cytotoxicity (48 h) = 94%)	[83]
Pegylated folate and peptide-modified GO (PEG-FA-Pep-GO)	CPT loading is 90%	HeLa cells	MTT	IC_{50} = 3.1 μM	[88]
Graphene quantum dots-carboxymethylcellulose hydrogel (GQD-CMC)	DOX loading depends on GQD GQD (10%)-CMC ~4.5%; GQD (20%)-CMC ~5.5%; GQD (30%)-CMC ~6%	K562	MTT	C = 2–32 μg·ml^{-1}. IC_{50} = 5.1 μg·ml^{-1} (% of cytotoxicity = 93%)	[89]
GO-PVP and GO-β-cyclodextrin (CD)	Antineoplastic drug SN-38 (7-ethyl-10-hydroxy-camptothecin). Loading: in 1 g GO-PVP is 0.17 g SN-38; in 1 g GO-β-CD is 0.14 g SN-38	MCF-7	MTT	C = 5 and 10 μg·ml^{-1}. IC_{50} (GO-PVP-SN-38) = 97 μM; (% of cytotoxicity = 68%). IC_{50} (GO-β-CD–SN-38) = 170 μM; (% of cytotoxicity = 65%)	[90]

Conclusion

Current data provide sufficient results concerning molecular and cellular events providing mutual influence of tumour cells and TME cells, as well as factors of cancer progression. It has been shown that the tumour cells *per se* and their cellular TME create an integrated system that promotes tumour progression and development of multiple drug resistance.

Thus, the following requirements must be met for modern therapeutic agents: targeted action, polyfunctionality with respect to ability of loading various molecules on the GBN surface, low toxicity, opportunity of selective inactivation of immunosuppressive components in the TME. The last issue deserves special attention. The chance to resolve this complex problem is shown by the example of GBN usage.

List of abbreviations

IL – interleukin
TNF-α – tumour necrosis factor alpha
TGF-β1 – transforming growth factor receptor-β1
VEGF-A – vascular endothelial growth factor A
CAF – cancer-associated fibroblasts
CCL – C-C motif ligand
CCR2 – C-C chemokine receptor type 2
CPT – camptothecin
CSF-1 – the colony stimulating factor 1
CTX – chlorotoxin
CXCL – the chemokine (C-X-C motif) ligand
DOX – doxorubicin
FA – folic acid
GBN – graphene-based nanomaterials
GO – graphene oxide
iNOS – Inducible nitric oxide synthase
bFGF – basic fibroblast growth factor
FGF1 – fibroblast growth factor 1
HIF-1α – hypoxia inducible factor 1 subunit alpha
PD-L1 – ligand of programmed death-1 receptor
PLGF – placental growth factor
STAT3 – signal transducer and activator of transcription 3
Th – T helper cells
TME – tumour microenvironment

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Conflict of interests

The authors declared no potential conflict of interest.

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Взаимное влияние опухолевых клеток и клеток микроокружения опухоли. Перспективы манипулирования опухолевым микроокружением с помощью наноматериалов

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Резюме

Развитие и прогрессирование неоплазий происходит одновременно с изменениями окружающей стромы. Раковые клетки могут функционально формировать свое микроокружение за счет секреции различных цитокинов, хемокинов и формирования кислой среды. Данные факторы способствуют дифференциации иммунных клеток по иммуносупрессивному фенотипу, стимулируют синтез ряда ферментов обмена аминокислот, факторов роста, молекул адгезии, что промотирует инвазию, ангиогенез и метастазирование, а также снижает эффективность действия противоопухолевых препаратов и лучевой терапии. Для повышения эффективности химиотерапии возможно использование мультитаргетных углеродных наноматериалов. В частности, наноматериалы на основе модифицированного графена позволяют создавать многокомпонентные терапевтические конструкции, включающие макромолекулы, полимеры и эффекторные агенты. Первоначальные эксперименты с немодифицированными графенами продемонстрировали их токсичность, связанную с их накоплением в паренхиматозных органах и инициированием воспалительных процессов. В последние несколько лет вышла серия работ, в которых продемонстрирована возможность снижения токсичности оксида графена за счет функционализации. В данном обзоре обобщены экспериментальные данные по созданию ковалентных и нековалентных конъюгатов на основе оксида графена и показана их эффективность *in vitro* на различных опухолевых клеточных линиях. Отдельно представлены немногочисленные данные по влиянию наноматериалов на основе оксида графена на опухолевое микроокружение.

Ключевые слова

Опухоль, микроокружение, прогрессирование, цитокины, ацидоз, иммунная система, углеродные наноматериалы.