BioSCIENCE Review Article
DOI: https://doi.org/10.55684/2025.83.e00018

Nanotechnology for glioblastoma combat: a systematic review

Nanotecnologia para combate ao glioblastoma: uma revisão sistemática

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ABSTRACT

Introduction: Glioblastoma is the most common malignant cancer of the central nervous system and has a gloomy prognosis. Usually, the median overall survival is 15 months with treatments, such as surgical resection, radiotherapy and chemotherapy with temozolomide. However, the main reasons for the lack of improvement in patient survival are the low drug delivery at the tumor site and inadequate tumor sensitivity. In this regard, nanoparticles are being considered as a novel approach. They are small (1-100 nm), but have a large surface area, which increases the solubility and bioavailability of drugs by favoring diffusion through the blood-brain barrier, enhancing the solubility of hydrophobic drugs and ensuring a homogeneous distribution in the tumor.

Objective: To evaluate whether nanotechnology could improve the prognosis of specimens and patients with glioblastoma.

Method: Integrative review of the literature according to the PRISMA protocol, focusing on articles published in the last 10 years.

Result: Twenty-seven pre-clinical articles were included. Discussion: Iron and ferritin nanoparticles, iron oxide nanoparticles, superparamagnetic iron oxide nanoparticles, magnetite nanoparticles, and others were found. Nanoparticles have demonstrated their importance in addressing the tumor microenvironment and facilitating drug penetration at efficient concentrations through the blood-brain barrier. Plasmonic gold nanostar-mediated photothermal immunotherapy and the lactic-co-glycolic acid have shown to be promising therapies for the glioblastoma.

Conclusion: The identification of the most effective drug and the optimal functionalization of nanotechnology is still a challenge. Studies with greater statistical significance are needed for future clinical trials.

KEYWORDS: Nanotechnology. Glioblastoma, therapeutics. Review.

Central message

Regarding glioblastoma non-surgical treatment, there are external beam radiation, chemotherapy, radiotherapy, thermal therapy, extending survival by 2 years in vivo/vitro, and nanotechnologies, with signs of better blood-brain barrier penetration. This barrier limits drug entrance, so as the microenvironment peritumoral edema, which is associated to neurologic alterations and can be treated with high cost anti-angiogenic agents.

Perspective

Developing and promoting new approaches can be challenging and time-consuming. Nevertheless, promising therapies like plasmonic gold nanostar-mediated photothermal immunotherapy and PLGA, show potential when associated with various chemotherapy drugs. Despite promising results in vitro and in vivo studies, further research with standardized pre-clinical tests are necessary.

RESUMO

Introdução: O glioblastoma é o câncer maligno mais comum do sistema nervoso central e tem um prognóstico sombrio. Normalmente, a sobrevida global média é de 15 meses com tratamentos, como ressecção cirúrgica, radioterapia e quimioterapia com temozolomida. No entanto, as principais razões para a falta de melhora na sobrevida do paciente são a baixa entrega do medicamento no local do tumor e a sensibilidade inadequada do tumor. Nesse sentido, as nanopartículas estão sendo consideradas como uma nova abordagem. São pequenos (1-100 nm), mas possuem grande área superficial, o que aumenta a solubilidade e a biodisponibilidade dos fármacos, favorecendo a difusão através da barreira hematoencefálica, aumentando a solubilidade dos fármacos hidrofóbicos e garantindo uma distribuição homogênea no tumor.

Objetivo: Avaliar se a nanotecnologia pode melhorar o prognóstico de espécimes e pacientes com glioblastoma.

Método: Revisão integrativa da literatura de acordo com o protocolo PRISMA, com foco em artigos publicados nos últimos 10 anos.

Resultado: Vinte e sete artigos pré-clínicos foram incluídos. Discussão: Foram encontradas nanopartículas de ferro e ferritina, nanopartículas de óxido de ferro, nanopartículas superparamagnéticas de óxido de ferro, nanopartículas de magnetita e outras. As nanopartículas têm demonstrado sua importância no tratamento do microambiente tumoral e na facilitação da penetração do fármaco em concentrações eficientes através da barreira hematoencefálica. A imunoterapia fototérmica mediada por nanoestrelas de ouro plasmônico e o ácido lático-co-glicólico têm se mostrado terapias promissoras para o glioblastoma.

Conclusão: A identificação do fármaco mais eficaz e a funcionalização ótima da nanotecnologia ainda é um desafio. Estudos com maior significância estatística são necessários para futuros ensaios clínicos.

PALAVRAS-CHAVE: Nanotecnologia. Glioblastoma terapêutico. Revisar.

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Conflict of interest: None | Funding: None | Received: 21/05/2025 | Accepted: 30/06/2025 | Publication date: 15/08/2025 | Correspondence: julianaoliveira_md@outlook.com | Associate Editor: Gustavo Rassier Isolan

How to cite:
Oliveira JA, Tiede KOM, Parreira KC, Jacobsem FB, Almeida AFS, Bruch GE. Nanotecnologia para combate ao glioblastoma: uma revisão sistemática. BioSCIENCE. 2025;83:e00018

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INTRODUCTION

Glioblastoma (GBM), the most common central nervous system malign cancer, affects 18 500/100 000 people yearly[1] with a 3:1 correlation. It can be classified into 4 grades of aggressiveness, with different pathways and mutations: classical, mesenchymal, proneural, and neural. Its high heterogeneity distinguishes it as primary or secondary tumor, with varying characteristics evolving age, localization, and responsiveness to therapies.[2] GBM accounts for 47.7%-65% of malignant brain tumours and 82% of malignant glioma2, and only 5.6% of patients survive up to 5 years after diagnosis.[3] The median overall survival with treatment is 15 (12-18) months[4,5] and without treatment is of 3 months.[2]

Micrometastatic deposits in normal tissues makes surgical approach insufficient. In the United States, 24,000 glioblastomas and 50,000 brain metastases are resected yearly with positive surgical margins. Additionally, GBM tends to recur 2 cm within the original resection area (90%).[6]

Regarding GBM non-surgical treatment, there are: external beam radiation, chemotherapy,[6] radiotherapy,[5] thermal therapy, extending survival by 2 years in vivo/vitro,6 and nanotechnologies, with signs of better blood-brain barrier (BBB) penetration.[7] BBB limits drug entrance4, so as the microenvironment peritumoral edema, which is associated to neurologic alterations and treated with high cost anti-angiogenic agents.[7]

In chemotherapy, temozolomide (TMZ) shows local failure,[7] while lomustine and carmustine can cause myelosuppression, pulmonary fibrosis and hepatic toxicity.[4] Moreover, single drug therapy might cause resistance and tolerance, enabling metastasis or recurrence.[8]

Nanoparticles (NPs) are being studied as an innovative approach with high versatility. They are small (1-100 nm) with a large surface area, increasing drug solubility and bioavailability by improving BBB diffusion and enhancing hydrophobic drugs solubility[4] generating homogenous distribution within the tumour.[5] NPs can increase the drugs half-life through encapsulation, long-time release, and targeted tumour site attachment.[4]

So, this review aimed to evaluate whether nanotechnology could improve the prognosis of specimens and patients with glioblastoma in a systematic review looking for improvement in prognosis of glioblastoma.

METHOD

PubMed, Embase and Cochrane platform were searched on July 2022. Inclusion criteria were in vitro and/or in vivo studies involving animals or humans, published in the last 10 years. Xenographic models were excluded due to their limitations. The search terms used were "glioblastoma", "therapy" and "nanomaterials". Were used the mesh terms and boolean operator to combined them to their associated terms. No filters were applied. The screening process was performed by two double-blinded authors (Oliveira JA and Martins KO) (Figure). Data was collected by 4 authors and checked by one. No limitations were added to the outcomes, considering the diversity of the nanomaterials, so as it effects on pre-clinical subjects (Figure).

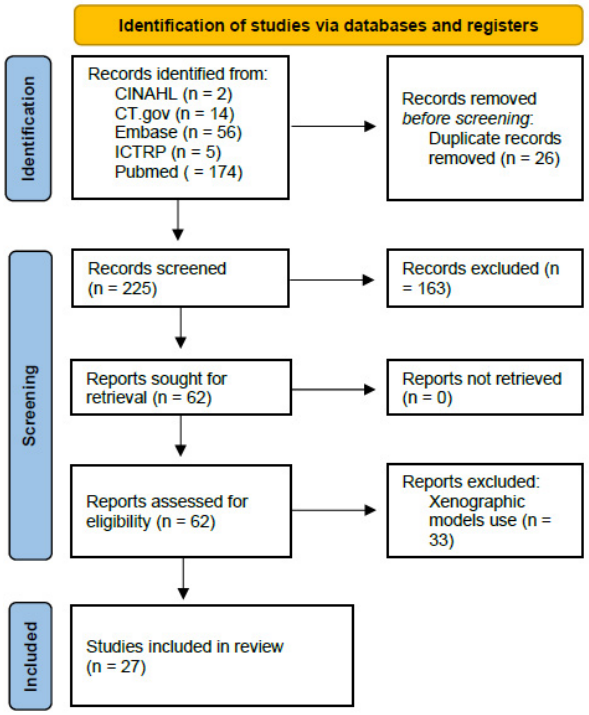

FIGURE — Flowchart PRISMA screening flow-chart

RESULT

A total of 225 articles were found. Most in English and published in 2015 (range: 2015-2022); 14 were in vitro, 9 in vivo, and 4 assessed both. Various nanoparticles were approached, challenging comparisons. Table provides the study's baseline characteristics

The administration protocol and population characteristics can influence the outcome, since GBM growth and aggressiveness may vary among genders. In animals, age affects the immunity baseline and hormone levels, which might impact GBM's evolution. Early adolescence in animals (4-18 weeks) and older age (65 years) in humans are relevant due to increased GBM risk. Additionally, key parameters are tumour volume, prognosis, for acute response evaluation, and non-invasive evaluation, for tumor's evaluation.[4] Most articles lacked age, sex, and tumour volume information.

DISCUSSION

Iron and ferritin nanoparticles

Nanomaterials (NM) combination to drugs (D-NPs) delivered through a hydrostatic pressure technique, named convection-enhanced delivery (CED), is being studied. This junction grants slow delivery and if associated to ferritin (F-NPs) contrast

TABLE — Principal characteristics and details of the articles selected

Author / publication year	Title	Drug(s)	Dose or/and NP size	Type of NPs	Population	Principal results
Strohbehn G, et al. 2015[1]	Imaging the delivered of brain-penetrating PLGA nanoparticles in the brain using magnetic resonance	-	Size: 70nm; 3 doses: 0.02, 0.1, and 0.5mg.	Copolymer PLGA NPs	Human glial cell line SVG p12 and Human neural stem cell line ReNCell (Millipore)	Less toxicity, can be co-administered and enables MRI monitoring of the delivery.
Rego G, et al. 2019[3]	Therapeutic evaluation of magnetic hyperthermia using Fe3O4-aminosilane-coated iron oxide nanoparticles in glioblastoma animal model	-	100uL of SPIONs at the concentration of 5mg/mL	Fe3O4-aminosilane-coated iron oxide	In vitro: C6 cell culture. In vivo: Ten mal Wistar rats at 2 months of age applicated with C6 cells.	Applying MHT with ideal AMF intensity and frequency tumour mass can be decreased.
Stauffer PR, et al. 2020[6]	Feasibility of removable ballon implant for simultaneous magnetic nanoparticle heating and HDR brachytherapy of brain tumour resection cavities	-	Size: 130nm; Iron concentration: 17.1mg/ml	Iron Oxide magnetic NPs	-	The balloon delivers heat uniformly, compared to other multi-catheters, to tumour bed around the brain tumour resection cavity. It can improve survival and quality of life.
Zhang Y, et al. 2015[11]	Versatile metal-phenolic network nanoparticles for multitargeted combination therapy and magnetic resonance tracing in glioblastoma	DOX	-	GA/FE2+ NPs	Nude mice injected with U87MG cells Luciferase-labeled (6 different groups)	DOX concentration in the nucleus gradually increased and inhibited DNA synthesis. Tumour growth was inhibited in the treated mice.
Mu Q, et al. 2015[12]	Stable and efficient Paclitaxel nanoparticles for targeted glioblastoma therapy	Cyclodextrin and CTX and PTX	Size: 44nm.	Iron Oxide magnetic NPs	SF-753 and U-118 MG human GBM cells	Tumour cell killing by IONP-PTX-CTX improved PTX potency against the tumour cells, independent of PTX resistance and of MGMT expression.
Norouzi M, et al. 2020[13]	Doxorubicin-loaded iron oxide nanoparticles for a glioblastoma therapy: a combinational approach for enhanced delivery of nanoparticles	Doxorubicin	Size: 51.8 ± 1.3nm. Free DOX concentration: 1ug/mL	Iron Oxide magnetic NPs	Mouse brain-derived microvessel endothelial bEnd.3, MDCK-MDR1, and human U251 GBM cells.	The NP facilitates drug delivery into cancer cells. Higher apoptosis-induced ell death, proliferation inhibition and ROS-induction in U251 cells.
Gupta R, Sharma D. 2019[14]	Biofunctionalization of magnetite nanoparticles with stevioside: effect on the size and thermal behaviour for use in hyperthermia applications	-	-	Stevioside coated Magnetite NPs	Rat C6 glioma cell line	Stevioside use improved cellular uptake and increased the NPs retention time.
Oleshkevich E, et al. 2019[15]	Combining magnetic nanoparticles and icosahedral boron clusters in biocompatible inorganic nanohybrids for cancer therapy	-	-	Magnetic nanoparticles coated with m-carboanylphosphinate	Human brain endothelial cells and GBM multiform A172 cell line	The technology is able to target the tumour cells, without damaging adjacent normal cells. No major signs of toxicity
Young JS, et al. 2018[16]	Convection-Enhanced Delivery of Polymeric Nanoparticles Encapsulating Chemotherapy in Canines with Spontaneous Supratentorial Tumors	TMZ	Size: <100nm. TMZ concentration: 5mg/kg/dose.	Polymeric magnetite nanoparticles	10 pet dogs with spontaneous intracranial tumours	The procedure was safe and there was 70% of accuracy. CED is important and need to be more studied.
Alizadeh D, et al. 2018[17]	Immunostimulatory CpG on Carbon Nanotubes Selectively Inhibits Migration of Brain Tumor Cells	CpG oligonucleotides	-	Single-walled Carbon Nanotube	GL261 cell line and Luciferase-expressing KR158B cells	SWCNT/CpG is immunostimulatory by itself, interfering with pro-tumor activity.
Ouyang M, et al. 2016[18]	Metronomic Doses of Temozolomide Enhance the Efficacy of Carbon Nanotube CpG Immunotherapy in an Invasive Glioma Model	TMZ and CpG oligonucleotides	TMZ dose: 2.5mg/kg/day per mouse	Single-walled Carbon Nanotube	Female C57BL/6 mice implanted with GL261 cell line and Luciferase-expressing KR158B cells	Single low-dose intracranial injection of SWCNT/CpG-1 eradicated GL261 gliomas in 50-60% of mice. Survival was improved.
Arshad A, et al. 2015[19]	Convection-Enhanced Delivery of Carboplatin PLGA nanoparticles for the Treatment of Glioblastoma	Carboplatin	Carboplatin NP dose: 1mg/ml; 10ul volume. Fluorescent Carboplatin NP: 1mg/ml; 5ul volume.	PLGA NPs	In vitro – small animals: Invasive GBM cancer cell lines. In vivo – small animals: Adult male Wistar rats.	High tissue retention of the drug was found, what could make possible to reduce dosing frequency. Limitation: only targeted peritumoral sites of tumour recurrence.
Saucier-Sawyer, et al. 2015[20]	Systemic Delivery of Blood-Brain Barrier Targeted Polymeric Nanoparticles Enhances Delivery to Brain Tissue	CPT	-	PLA-HPG-AD	In vitro: Immortalized mouse brain endothelial cells bEnd.3, and immortalized human glioblastoma cells. In vivo: Athymic nude mice at 8 weeks of age injected with intracranial U87 glioma cells	Failed to increase survival, but drug accumulation in the brain was optimized.
Norouzi M, et al. 2018[21]	Salinomycin-loaded nanofibers for Glioblastoma Therapy	Sali	Size: 165 ± 42nm without Sali and 170 ± 57 nm with Sali	PLGA nanofibers	Human glioblastoma U251 cells	50% of the tumour cells suffered apoptosis in 48 hours. PLGA alone didn't induce cytotoxicity in the cells. With Sali cytotoxicity and no proliferation of the cells were observed.
Tseng YY, et al. 2016[22]	Concurrent Chemotherapy of Malignant Glioma in Rats by Using Multidrug-loaded Biodegradable Nanofibrous Membranes	BIC	Size: 375-1200 nm	PLGA NPs	40 adult wistar rats with C6 glioma-bearing	Mortality risk, tumour volume and tumour malignancy significant reduction were observed.
Carvalho IC, et al. 2021[23]	Nanotheranostics through Mitochondria-targeted Delivery with Fluorescent Peptidomimetic Nanohybrids for Apoptosis Induction of Brain Cancer Cells	DOX	-	Hybrid nanostructure*	HEK 293T and U-87MG cell line	Lower systemic toxicity and fewer side effects were noted.
Juthani R, et al. 2019[24]	Ultrasmall Core-Shell Silica Nanoparticles for Precision Drug Delivery in a High-Grade Malignant Brain Tumor Model	Dasatinib	-	Ultrasmall fluorescent coe-shell silica NPs	mGBM single cell suspensions derived from murine RCAS/tv-a GBM	C'dots might be a promising NP for drug delivery, even the ones with high systemic toxicity, for overcoming technical details.
Zhang I, et al. 2020[25]	Nanotherapeutic Modulation of Human Neural Cells and Glioblastoma in Organoids and Monocultures	-	-	Dendritic polyglycerol (dPG)-Cy5 or dendritic polyglycerol sulfate (dPGS)-Cy5	U251N human glioblastoma cells and HMC3 human microglia	By modulating microglial activation, the tumor's microenvironment is controlled. They affect cellular stress and organellar function, but more research needs to be done in human neural cells. dPGS is not cytotoxic to human neural cells.

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Author / publication year	Title	Drug(s)	Dose or/and NP size	Type of NPs	Population	Principal results
Liang Y, et al. 2021[26]	Poly(p-phenylenevinylene) nanoparticles modified with antiEGFRvIII for specific glioblastoma therapy	-	-	Anti-EGFRvIII modified conjugated PPVN-A	BCLB/C nude female mice injected with ECFRvIII overexpressed LN229 cells	The fluorescent characteristic of the NP enables tumor boundaries identification during surgery. The generated ROS can kill the marked cells and surrounding EGFRvIII negative cells.
Li Y, et al. 2021[27]	Neutrophil Delivered Hollow Titania Covered Persistent Luminescent Nanosensitizer for Ultrosound Augmented Chemo/Immuno Glioblastoma Therapy	Paclitaxel and anti-PD-1 antibody	-	Neutrophil-delivered nanosensitizer	Mice injected with GL261 tumor cells	Primary GBM was eliminated and metastasis were inhibited, increasing survival time. Besides, immunological memory was created and can be considered a protective factor.
Zhang CX, et al. 2015[28]	A nanostructure of functional targeting epirubicin liposomes dually modified with aminophenyl glucose and cyclic pentapeptide used for brain glioblastoma treatment	Epirubicin	Size: 109nm	DSPE-PEG2000-Glu and DSPE-PEG2000-cRGD	In vitro: Human U251 glioblastomas cells and human umbilical vein endothelial cell. In vivo: Glioblastoma-bearing nude mice.	GBM cells and in brain GBM were destroyed. The use of liposomes was important to achieve the results.
Galstyan A, et al. 2019[29]	Blood-brain barrier permeable nano immunoconjugates induce local immune responses for glioma therapy	a-CTLA-4 and a-PD-1 antibodies	Size:28.0-28.5nm	NICs with PMLA	Mice bearing intracranial GL261 GBM	Prolonged survival, increased systemic immune response, including Tcells cytokines and higher anti-tumor immunity was observed. It transposes BBB and enhances the brain immunity system.
Liu Y, et al. 2019[30]	Plasmonic gold nanostar-mediated photothermal immunotherapy for brain tumor ablation and immunologic memory	Anti-PD-L1 antibody	Size: 12nm	Plasmonic gold nanostars	Female mice age 6-12 weeks with CT-2A glioma cell line	The mice were cure and anticancer memory was observed, being compared to an "anticancer vaccine" by the authors.
Parekh G, et al. 2014[31]	Layer-by-layer nanoencapsulation of camptothecin with improved activity	CPT	Size: 160nm	Layer-by-layer assembly of heparin and block-copolymer of poly-l-lysine and polyethylene glycol	Rat brain GBM cells CRL2303	After 40h cell membranes disruption and cell necrosis was observed. Cell growth, independent of CPT, was interrupted in 16h. Tumour decrease in 30% after 40h was observed in CPT containing NPs.
Kucheryavykh YV, et al. 2019[32]	Targeted Delivery of Nanoparticulate Cytochrome C into Glioma Cells Through the Proton-Coupled Folate Transporter	FA-Cyt C	-	FA-PEG-PLGA-S-S-Cyt c NPs	GI261, U-87 A172 glioma cells and primary cultured astrocytes	Reduced health tissue exposure to drugs. Could be used in some gliomas. Glioma cell death was of 40% in GL261 and 30% in A172 cell lines.
Pucci C, et al. 2022[33]	Ultrasound-responsive mutli-loaded nanoparticles for combined chemotherapy and piezoelectric treatment of glioblastoma cells	Nutlin-3a	-	ApoE-functionalized P(VDF-TrFE)	T98G, U251MG, U87MG GBM cell lines	pH can interfere with nutlin-3a release, which is non-genotoxic. Ultrasound exposure reduced cell migration and invasion ability and cause apoptotic and necrotic events..
Chowdhury, et al. 2014[34]	Graphene nanoribbons as a drug delivery agent for lucanthone mediated therapy of glioblastoma multiforme	Luc	-	PEG-DSPE coated oxidized graphene nanoribbons	U251 and CG-4 cell line	Luc toxicity was decreased by ~30 and 40% in U251 and APE-1 overexpressing U251 cells, compared to free drug. No toxicity was seen in CG-4 cells with the compound, but free drug was toxic. Cell death was increased by the loaded NP used.

Legend: Alternative magnetic field (AMF); biodegradable 1,3-bis[2-chloroethyl]-1-nitroso-urea-, irinotecan-, and cisplatin-eluting (BIC); chlorotoxin (CTX); convection-enhanced delivery (CED); camptothecin (CPT); cytotoxic T-lymphocyte-associated antigen 4 (a-CTLA-4); doxorubicin (DOX); epidermal growth factor receptor receptor variant III (EGFRvIII); folic acid (FA)-conjugated cytochrome c associated to Cyt c by succinimidyl-3-(2-pyridyldithio) propionate (FA-PEG-PLGA-S-S-Cyt c); lipid-glucose conjugate, distearoyl phosphatidylethanolamine polyethylene glycol-4-aminophenyl βD-glucopyranoside (DSPE-PEG2000-Glu); lipid-cyclic pentapeptide derivative containing the arginine-glycine-aspartic acid motif (DSPE-PEG2000-cRGD); hyperbranched polyglycerol (HPG); madin-darby canine kidney transfected with multiple-drug resistant protein 1 (MDCK-MDR1); lucanthone (Luc); magnetic resonance imaging (MRI); nanoparticles (NPs); nanoscale immunoconjugates (NICs); O6-methylguanine-DNA methyltransferase (MGMT); paclitaxel (PTX); polymer 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino polyethylene glycol (PEG-DSPE); polylactic acid and hyperbranched polyglycerol, surface modified with adenosine (PLA-HPG-Ad); poly (lactic-co-glycolic acid) (PLGA); poly(B-L-malic acid) (PMLA); polymer nanoparticles (PPVN-A); programmed cell death-1 (a-PD-1); programmed death-ligand 1 (PD-L1); salinomycin (Sali); scanning electron microscopy (SEM); superparamagnetic iron oxide nanoparticles (SPION); superparamagnetic iron oxide (magnetite); temozolomide (TMZ); thiol-end amphiphilic polymer folate-poly (ethyleneglycol)-poly(lactic-co-glycolic acid)-thiol (FA-PEG-PLGA-SH); transmission electron microscopy (TEM); (*) hybrid nanostructure comprising a fluorescent semiconductor core (AgInS2, AIS) and cysteine-modified carboxymethylcellulose conjugated with mitochondria-targeting peptides (KLA).

production allows MRI imaging, compound detection and GBM treatment improvement.[9,10]

When associated to magnetic particles (M-NM), CED creates magnetization-demagnetization cycles with heat production, a process known as specific loss power (SLP). The dissipated energy can be associated to chemotherapy through D-NPs and to thermotherapy through F-NPs. F-NPs heat production can disrupt cells homeostasis and its fenton reaction, glutathione depletion and ROS production elevation, associated to chemotherapy, can cause ferroptosis.[10] Besides, Fe2+ and galic acid (GA/Fe2+) union to a NP (GFNPs), can be a substrate to sustained Fenton reaction. The reaction, associated to near-infrared (NIR) light irradiation (808 nm), promotes a photothermal conversion favoring Fe2+ release from the NP and cells death due to local temperature elevation.[11]

If added, a cyclic Arg-Gly-Asp (cRGD) mediates endocytosis, once it interacts with a highly expressed receptor, αvβ3 integrin, at the tumour surface and neovascular endothelial cells. As a prodrug, intravenous (IV) inert platinum is cytotoxic to the tumour vesicles cells acid environment. While the prodrug is reduced, GFNPs loses some centre ligands and releases GA/Fe+2 with fewer side effects. This NP can synergically work with DOX, due to high Fe+2 release caused by NIR light stimulation, inducing a Fenton reaction and consequent ferroptosis.[11]

The pH-responsive cRGD-DOX delivered by GFNPs exhibits degradation behaviour. Red fluorescence emission increased signal intensity, enabling DOX to reach U87MG cell nucleus, suggesting DNA synthesis inhibition. This compound has a dual effect: inhibiting GBM cells and marking tumor boundaries. Laser exposition for one hour interrupted GBM growth, increased tumour site blood flow and drug accumulation and release. It significantly intensified

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treatment effects compared to the control group.[11]

Iron oxide nanoparticles (IONPs) and superparamagnetic iron oxide nanoparticles (SPIONs)

IONPs repeatability produce heat, allowing particles reuse.[7] However, high concentrations can be toxic to near tissues and affect biodistribution and NP's elimination through liver, kidneys, and spleen damage.[3]

Efficient cancer treatment's NP must have high stability, uniformity, targeting potential, and sufficient drug loading. IONPs conjugated with cyclodextrin (CD) and chlorotoxin (CTX) coated by polyethylene glycol (PEG) and loaded with fluorescein and paclitaxel (PTX)(IONP-PTX-CTX-FL) might have these characteristics. Thus, when evaluating IONP-PTX-CTX-FL nanoparticles, PTX rapidly initiated released (4 h), and ~50% of it remained in NPs after 3 days incubation. Analysing SF-763 and U-118 MG cell lines through flow cytometry 1-6 h after incubation with 40 µg/mL of NPs with CTX, higher uptake (30%) was found in the target cells. Colorimetric ferrozine and Bradford assays quantified the iron content 1 h after incubation. SF-763 with IONP-PTX-CTX incubated more iron content (~0.36Fe/µg) than normal cells with IONP-PTX (~0.23Fe/µg) and U-118 MG. For this, CTX in NPs might increase NPs uptake in some cell lines.[12]

In 72 h after treatment with free PTX, IONP-CTX, IONP-PTX or IONP-PTX-CTX, SF-763 and U-118 MG cells viability were evaluated by Alamar Blue assay. Free PTX had high therapeutic potency in both experiments, IONP-CTX showed no cell death (demonstrating that CTX doesn't affect cell viability), unguided IONP-PTX had lower potential compared to free PTX, and IONP-PTX-CTX considerably enhanced cell death. Such enhancement was apoptosis-dependent, confirmed by flow cytometry.[12]

Two PTX-resistant cell lines, SF-763-PTXR and U-118 MG-PTXR, were treated with PTX and analysed by Alamar Blue assay. U-118 MG-PTXR had significant resistance (IC50, dose capable of inhibiting 50% of a specific biological or biochemical function, changed from 5.06nM to 18.3nM) and SF-763-PTXR had slight resistance (3.24 nM to 6.71 nM) to PTX. However, both cell lines showed no resistance to IONP-PTX-CTX treatment. U-118 MG-PTXR was more sensitive to IONP-PTX-CTX than U-118 MG. Thus, the NP improved PTX efficacy for resistant GBM cells.[12]

When associated with temporary implanted silicone balloon catheters, called Thermobrachytherapy (TBT) balloon devices, IONPs can be reused ~30 times in 5 months. It can be used to treat tissues close to the GBM resection cavity, reaching therapeutic temperatures (40-48ºC) through magnetic hyperthermia (MHT). The local heat, caused by an external magnetic field, can activate the NPs. In white matter a 5 mm annular ring of tumor bed reached therapeutic levels through a 2-5 cm balloon filled with 0,5 mg/mL of IONPs. The TBT balloon delivers radiation and heat in a uniform way when compared to implant technologies. Compared to RT alone, it enhanced the thermal enhancement ratio (TER) 5.^{0} times. Therefore, there can be fewer complications to the healthy area around the tumour and, if applied right after surgery, quality of life and survival improvement might be possible.[6]

SPIONS coated with aminosilane using MHT (therapeutic temperature: 42-45ºC) was tested in C6 cells, histologic like human cells, which affected the tumour, but none surrounding areas. Neither isolated, coated SPIONs, or AMF affected the tumour cells, but when conjugated to a highly sensitive bioluminescence (BLM) technique, cellular viability reduced 52% compared to controls (1.14x108 photons/s; in vivo). With luciferin application before AMF, the tumour signal reached 3.45x109 photons/s. In 24 h later, MHT was applied for 40 min, the signal decayed (2.32x109 photons/s) and tumour mass decreased 32,8% compared to controls (in vitro). Concerning the SPIONS, it prevented cluster's formation (100%), making MHT a more effective technique. Besides, particle's hydrodynamic and distribution were conserved during the study.[3]

Another approach was the development of a 70 nm non-adherent NP with poly (lactic-co-glycolic acid) (PLGA). Since normal brain interstitial space measures 38-64 nm and whenever the tumour is present its size increases to 70-100 nm, NP accumulation in the injured area is favored. It had better dispersion associated to convection and diffusion techniques. When conjugated to N-(4-[18F] fluorobenzyl)propanaamide ([18F]NPB4), non-invasive monitoring of the particle penetration by MRI pre- and post-surgery was possible to be realized. With a single PGLA injection a strong and long-lasting signal was observed, being speculated that 5 mg/ml of PGLA administered with a considerable amount of the synthesised NP could deliver drugs and enable monitoring. Since SPIONs are considered safe and PLGA is approved by the U.S. Food and Drug Administration (FDA), this NP can be safe and non-toxic. Positron emission tomography (PET) evaluation was not performed during surgery due to it's high cost and the particle's short half-life.[1]

IONPs associated to DOX coated with EDTs, might improve BBB penetration. Higher DOX absorption and high apoptosis induction was found in 48 h (>90%). Its absorption is concentration dependent and can be magnified with an external magnetic field (2,8 ± 0,5 times). Without EDT, there was significant cell population and proliferation reduction (>90%) and higher cytotoxicity. Therefore, NP association to magnetic fields enhances GBM treatment. There were differences depending on the cell tested (U251, bEnd.3 or MDCK-MDR1), but no toxicity was found in cell lines treated with 0,25-30 ug/mL doses.[13]

Magnetite nanoparticles (MNPs)

MNPs are currently used to produce hyperthermia. However, to increase Magnetic Hyperthermia-mediated Cancer Therapy (MHCT) efficiency and avoid self-particles agglomeration, carbohydrate-

coated NPs was associated reducing cytotoxicity and improving its geometrical properties (size and shape). The Stevioside (STE), a biosurfactant for NPs stabilization, seems viable for tumour treatment due to its antihyperglycemic and immunomodulatory effects, and antitumor action. Therefore, this combination has dual pathways of action, one due to MHCT and another due to STE.[14]

Overall, X-ray diffraction patterns and TEM imaging showed that high STE concentration reduced the hydrodynamic size of MNPs by 86%. Thus, STE-coated magnetite (Fe3O4) nanoparticles (STE-Fe3O4) have a higher uptake by the C6 mice GBM cells in comparison to other MNP. STE coated MNPs provide potential hyperthermia by exhibiting temperature variation of 9-13ºC, while others commonly used surfactants only variates 4ºC. Besides, higher NPs dispersion generates higher final temperature elevation. Given pre-established parameters of magnetic field strength, frequency, and concentrations, it only took 2 min to reach the required temperature for cancer treatment by hyperthermia. This rapid temperature variation may represent a plus for this therapy.[14]

Carboranylphosphinates, a hydrophobic one o-carborane attached to MNP's with low oxidation tendency, have high affinity to MNP's and its Boro element. For this, Capture Therapy (BNCT) use through nuclear capture and fission reactions when Boron is irradiated with epithermal neutron beam radiation, which can selectively destroy tumour cells, was attempted. TEM images showed that nanohybrid MNPs coated with m-carboranylphosphinate (1-MNPs) penetrates the A172 GBM and the hCMEC/D3 cells of capillary-derived human brain endothelial cells. Compared to control cells, MNPs decreased tumour cell proliferation rate the day after BNTC, decreasing 2.5 times more on the 6th day. This approach could be used for cancer imaging and to provide a selective and orientated cancer cells approach avoiding unwanted damage to healthy cells. No toxic side effect was observed.[15]

Polymeric NPs, as magnetite, can carry chemotherapeutic drugs, improved by CED association, be targetable, and incorporate contrasting agents for real-time imaging, by MRI association. An animal model was used to evaluate Polymeric Magnetite-loaded Nanoparticles (PMNPs) and temozolomide (TMZ) by MRI and CED analyses. Seven animals (70%) showed PMNPS delivery accuracy of 70% after catheter injection and good tumour area coverage by MRI evaluation. The other animals (30%) missed targets, but presented tumour shrinkage, clinical improvement, and prolonged survival (10%). Two were able to be re-examined and presented tumour reduction. Nine recovered from the acute procedure effects, one died on the first postoperative day, probably due to herniation, and one was alive two years after the procedure. PMNPs might spread into the cerebrospinal fluid, the subarachnoid space, or stay in the tumour due to the tissue anisotropic characteristics. As of CED, regardless of the encapsulated drug, it is a minimally invasive intracranial tumours approach being ideal for deep-seated unresectable tumours or the tumour's surrounding area treatment, followed by resection.[16]

Single-walled carbon nanotubes

Single-Walled Carbon Non-covalently Tubes (SWNT) can functionalized with CpG (SWNT/CpG), a DNA oligonucleotide that can induce an antitumor immune response through macrophage activation in gliomas. Since a high nuclear localization of NF-κB p65 was seen in untreated K-Luc cells (a highly invasive murine glioma line of cells), indicating NF-Kb activation and, for this, an immune response, it was attempted to treat this cell line with SWNT/CpG. SWNT/CpG decreased NF-κB expression in K-Luc cells and treated K-Luc and RAW macrophages that presented an increased expression of TLR9 and NF-κB.[17]

SWCNT/CpG increased NF-κB activity and pro-inflammatory cytokines expression (IL-1β, IL-12β and TNFα) in human Peripheral Blood Mononuclear Cells (PBMCs), being more expressive, respectively, in lymphocytes, monocytes, and dendritic cells.[18]

Mice with invasive K-Luc tumours presented higher treatment efficacy when combined with TMZ compared to RSS-CpG (fully phosphorothioated CpG-28 oligonucleotides bearing a terminal dithiol) or SWCNT/CpG-2, using equivalent doses of CpG alone combined to TMZ ($p<0.025$). Besides, SWCNT/CpG-2 with TMZ increased antitumor cytotoxic activity and was not related to tumour depletion. The animals weighed was monitored, and the control group had greater loss after the 12th day while SWCNT/CpG-2 group had a brief and transient weight loss after treatment. Treatment was well tolerated and improved mice survival. Furthermore, SWCNT/CpG efficacy was higher when combined with TMZ.[18]

PLGA (poly-lactic-co-glycolic acid) and PLA (poly-lactic acid) nanoparticles

The Poly(lactic-co-glycolic acid) (PLGA), a biodegradable copolymer, can be hydrolysed into lactic and glycolic acid, which can be cleared by innate interstitial fluids of the brain.[19] Polymeric NPs, such as PLGA and Polylactic Acid (PLA), have potential benefits, such as controlled release and protection of fillers from degradation. Both have inherent biodegradability, low toxicity, and can deliver hydrophilic compounds, as nucleic acids, hydrophobic agents, Camptothecin (CPT) and drug/nucleic acid combinations.[20]

PLGA, when encapsulated by carboplatin and delivered with CED can increase tumour cytotoxicity and reduce neurotoxicity. Carboplatin NPs, when compared to free carboplatin NPs in two GBM cell lines (UPAB and SNB19), achieved increased cytotoxicity when 24 and 48 h in SNB19 cultures ($p = 0.001$), while a non-significant increase was observed in UPAB cell line. The carboplatin cytotoxic

effect was equivalent to free carboplatin in both cell lines in 72 h.[19]

As of B3tubulin, a neuronal integrity marker studied by immunofluorescence, and Glial Fibrillary Acidic Protein (GFAP), a glial cells marker, had different effects when used with carboplatin NP and free carboplatin. Carboplatin alone can cause complete neuron dysregulation and glial cell loss after 72 h, while carboplatin NPs leave intact neurons and glial cells, revealing a significant neurotoxicity reduction ($p<0.001$).[19]

Free carboplatin, carboplatin coated NP, and vehicle (artificial cerebral spinal fluid) infused into rat brains, analyzed by Inductively Coupled Mass Spectrometry (ICP-MS), showed longer tissue retention in NPs presence ($p = 0.03$). No gross morphological changes were observed, and minimal neuronal and glial disruption was found in the neuronal injection pathway in the groups. Reduced neuronal toxicity and increased tumour cytotoxicity were achieved by prolonging the tissue half-life.[19]

PLGA association to nanofibers (PLGA NFs) loaded with salinomycin (Sali), an ionophore antibiotic and anticoccidial, was tested in U251 GBM cells to evaluate Sali's toxicity. A concentration-dependent effect on cell viability was found, since 500 ng/ml of Sali demonstrated a slight increase in PLGA NFs associated with Sali cytotoxic responses compared to free Sali. Comparing 1000 ng/ml of Sali and PLGA NFs associated to Sali, cell viability of 49±4% and 39±3%, respectively, was found.[21]

In U251 cells free Sali and NFs associated with Sali could induce apoptosis and necrosis (by flow cytometry) and cause morphological changes, such as cytoskeleton damage and cell shrinkage (by immunofluorescence analysis). PLGA NFs alone showed no cytotoxicity in U251 cells. Both free Sali and NFs associated to Sali decreased WNT1 expression, reduced intracranial tumour formation in vivo, increased caspase 3 expression by 3 times, Rbl1 (up to 2-fold) and Rbl2 (up to 10-fold) expression after treatment, which may inhibit tumour cell cycle progression.[21]

Another possibility is to load PLGA to Biodegradable Nanofibrous Membranes (BCNU, irinotecan, and cisplatin) (BIC/PLGA) with electrospinning technique use. BIC/PLGA, in C6 glioma-bearing mice brain surface, provided higher drug concentration in the brain than in the plasma ($p<0.01$). In MRI serial imaging, the initial tumour volume of the control group (62.73×10-3 mL) was like the mean volume in the vehicle-treated (no drug loading) group (60.36±38.69×10-3 mL). In the control group, the largest tumour volume was reached at week 4 (401.44±460.62×10-3 mL), followed by a steady decrease and by important reduction at the end of the study (15.99±7.88×10-3 mL). The vehicle-treated group showed an increase of the central necrotic area and suppression of the GFAP, related to the cellular undifferentiation state, often observed in high-grade astrocytoma. The control group had a central necrotic area decrease and an GFAP overexpression.[22]

A different approach involves Rabies Virus Glycoprotein (RVG), TGN (12 amino acid peptide), and an adenosine (Ad), the 3 most promising BBB transport ligands. They were used as part of a NP synthesis and bound to PLA (PLA-HPG) and to PLGA surface with a PEGylated phospholipid ligand (PLGA-DSPE-PEG). Both NPs were loaded with CPT, a topoisomerase I inhibitor. U87 cells were inoculated into mice with one of the NPs or none (control group). No survival increase was observed with 4 or 10 mg/kg of CPT, and the higher dose caused adverse reactions.[20]

Fluorescent nanoparticles

KLA peptide, composed by peptides such as leucine, alanine and lysine, has pro-apoptotic characteristics that causes its structural collapse by mitochondrial membrane interaction. Considering it, hybrid organic and inorganic structures have been tested for diagnosis and treatment of GBM, such as AIS@CMC_Cys_KLA-DOX, with multiple components discussed ahead. AgInS2 Quantum dots (AIS QDs), an inorganic part of a carrier with notorious fluorescent agents, can be used for bioimaging and tracking target cells due to its good photostability, brightness and ability to associate with specific ligands such as proteins, peptides, and bioactive portions. L-cysteine (Cys) can mediate the particles connection to overexpressed GBM receptors, causing endocytosis. As for carboxymethyl cellulose biopolymer (CMC), a very strong KLA binder, can be used for mitochondria damage and cell death. Finally, doxorubicin (DOX), a chemotherapy drug, couples to DNA creating a stable complex to render its dysfunction.[23]

Then, the AIS@CMC_KLA complex use presented cytotoxicity under 25% in U87 incubated cells for 6 and 24 h, being characterized as non-toxic. If L-cysteine is added, its destructive power increases 20% and AIS@CMC_Cys_KLA reaches 48% of cytotoxicity. Using Confocal Laser Scanning Microscopy (CLSM) technique moderate signalling of AIS@CMC_KLA and high signalling of AIS@CMC_Cys_KLA were noticed, indicating apoptosis without breaking CMC and KLA bound, due to the KLA complex. Free DOX was used in U-87MG and HEK 293T cells, being found that AIS@CMC_KLA-DOX is less lethal for both cell lines. The AIS@CMC_Cys_KLA was more effective in killing GBM cells than free DOX, which is important due to the undesired effects of isolated DOX to non-target cells, especially in the heart. Dose managing is needed, and DOX's use may reduce the patient's quality of life under treatment.[23]

Another fluorescent NP is a silica core-shell nanomolecule, called Cornell prime dots (C' dots) which can evaluate the Accumulation, Distribution and Retention (ADR) of chemotherapeutic drugs against GBM. It has a dual platform (positron emission tomography and optical) which overcame small molecule's barriers. By adding the Arg-Gly-

Asp (cRGD) peptide to the C'dot NP cell attachment capacity and internalization into the GBM cell surface integrins increased, improving further when 18 cRGD peptides per particle were added.[24]

When C' dots were coupled with radioisotopes for ADR determination and imaging by PET-Computed Tomography (PET-CT), C' dots showed efficient drug release kinetics in the presence of proteases. For this, it's a promising technique, despite its sensitive to dasatinib in mouse models, which has no benefits in patients, due its high feasibility for drug delivery in cancer therapy.[24]

Two studies associated fluorescence to gene overexpression and Dendritic Polyglycerol (dPG) and dPG Sulphate (dPGS), both with terminal sulphate filaments and slight anticoagulant properties. dPGS internalization in the microglia and astrocytes cells was observed even without the fluorescent markers, being ascertained and significant after 24 h. The dPGS modulation of the tumour environment, due to lipid droplets formation inhibition, was induced by inflammatory mediators, which decreases microglia activity, reduces Lipocaine-2 synthesis, and reduces growth factors production within the tumour. For this, dPGS was able to modulate microglial activity and decrease tumour invasion.[25]

Concerning oncogenes overexpression, due to genetic alteration and epidermal growth factor receptor (EGFR) variant III (EGFR-vIII), a study targeted anti-EGFRvIII antibodies production conjugated to Polymer Nanoparticles (PPVN-A). PPVN are highly specific in targeting and have low toxicity. Murines with implanted tumours and in vitro human GBM cell lines were studied. Bounded NP formed an amide bond which associates to fluorescent compounds, allowing tumour margins identification during surgery. The treated mice had longer survival time and slower tumour growth compared to the control group.[26]

Liposomes involvement

Liposomes loaded with luminescent agents, such as ZnGa2O4:Cr3+ (ZGO) to obtain images, associated to nanosensitizing particles, as TIO2, to produce ROS and control drug and anti-body release, as paclitaxel (PTX) and Anti Programmed cell death-1 (PD-1) inhibitors, generated the liposomal formulation ZGO@TiO2@ALP. This compound, internalized by neutrophils (ZGO@TiO2@ALP-NE) to cross the BBB, favors drug distribution at the site of interest. The compound generates local inflammation, attracting more molecules and starting a constant attack cycle to the tumour. Associated to ultrasound, which by radiation under TIO2 particles produces ROS, liposomal wall lysis occurs and ensures drugs release.[27]

In vitro experiments, the compound did not hinder neutrophil chemotaxis and in GBM presence, more neutrophils crossed the BBB and accumulated in the GBM when compared to the control drug (PTX content in the lower chamber increased from 1.2% to 35.6%). Initially, neutrophils perceived systemically in the rats. After 2 hours, brain tissue concentration was observed. Reaching 4 h, after 5 min US application, the luminescence signal increased considerably (1.52 times).[27]

After ZGO@TiO2@ALP-NEs and ultrassound application, histologically, GBM almost disappeared and negligible migration into healthy tissue was noted. In contrast, the groups treated with Taxol, saline, NEs, ZGO@TiO2@ALP and ZGO@TiO2@ALP-NEs still had aggressive GBM with infiltrated borders. In 75 days after the experiment, 40% of the rats in the successful group remained alive, and all other died. Ultrasson triggered local chemotherapy and immunotherapy inhibited metastasis and eradicated primary GBM. Besides, it promoted antitumor immune memory, preventing tumour recurrence, resulting in a significant survival increase.[27]

By flow cytometry, chemotherapy reduced immune response at the tumour site by elevating the lymphocytes CD4, FoxP3, and regulatory T cells (T reg) presence rates. As for anti-PD-1 antibody addition, Treg was decreased. Besides, when treated by PTX, the isolated CD8/CD4 ratio dropped, due to its immunosuppressive action. When an antibody was added, the value increased. Consequently, adding an antibody, greatly improves the PTX efficiency and allows greater GBM surveillance.[27]

As of the liposome membrane, when associated to DSPE-PEG and glucose (DSPE-PEG-GLU), it activates the glucose transporter (GLUT-1) on the BBB, favoring compound entrance. If the integrin ligand cRGD (DSPE-PEG-cRGD) is used, binding highly over-expressed integrin receptors, angiogenic endothelial tumor cells are found.[28]

Epirubicin, a lipophilic fluorescent probe (coumarin 6, DiI or DiR), can be encapsulated within the liposome lipid bilayer. In vitro, its release rate was <1% in the first hour and 2% in 36 h. At low concentrations, functional targeted nanoconjugates demonstrated stronger effects regarding GBM destruction when compared to the free drug. However, high dosages have cytotoxic effects for both.[28]

By flow cytometry, liposomes uptake by Brain Microvasculature Endothelial Cells (BMVECs) was illustrated and exposed higher cellular uptake in functional coumarin liposomes (2.34±0.04), than in GLUT-1 (2.24±0.03) and cRGD-targeted coumarin liposomes (1.11±0.10). As for Epirubicin, it had better function (1.81±0.08) than cRGD (1.63±0.06) and Glu-targeting epirubicin liposomes (1.09±0.04).[28]

The BBB transport of epirubicin within 3 h was better with free epirubicin (7.33±3.51%), than with epirubicin liposomes (3.33±3.21%), cRGD-targeting (1.33±0.58%), GLUTE-targeting (11.00±7.00%) and functional epirubicin liposomes targeting (15.00±6.24%). The percentage of GBM cells surviving in 48 h was of 59.39±3.70%, 51.70±0.95%, 49.71±2.01%, 49.00±1.52%, and 40.13±2.48%, respectively.[28]

Highest cytotoxicity was found, respectively, in functionally targeted epirubicin liposomes; cRGD-

targeted epirubicin liposomes; epirubicin liposomes; GLU-targeted epirubicin liposomes; free epirubicin. For this, targeted epirubicin liposome's function might have stronger inhibitory effects on endothelial cells.[28]

Besides, mice treated with functional target epirubicin liposomes survived ~28 days compared to 17.5 of those treated with saline. Statistical analysis showed that functional target epirubicin liposomes treatment extended survival compared to saline ($p = 0.0147$), free epirubicin ($p = 0.0205$), epirubicin liposomes ($p=0.0463$), cRGD-targeted epirubicin liposomes ($p = 0.0435$) or GLU-targeted epirubicin liposomes treatment ($p = 0.0118$).[28]

For this, GLUT-1 functions as a pathway since functional targeted liposomes or Glu-targets had higher efficiency in BBB transport. As of cRGD, it prevents migration, invasion, survival, and proliferation of endothelial cells, reducing the neovasculature growth in solid cancer tissues. In mice, target-functionalized epirubicin liposome destroyed neovasculature and extended survival chances of GBM-bearing mice.[28]

Other nanoparticles

Poly (B-L-malic acid) (PMLA), natural polymers that attach immunoconjugates to nanoparticles, can be used as a vehicle to cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and PD-1, endocytosed after crossing the BBB. Yet, its systemic delivery allows tumour immune response activation. When nanoscale immunoconjugates (NICs) are conjugated to CTLA-4 and PD-1, an increase of TCD3 (of 15.15), TCD4 (of 12.91), TCD8 (of 13.06) lymphocytes ($p<0.0001$), cytotoxic lymphocytes and tumour macrophages was found at tumor site. Therefore, NIC's bondage increases brain immune system activity and limits checkpoint inhibitors activity. Besides, NICs are associated to IL-2, 4, 5, 10 and 12 ($p<0.05$) and to TNFα ($p<0.001$) and their increased production when compared to the phosphate buffered saline (PBS) associated to IL-1β (pro-inflammatory cytokines) and IL-6 administration ($p<0.01$). Longer survival was noticed when compared to the PBS-treated groups.[29]

Another line of research is the Gold Nanostars (GNS) or "plasmonic nanoparticles", metallic nanoparticles that amplify optical properties of light and enables photothermal removal of neoplasms. Since photon transduction can be directed and adapts to tumor margins, higher assertiveness and specificity is expected. GNS efficiency alone is lower than photothermal immune nanotherapy (SYMPHONY), which restricts tumor growth and, if associated to laser trigger, has greater immune response, being able to treat primary glioblastoma and its metastases. Besides, greater tumour cells ablation, tumour antigens release, and possible molecular damage associated to cell damage was found. All those tumour antigens favored T cells presentation.[30]

Another approach evolves implanting or injecting NPs directly in the tumour through, injectable nanocapsule formulations, constructed layer-by-layer (LBL), carrying highly stable chemotherapeutic drugs. CPT nanocapsules coated LBL, covered the NP crystalline core in two forms, as: lactone, the most active and least toxic form; and carboxylate, the most toxic form. The lactone showed higher stability for 17 h at all pH ranges, except pH of 9, when in PBS, allowed greater protein resistance against pH changes. Free CPT was rapidly degraded in all pH ranges. The complex had slower and longer delivery time to the brain, allowing a 3-fold efficiency in contrast to free CPT.[31]

To minimize toxicity and increase survival rates, cytochrome C was associated with NPs and induced apoptosis in cancer cells. When combined to FA, target Proton-Coupled Folate Transporter (PCFT), present and overexpressed in the glioma cell membrane. FA was an important internalizing mediator and depositor of nanodrugs, being effective at targeting and in reducing side effects. In vitro, targeting and cell death increased in Gl261 (by 40%) and A172 (by 30%) cell lines. When treated with FA, Cyt C and nanoparticles, mean survival time increased 3.5 days (17.5%) compared to the control group (20 days). There was significant compound internalization, targeted delivery and tumour size reduction.[32]

A better-known approach uses nano-piezoelectric materials, which generates electrical charges under mechanical stimulation. Inorganic piezoelectric polymers, such as zinc oxide, despite generating significant charges upon mechanical deformation and high piezoelectric coefficient, lack information on its biodegradation and biocompatibility. As of organic materials, such as poly (vinylidene fluoride) and its copolymer poly (vinylidene fluoride-trifluoroethylene), are known for their good biocompatibility and ease adjustment and processing.[33]

However, organic materials are hard to coat into high-performance NPs without inorganic components. A hybrid NP with a pyroelectric polymeric core, coated with biocompatible lipids, was loaded with apolipoprotein E (ApoE) and Nutlin (Nut). Nut inhibits murine double minute-2 (MDM2) protein, which negative regulates the tumour suppressor protein p53. In a pH >4.5, associated with ultrasound stimulation, nut was effectively delivery into nanoparticle platforms (PNPs), enhancing compound delivery and NPs stability. Besides, ApoE allowed BBB transcytosis. Quantitatively, functional and bare PNPs differed by 55-43±1μg, respectively, corresponding to a 20% increase of PNPs crossing the barrier ($p<0,05$).[33]

Another study of particle inhibition uses APE-1, an endonuclease frequently overexpressed in GBM with transcription factors related to intermittent synthesis, which gene is related to tumour resistance. Oxidized graphene nanoribbons (O-GNR-PEG-DSPE), coated with lucantone, an APE-1 inhibitor, were delivered to U251 glioblastoma cells with APE-1 overexpression. 30-40% and 50% viability reduction was found in O-GNR-PEG-DSPE isolated and conjugated to Luc when compared to the control group, respectively. NPs

presence increased cell death (70%) and significantly reduced Luc toxicity (30%) when compared to the O-GNR-PEG-DSPE-free group.[34]

This discussion might lead and help new researchers to define the best method and approach to be chosen for clinical studies aiming to treat glioblastoma.

CONCLUSION

GBM, an incurable disease, have limited survival rate improvements due to drug resistance, necessitating the exploration of multiple pathways to enhance efficacy. Tumour heterogeneity and microenvironment, and BBB pose significant challenges. Different nanoparticles offer potential solutions but selecting the most effective methods requires addressing these challenges. Few models accurately replicate human GBM and the scarcity of patients limits statistically significant studies. Developing and promoting new approaches can be challenging and time-consuming. Nevertheless, promising therapies like plasmonic gold nanostar-mediated photothermal immunotherapy and PLGA, show potential when associated with various chemotherapy drugs. Despite promising results in vitro and in vivo studies, further research with standardized pre-clinical tests are necessary.

Author´s contribution

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