Recent advances in targeted therapy of colorectal cancer: impacts of monoclonal antibodies nanoconjugates

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Article Info

Summary

Despite rapid advances in diagnostic and treatment approaches, the overall survival rate of cancer has not been improved. Colorectal cancer (CRC) is recognized as the third leading cause of neoplasm-related deaths worldwide, in large part due to its considerable metastasis and drug resistance. For developing new anticancer strategies, rapid progression of multimodal nanomedicines and nanoconjugates has provided promising treatment modalities for effective therapy of cancer. The limitations of cancer chemotherapy might be overcome through the use of such nanosized therapeutics, including nanoconjugates of monoclonal antibodies (mAbs) along with drugs and organic/inorganic nanoparticles. CRC cells express various molecular markers against which mAbs can be designed and used as targeting/therapeutic agents. This editorial highlights the importance of such targeted nanosystems against CRC.

Authors' Biosketch

Mostafa Akbarzadeh Khiavi M.Sc., is a Ph.D. candidate in medical genetics at Liver and Gastrointestinal Diseases Research Center (LGDRC) and Research Center for Pharmaceutical Nanotechnology (RCPN), under the mentorship of Prof. M.H. Somi and Prof. Y. Omidi, working on the development of advanced nanoformulated enzyme/antibody used for the targeted drug delivery. Presently, he is involved in projects for the delivery of targeted ribonuclease nano-enzyme by monoclonal antibody for solid tumor therapy.

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Colorectal cancer (CRC) ranks as the third most prevalent cancer globally and the second potent cause of cancer-associated deaths in developed countries.[1] Different strategies such as chemotherapy, surgery, radiation therapy, and immunotherapy, as well as nutritional-supplement therapy have been employed for CRC treatment.[2] However, these approaches are accompanied with certain pitfalls and restrictions such as bleeding, rash, nausea, diarrhea, neuropathy, hair loss, healthy cells damages, and decreased bioavailability of high molecular weight chemotherapeutic agents, as well as drug resistance.[3] Moreover, several parameters such as the lack of efficiency and selectivity in drug delivery systems, drug influx and efflux, metabolic alterations, drug sequestration or repossession, disruption of apoptotic pathways, and certain changes in signal transduction pathways, as well as activation of DNA repair mechanisms can lead to the development of drug resistance.[4] Regarding these limitations, the development of effective site-specific drug delivery systems are required to prevent the growth, progression, and spread of cancer, and to leave out all rapidly dividing cells.[5,6] In solid tumors such as CRC, the cancer cells for a permissive microenvironment (TME: tumor microenvironment),[7,8] within which they represent higher ability to overexpress the molecular markers and receptors including vascular

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endothelial growth factor (VEGF), epidermal growth factor receptor (EGFR), epithelial cell adhesion molecule (EpCAM), insulin-like growth factor 1 receptor (IGF-1R), death receptor (DR5), mucin 5AC (MUC5AC), alpha v beta 3 integrin (aVb3 integrin), Human epidermal growth factor receptor-2 (HER2/neu), and Cytotoxic T-Lymphocyte Associated Protein 4 (CTLA-4) on their cell membranes compared to normal cells. Therefore, the active targeting approaches would provide beneficial results in cancer therapy.[9-11] Following the activation of these transmembrane receptors, multiple intracellular signal transduction pathways are stimulated, which finally lead to cell proliferation, dedifferentiation, and inhibition of apoptosis, as well as the induction of neoangiogenesis.[12]

VEGF and EGFR are two key molecular markers and receptors in the growth and dissemination of tumors especially CRC.[13, 14] EGFR expression has been observed in almost 70% of human colorectal carcinomas [15] and VEGF is minimally expressed in approximately 50% of CRCs. However, these receptors have a comparatively lower expression in normal colonic mucosa and adenomas.[16] The VEGF and EGFR share common downstream signaling pathways. Moreover, the epidermal growth factor (EGF) has the potential to trigger the expression of VEGF.[17]

Regarding that VEGFR and EGFR play pivotal roles in tumor progression, invasion, and metastasis, their signaling pathways can be potential and feasible targets for pharmacologic intervention in solid tumors. Moreover, they have the great potency to be employed in targeted drug delivery systems against CRC.[18, 19]

Recently, interests have been focused on an important molecular marker namely DR5 as a target in cancer therapy.[20, 21] DR5 overexpression in CRCs has been substantiated in some studies.[22, 23] Specific bio-molecular approaches to CRC therapies provided considerable relevance in an attempt to find a more selective action in the last few years.[24] The present targeting moieties are categorized in two groups; the first one is monoclonal antibodies (mAbs), which bind to the ligand or the external domain of a receptor, and the second one is small-molecule tyrosine kinase (TK) inhibitors that recognize TK domain in the intracellular part of the receptor. These targeting molecules hinder the TK receptors-generated signaling pathways that are essential for the growth of tumor cells.[25] MAbs are favorable tools owing to their specific targeting and powerful anticancer functions and happen via several mechanisms.[10] Among mAbs, only cetuximab, bevacizumab, and panitumumab have been authenticated for CRC treatment in the USA; while many others are still undergoing clinical trials.[26, 27] Targeting mAbs affect tumor cells through multiple mechanisms. They can perturb tumors growth signaling pathways by altering the activation state of membrane-bound receptors or neutralizing cytokines that are essential for cellular growth and proliferation. Furthermore, the binding between the Fc portion of Abs and Fc receptor

(FcR) present on immune effector cells takes part in an anti-tumor activity by stimulating antibody-dependant cell-mediated cytotoxicity (ADCC).[28]

MAbs display great ability to exclusively identify cancer cell-surface receptors.[29] Nevertheless, the applications of these biomolecules have been restricted due to some resistance (intrinsic or acquired) to the receptor inhibitors.[30, 31] For instance, studies have shown that anti-EGFR therapy has no beneficial effect on approximately 80% of unselected mCRCs, which indicates the prevalence of primary resistance to anti-EGFR therapy in CRC treatment.[32, 33]

To overcome these major complications, various forms of multidrug-resistant nano-based drugs have provided new opportunities due to their fast drug design, flexibility, and production based on genetic tumor profiles.[34-36] Investigators have unprecedentedly explored nanotechnology for synthesizing biodegradable nanoscale drug carriers with negligible side effects, which are able to specifically target tumor sites.[37] The goal of nanotechnology is to boost effective and reliable systems for precise diagnosis and anti-cancer therapy. Multifunctional diagnostic and therapeutic nanosystems (NSs) have been developed by arming NSs with various imaging probes, targeting agents [e.g., antibodies (Abs)/aptamers (Aps)], and enzymes.[13, 38] These targeted NSs are successfully being used for simultaneous detection and treatment of various cancers.[39, 40] Aps, as short length double/single-stranded DNA or RNA molecules, can bind to their specific biological targets (e.g., genes, peptides, proteins, and even cells) with high affinity. However, some problems of Aps such as less circulating half-life, renal filtration due to small size, and fast degradation by nucleases have to be solved before clinical applications.[41] In order to establish a targeting approach and to accomplish the aforementioned goal, bio-conjugation of nanoparticles (NPs) loaded with therapeutic agents by using mAb (Fig. 1) or their analogs have been considered both *in-vivo* and *in-vitro*.[42] Surface modification of NPs using specific ligand conjugation may eliminate nonspecific uptake of nanocarriers to tissues other than tumor ones.[13] These ligands have high specificity against receptors that are overexpressed on the surface of tumor cells, such as EGFR and VEGFR.[5, 43] Up to now, several mAbs and their nanoformulation by using liposomes, dendrimers, micelles, and polymeric, as well as inorganic NPs have been approved for clinical applications in CRCs (Table 1). It has been shown that the encapsulated celecoxib within the targeted liposome with mAbs has improved toxicity in EGFR-overexpressed cancer cells.[44] Furthermore, it has been demonstrated that targeted carbon nanotubes (CNTs) with cetuximab (EGFR-antibody) specifically binds to EGFR-expressing cells; besides, the cellular uptake of targeted CNTs were much higher than that of the negative control.[45]

Nanomedicine technology can provide different tools for developing new anticancer strategies and the
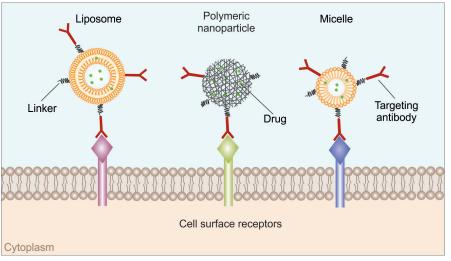
Fig. 1. Schematic illustration of monoclonal antibodies nanoconjugates.

Table 1. Monoclonal antibodies and their nanoformulations for colorectal cancer targeting

Name of mAb	Target	Formulation	Bioactives	Ref
Bevacizumab	VEGF	Mesoporous silica NPs	MiR-328	50
Cetuximab	EGFR	Magneto-fluorescent silica NPs (MFSN)	-	51
Panitumumab	EGFR	Platinum-Cored Apoferritin Nanocages	Oxaliplatin	52
Matuzumab	EGFR	Liposomes	Doxorubicin	53
Conatumumab	DR5	Poly (lactic-co-glycolic acid) (PLGA)	-	22
Trastuzumab	HER2/neu	Polycaprolactone- polyethylene glycol (PCL-PEG)	AMO-21 /5-Fu	54
Cetuximab	EGFR	Liposomes	Celecoxib	48
Cetuximab	EGFR	Micelles	IR-780 iodide	55
Cetuximab	EGFR	Carbon nanotubes	7-Ethyl-10-hydroxy-camptothecin	49
Adecatumumab	EpCAM	-	-	11
Dalotuzumab	IGF-1R	-	-	56
Drozitumab	DR5	-	-	57
Edrecolomab	EpCAM	-	-	58
Ensituximab	MUC5AC	-	-	59
Etaracizumab	αVβ3 integrin	-	-	11
Necitumumab	EGFR	-	-	60

limitations of cancer chemotherapy can be overcome through the utilization of nanotechnology-based therapeutics. For this objective, developing actively targeted nanotherapy against overexpressed molecular markers on the CRC cells utilizing the nanoformulation of therapeutic mAbs by nanocarriers can represent great potentiality. The employment of nanomaterials can improve the pharmacokinetic properties of anticancer agents and provide effective and selective treatment for multidrug-resistant cancers.

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Ethical statement
There is none to be declared.

Competing interests
The authors declare no competing interests.

Authors' contribution
MHS conceived the original idea and supervised the project. AS and MAK contributed to the conceptualization of the manuscript and to the overall writing and editing of the manuscript. MAK collected the data and drafted the manuscript. All authors discussed the contents and contributed to the final manuscript.

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