BBA - General Subjects 1867 (2023) 130443

Contents lists available at ScienceDirect

BBA - General Subjects

journal homepage: www.elsevier.com/locate/bbagen

Hepatocellular carcinoma: Preclinical and clinical applications of nanotechnology with the potential role of carbohydrate receptors

Sanya Batheja [a], Rakesh Kumar Sahoo [a], Sofiya Tarannum [a], Klaudi K. Vaiphei [c], Shikha Jha [c], Amit Alexander [c], Amit Kumar Goyal [b], Umesh Gupta [a,*]

[a] *Nanopolymeric Drug Delivery Lab, Department of Pharmacy, School of Chemical Sciences and Pharmacy, Central University of Rajasthan, Bandarsindri, Ajmer, Rajasthan 305817, India*

[b] *Department of Pharmacy, School of Chemical Sciences and Pharmacy, Central University of Rajasthan, Bandarsindri, Ajmer, Rajasthan 305817, India*

[c] *Department of Pharmaceutics, National Institute of Pharmaceutical Education and Research, Sila Katamur, Changsari, Kamrup, Guwahati, Assam 781101, India*

ARTICLE INFO

Keywords:
Hepatocellular carcinoma
Biomarkers
Nanotechnology
Targeting strategies

ABSTRACT

Hepatocellular carcinoma (HCC) is one of the most common types of liver cancer; accounts for 75–85% of cases. The treatment and management of HCC involve different sanative options like surgery, chemotherapy, immunotherapy, *etc.* Recently, various advancements have been introduced for the diagnosis and targeting of hepatic tumor cells. Among these, biomarkers are considered the primary source for the diagnosis and differentiation of tumor cells. With the advancement in the field of nanotechnology, different types of nanocarriers have been witnessed in tumor targeting. Nanocarriers such as nanoparticles, liposomes, polymeric micelles, nanofibers, *etc.* are readily prepared for effective tumor targeting with minimal side-effects. The emergence of various approaches tends to improve the effectiveness of these nanocarriers as demonstrated in ample clinical trials. This review focuses on the significant role of carbohydrates such as mannose, galactose, fructose, *etc.* in the development, diagnosis, and therapy of HCC. Hence, the current focus of this review is to acknowledge various perspectives regarding the occurrence, diagnosis, treatment, and management of HCC.

1. Introduction

Cancer is the major cause of deaths worldwide. Among various cancers, hepatocellular carcinoma (HCC) is ranked as the fourth most leading cause of cancer-associated deaths. According to GLOBOCAN 2020 factsheet, liver cancer is estimated with 4.3% of new cases which tends to be 905,677 incidences whereas, mortality rate leads by 8.3% accounting 830,180 deaths worldwide [1]. Global demographics represented in the statistical data predict the rate of incidence and prevalence with the hike of about 70% in the next two decades [2]. HCC is one of the most prevailing and cataclysmic form of liver cancer.HCC is a multi-step process which involves assemblage of alterations and mutations in genetic and epigenetic centers culminating the aberrant activation of molecular signaling pathways [3].Various sanative options are available for different stages of HCC such as for the early-stage carcinoma surgical resection, ablations, and transplantation are recommended, whereas, trans-arterial chemoembolisation (TACE) and trans-arterial radioembolisation (TARE) are recommended for intermediate stage of HCC treatment. Certainly, an adequate pharmacological alternative requires established guidelines. However, the pursuit of

Abbreviations: HCC, Hepatocellular carcinoma; HBV, Hepatitis B virus; HCV, Hepatitis C virus; OLT, Orthotopic liver transplantation; RFA, Radiofrequency ablation; NLR, Neutrophil-lymphocyte ratio; TACE, Trans-arterial chemoembolisation; TARE, Trans-arterial radioembolisation; HAI, Hepatic arterial infusion; ROS, Reactive oxygen species; TAMs, Tumor-associated macrophages; MDSCs, Marrow-derived suppressor Cells; TANs, Tumor-associated neutrophils; CAFs, Cancer-associated fibroblasts; AFP, Alpha-fetoprotein; DCP, Des-γ-carboxyprothrombin; PGM5, Phosphoglucomutase-like protein 5; AFU, α-L-fucosidase; GP73, Golgi protein 73; OPN, Osteopontin; MMP2, Matrix metalloproteinase-2; CA19–9, Carbohydrate antigen 19–9; GPC-3, Glypican-3; HSP70, Heat shock protein 70; CK, Cytokeratin; GS, Glutamine synthetase; Arg-1, Arginase-1; TERT, Telomerase reverse transcriptase; PTEN, Phosphatase and tensin homologue deleted on chromosome 10; PI3K, Phosphatidylinositol 3-kinase; MDM2, Murine double minute 2; JAK1, Janus kinase-1; EGFR, Epidermal growth factor receptor; Hep Par-1, Hepatocyte paraffin-1; c-Met, Mesenchymal epithelial transition factor; VEGF, Vascular endothelial growth factor; ADC, Antibody drug conjugate.

* Corresponding author at: Department of Pharmacy, School of Chemical Sciences and Pharmacy, Central University of Rajasthan, Bandarsindri, Ajmer, Rajasthan 305817, India.

E-mail address: umeshgupta@curaj.ac.in (U. Gupta).

https://doi.org/10.1016/j.bbagen.2023.130443
Received 15 February 2023; Received in revised form 4 August 2023; Accepted 9 August 2023

Send Orders for Reprints to reprints@benthamscience.net

Current Drug Metabolism, 2022, *23*, 708-722

REVIEW ARTICLE

Surface Engineered Dendrimers: A Potential Nanocarrier for the Effective Management of Glioblastoma Multiforme

Rakesh Kumar Sahoo[1], Tanisha Gupta[1], Sanya Batheja[1], Amit Kumar Goyal[1] and Umesh Gupta[1,*]

[1]*Department of Pharmacy, School of Chemical Sciences and Pharmacy, Central University of Rajasthan, Bandarsindri, Ajmer, Rajasthan 305817, India*

ARTICLE HISTORY

Received: March 07, 2022
Revised: April 25, 2022
Accepted: May 18, 2022

DOI:
10.2174/1389200223666220616125524

Abstract: Gliomas are the most prevailing intracranial tumors, which account for approximately 36% of the primary brain tumors of glial cells. Glioblastoma multiforme (GBM) possesses a higher degree of malignancy among different gliomas. The blood-brain barrier (BBB) protects the brain against infections and toxic substances by preventing foreign molecules or unwanted cells from entering the brain parenchyma. Nano-carriers such as liposomes, nanoparticles, dendrimers, *etc*. boost the brain permeability of various anticancer drugs or other drugs. The favorable properties like small size, better solubility, and the modifiable surface of dendrimers have proven their broad applicability in the better management of GBM. However, *in vitro* and *in vivo* toxicities caused by dendrimers have been a significant concern. The presence of multiple functionalities on the surface of dendrimers enables the grafting of target ligand and/or therapeutic moieties. Surface engineering improves certain properties like targeting efficiency, pharmacokinetic profile, therapeutic effect, and toxicity reduction. This review will be focused on the role of different surface-modified dendrimers in the effective management of GBM.

Keywords: Glioblastoma multiforme, surface engineering, dendrimers, PAMAM, PLL, PPI.

1. INTRODUCTION

Gliomas are the most prevailing intracranial tumors, commonly observed among adults. They are also known as aggressive intra-axial brain tumors due to the rise within the brain's substance and often mix with normal brain tissue [1]. It accounts for approximately 36% of primary brain tumors of glial cells that encompass and aid neurons in the brain [2]. Among the other forms of gliomas, glioblastoma multiforme (GBM) accounts for a higher degree of malignancy. GBM is a malignant CNS tumor from glial cells, predominantly expressed by astrocytes. Histologically, it can be identified by cellular polymorphism, nuclear atypia, increased mitotic activity, microvascular proliferation, and necrosis. According to the revised WHO 2016 classification, GBM is a grade IV malignant diffuse glioma, which is classified into three categories, *i.e*. GBM, IDH wild type; GBM, IDH-mutant (also termed as secondary GBM); and GBM, NOS (not otherwise specified). The primary GBM (about 90% of cases) is observed in patients above 55 years of age [3]. In comparison, secondary GBM (about 10% of cases) is observed in younger patients with a history of primary low-grade diffuse gliomas [4]. GBM and NOS are not specific and reported for those tumors for which IDH evaluation cannot be performed.

Primary GBM is generally located in the supra-tentorial region and is rarely observed in the cerebellum and the spinal cord [3]. The cerebellar tumor has a reported low survival rate compared to the supratentorial region [5]. The population-based analysis (2005 to 2015) also found increased chances of survival with effective treatment. The treatment of GBM indulges palliative treatment, surgical resection, radiotherapy, chemotherapy, and tumor treating fields (TTF) therapy [6, 7]. Surgical resection is the most commonly employed therapy, having a mean survival rate of 10-16 % for 5-year and 3-year, respectively. While chemotherapy is the second most common treatment against GBM, comprising temozolomide as a drug of choice with a mean survival duration of 14 months. The recurrence of GBM can be prevented by using palliative treatments (corticosteroids), TTF therapy, and inhibition of angiogenesis (using bevacizumab) [7]. Recently, molecular and gene targeting has been explored as a potent treatment against GBM. Various receptor-mediated cellular pathways are directly or indirectly involved in the regulation of cell proliferation, survival, differentiation, and angiogenesis. Some primary receptors having an essential role in the management of GBM are epidermal growth factor receptor, vascular endothelial growth factor receptor, platelet-derived growth factor receptor (PDGFR), *etc*. [8].

Nanotechnology-mediated approaches have shown remarkable results in treating GBM. Dendrimers exhibited excellent drug targeting with enhanced selectivity. This review will be focused on the role of different surface-modified dendrimers in the effective management of GBM.

2. CHALLENGE: THE BLOOD-BRAIN BARRIER

The blood-brain barrier (BBB) is a unique structural component composed of a network of brain endothelial cells connected by tight junctions to the neurovascular unit. The neurovascular unit is composed of proteins such as occludins, claudins, and junctional adhesion molecules. The BBB is situated between the blood compartment and the brain to obtain the proper functioning of the neurons. BBB protects the brain against infections and toxic substances by preventing foreign molecules or unwanted cells from entering the brain parenchyma. The integrity of BBB alters and disrupts under various pathological conditions such as sclerosis, brain cancer, AIDS, *etc*. The alteration in the barrier evoked by GBM usually results in a disrupted and leaky BBB. Hence, the local rupture of BBB may cause a hypoxic environment and angiogenesis, leading to the abnormal functioning of BBB. The disruption of BBB causes the proliferation of malignant cells inside the normal brain cell that can be assessed by contrast accumulation within the tumor cell

*Address correspondence to this author at the Department of Pharmacy, School of Chemical Sciences and Pharmacy, Central University of Rajasthan, Bandarsindri, Ajmer, Rajasthan-305817, India;
E-mails: umeshgupta175@gmail.com; umeshgupta@curaj.ac.in

1875-5453/22 $65.00+.00