SITE-SPECIFIC DRUG DELIVERY BY USING MONOCLONAL ANTIBODIES: A REVIEW

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ABSTRACT:

Drugs administered systemically can have off-target effects, which have made it difficult to design and develop novel therapies with the best possible efficacy and therapeutic index. In these regards, there are high hopes for the development of site-specific drug delivery solutions. Over the past three decades, a significant amount of effort has been put into comprehending and overcoming the biological barriers that prevent targeted drug delivery and distracting: developing techniques to remove such difficult barriers. As a result of these efforts, several targeting techniques, such as antibody, nucleic acid, peptide, small molecule, and n cell-based approaches, have been developed that impact drug delivery in preclinical and clinical contexts. Specifically, either alone or in conjunction with strong payloads' activity and antigen-directed recognition to target specific cells, antibodies (Abs) and antibody-drug conjugates have become effective treatment modalities for a number of serious human illnesses, including cancer. Thus, we will concentrate on this site-specific collection of drug delivery systems in this chapter and provide an update on the noteworthy progress made in site-specific antibody-drug conjugate (ADC) and Ab-based drug delivery approaches toward their clinical application.

Keywords: Off Target effect, Monoclonal Antibodies, Peptides, Conjugates,distracting

INTRODUCTION:

Paul Ehrlich announced the discovery of antibodies at the start of this century[1]. Since then, numerous researchers have worked extensively in immunocytochemistry, radioimmunoassay, and clinical medicine, employing a broad range of antibody molecules. Somatic-cell hybridization was the technique used by Kohler and Milstein in 1976 to successfully create a continuous "hybridoma" cell line that could produce monoclonal antibodies (MAb) with a specified specificity[2]. A number of MAbs have since demonstrated target site specificity. Because of this characteristic, monoclonal antibodies (MAbs) are great options to transport therapeutic agents to targeted sites[3,4].
Antibody conjugation The field of chemotherapy has benefited most from drug targeting and delivery using antibodies[5,6]as this is an area of research in in which target-site specificity is most necessary. Specifically, anticancer medications frequently exhibit high toxicity and a low therapeutic index[7,8]

Simple covalent-bond coupling was used in early attempts to conjugate polyclonal antibodies with anticancer medications. For instance, the conjugation of methotrexate to antimouse leukemic antibodies for drug targeting was reported by Mathe et al.15 in 1958. Chlorambucil was combined with polyclonal goat or rabbit antitumor antibodies almost fifteen years later[9] Following this, studies on drug targeting were conducted with rabbit antibodies against a mouse lymphoma in combination with medications like daunomycin, adriamycin, melphalan, methotrexate, and chlorambucil. Drug-polymeric carrier complexes have also been linked to antibodies in related investigations. These polymeric carriers were developed by researchers at the Weizmann Institute in Rehovot, Israel, and they were successful in coupling platinum, cytosine arabinoside, and methotrexate to polyclonal and monoclonal antibodies (MAbs) against tumor targets in humans and animals[10] In the years 1980 through 1988, hybridoma Technology advancements were made. Through its application, complex molecules including serum proteins, hormones, neurotransmitters, tumor-specific antigens, developmental and differentiation antigens, and various types of receptors were identified, isolated, purified, quantified, and biochemically characterized. Additionally, the corresponding antibodies were made available for targeting to specific sites[11,12]

Production of monoclonal antibodies:

Immunoconjugate-based targeting has been expanded due to the early success of hybridoma technology, particularly in the detection and treatment of human tumors[13] Rowland provided a method for determining which antigens are connected to hematological cancers. Additionally, he underlined that when testing antibodies for therapeutic immunotargeting, the selection of normal cells and the screening procedure are crucial[14-17]The procedure outlined by Brown et al. (2019) for the generation of monoclonals with anticancer targeting is generally recognized, as it involves using the proper kind of malignant cell as the immunogen. The following is a brief description of the step-by-step traditional small-scale culture processes commonly used to create hybridomas using hybridoma technology[18,19]

1.A mouse is given an injection of the antigen, which is a foreign material like a lung cancer cell. The lung cancer cell is identified by the mouse immune system as alien, and it is this recognition that prompts the spleen to generate particular antibodies targeted at the antigen. After that, the spleen is removed, and the cells that make antibodies are gathered.
2. A mouse tumor is used to isolate myeloma cells. In the lab, these cells are capable of perpetual replication.
3. Tumor and spleen cells combine to create "hybridomas." To eliminate the tumor cells that don't merge, a medication is administered. The tumor cell's ability to proliferate and the spleen cell's capacity to make antibodies are shared by the hybridomas that have survived.
4. To make a single MAb, each hybridoma is separated and given the opportunity to develop into a sizable colony of cells.
5. The capacity of each monoclonal antibody (MAb) to destroy the original cancer cells is tested, and the hybridomas that yield the appropriate antibody are retained.
6. After being injected into a mouse, the intended hybridoma cells develop into a tumor that secretes a lot of concentrated antibodies.

After initial isolation, producing the antibody product is a crucial first step towards developing a therapeutic or diagnostic MAb. A technique for microencapsulation has been developed by Needham Heights, Massachusetts-based Damon Biotech to generate large amounts of therapeutic monoclonal antibodies. This delicate chemical technique, called the Encapsel method, forms a semipermeable membrane around a cluster of hybridoma cells. These cells multiply quickly within the microcapsule membrane, secreting the MAb. After two to three weeks of incubation, the antibody is extracted from the intracapsular region. Drug-monoclonal antibody combinations for targeted drug delivery

Principles:

It has been researched for more than 20 years to use MAbs to target cytotoxic medications to particular tissues[20-22] It has been discovered that antibodies are useful in treating a wide range of human cancers, including colorectal, gastric, ovarian, endometrial, breast, lung, and pancreatic cancers[23-25] Considerations for evaluating the use of monoclonal antibodies (MAbs) in cancer treatment have been compiled by Schlom in his publications on cancer therapy[26,27]

Here is a summary of them: Tumor mass size; antigen-antibody complex fate (stability on cell surface, internalization, capping, shedding); degree of tumor vascularization; degree of tumor mass infiltration and necrosis; presence and reactivity of circulating antigen in the blood; number of antigen molecules per cell surface; number of cells expressing the reactive antigen in the tumor mass; length of time that monoclonal antibody (MAb) binds to the cell surface; immunoglobulin isotype (IgG subtypes or IgM); species of immunoglobulin (human, murine, or chimeric recombinant); whole immunoglobulin or fragments (Fab, Fab', F(ab')2); removal of MAb from blood, excretion, or reticuloendothelial system; dose of MAb utilized; route of inoculation of MAb (intravenous, intraperitoneal, intralymphatic, or intraarterial); and emergence of a human immune response. When using a radiolabeled monoclonal antibody (MAb), certain factors need to be taken into account. These include the MAb's capacity to be labeled with a particular radionuclide, its specific activity, its affinity, the depth of the tumor from the body surface (for tumor localization), the scanning time (for tumor localization), the radionuclide of choice, and the method of linking the radionuclide to the MAb (metabolism and MAb-radionuclide complex catabolism), as well as dose fractionation of given MAb.[28]

A number of criteria have been listed by Widder et al.[29] for the perfect carrier.

Drug antibody bonding:

Lysine residues occur abundantly in immunoglobulins, with the epsilon amino side chain, the commonly preferred site for drug conjugation.[30] Binding of a drug to the epsilon amino group of the immunoglobulin near its carboxylic acid group forms a carboxamide bond. If the drug's carboxylic acid group is not responsible for its pharmacological action, then conjugation should not affect efficacy. In studies using chlorambucil, the formation of an ionic complex and not a covalent link is also possible. Gallego et al. have reported that a cis-aconityl linkage gives rise to a stable conjugate in the case of daunomycin and amino sugars.[31]

Drawing general conclusions about drug-to-antibody coupling methods when using monoclonals is fraught with difficulties since one monoclonal antibody may behave quite differently from another. This is evident from the studies using an active azide derivative of a vinca alkaloid to produce vindesine-monoclonal antibody conjugates. [32]

It has also become clear that when highly homogeneous monoclonal preparations are used in experi_ments, each antibody needs to be evaluated individually for any particular type of drug-coupling procedure requiring chemical manipulations.[32] Similar conclusions have been reached when attempting to couple cytosine arabi_noside to a MAb recognizing a human T cell. [33]

Recent studies with monoclonal antibodies

Highlights of current research:

Several investigators have prepared "second-generation" MAbs. In this process, the MAb first evaluated was used to purify the target antigen, which was then used as an immunogen to prepare a new generation of MAbs that were reactive with that molecule. However, a priori reasons exist for the assumption that the first MAb directed against a given tumor antigen will be the best. Amino acid sequence data obtained from purified antigen of DNA sequences obtained from cloned genes that code for these antigens provide sufficient information for the preparation of synthetic peptides and the subsequent development of MAbs of predefined specificity .A conjugate of a MAb and the anticancer agent desacetyl vinblastin has been found to recognize lung, colorectal, breast, ovarian, and prostate tumors.[34]

MAbs have also been used in trials designed to control the common cold. In this case, the MAbs do not attack the cold virus directly. Instead, they interact with receptors on the surface of the epithelial cells lining the nasal passages. By blocking these receptors, the MAbs prevent viral entry.[35] Antigenic heterogeneity has been a major consideration in the therapy of solid tumors. Unlike many antigens that are associated with leukemias, lymphomas, and melanomas, many of the oncofetal antigens associated with pancarcinomas are not always expressed in all cells within a given tumor mass. Studies have demonstrated that recombinant a-(clone A), b-ser, and g-interferons can regulate the expression of certain tumor-associated antigens, such as CEA and TAG-72. These studies have also shown that when cells do not express CEA or TAG-72 as in the case of normal cells and noncarcinomas, such as melanoma the exposure of these cells to recombinant interferons does not affect antigen expression. It

has also been reported that interferons can up-regulate tumor targeting of radiolabeled MAbs in an in vivo animal model and in clinical trials. Preclinical studies have demonstrated that recombinant interferons can increase both the amount of tumor antigen expressed by a given tumor cell and the percentage of tumor cells that express the antigen. Thus, together with MAb combinations, radionuclides can kill several cell diameters, and the use of recombinant interferons and antigenic heterogeneity of tumor masses can be addressed. 74 I125-labeled MAb B72.3 has been used in radioimmunoguided surgery (RIGS) to localize up to 70% of colorectal carcinoma lesions. Significantly, RIGS also reportedly identified tumors not detected by conventional surgical procedures in 20% of the cases. The RIGS diagnostic procedure also identifies those patients whose tumors are targeted by a given MAb; therefore, the procedure can be used to select patients who are more likely to respond to a specific MAb therapy.[36]

Another drug that has been experimentally piggybacked on MAbs is urokinase, the thrombolytic agent. Urokinase is not a clot-specific agent — it causes the breakdown of fibrinogen, a property that leaves open the possibility of major bleeding problems in patients. Laboratory workers have now succeeded in attaching urokinase to antibodies against fibrin.[37] The method for dissolving blood clots that cause myocardial infarction is based upon a specially designed MAb that activates clot-dissolving chemicals only at the site of the clot. In theory, the new technique should dissolve blood clots with less risk of bleeding occurring in other parts of the body, as can happen with current clot dissolvers. It also could reduce or even eliminate the use of manufactured clot dissolvers, utilizing instead clot-dissolving substances naturally present in the body. The basic strategy behind this is to take the antibody that interacts with fibrin and use it to concentrate the natural clot dissolver directly on the clot. One major natural clot dissolver is known as tissue plasminogen activator, or TPA. TPA activates plasminogen that ordinarily lies latent in the blood. Once activated, plasminogen triggers a chemical chain reaction that destroys fibrin and dissolves the blood clot. Current artificially produced versions of the clot dissolvers are infused into the bloodstream where they promote a freer flow of blood throughout the body. However, this is done at the risk of causing hemorrhage, something that should be minimized by the antibody, which should trigger the clot-dissolving reaction only in the vicinity of the clot.[38] Other examples of studies using MAbs include agents such as immuno_absorbents, hypolipemics, cytokines, porphyrins, antiferritin, and Techni_clone (Lym-1). In addition, significant products involving the use of recom_binant technology and genetic engineering are: Recombivax HB (a recombinant hepatitis-B vaccine), kidney plasminogen activator, Eminase (anisylated-plasminogen-streptokinase-activator complex),alpha-2 inter_feron (Intron A), alpha-A interferon (Refron-A), beta interferon (Betaseron), alpha-1 antitrypsin (AAT), and Activase (recombinant version of t-PA).[38] The IgG murine MAb Alz-50 has been derived from a mouse immunized with homogenates of postmortem ventral forebrain tissue from four patients with Alzheimer’s disease. Hybridoma cell-culture supernatants were ini_tially screened based on the comparison of their binding to Alzheimer’s brain homogenates immobilized onto polyvinyl plates with identically prepared control homogenates. Alz-50 was described as recognizing an antigen in the affected region of the Alzheimer brain that was elevated 15 to 30 times. Immunocytochemical analysis of the antibody revealed it labeled Alzheimer neurofibrillary tangles, as well as selective neuronal populations.[39]

Many procedures have been reported for coupling anthracycline drugs to an antibody for drug targeting. A recent report describes a new coupling procedure that uses an activated daunorubicin derivative that is later added to the antibody. Utilizing this procedure produced no significant polymerization of the conjugate and a full recovery of pharmacological activity as tested in vitro on CEA-producing human colon adenocarcinoma cells. Acti_vated drug was found stable for one week at 25∞C, and the coupling proce_dure is highly reproducible.[40]Molecules, such as antibodies that bind to cell surfaces, can be used to deliver cytotoxic drugs to selected cells. To be effective, the drug must usually be taken into the cells by endocytosis. Yemul et al. have reported that a T-cell line (CCRF-CEM) was effectively suppressed by liposomes carrying a photosensitizer and bearing the antibody OKT4 (anti-CD4).[41] A procedure has also been described whereby a photosensitizer, benzoporphy_rin-derivative monoacid ring (BPD-MA), is covalently linked to a MAb in a manner that is reproducible, quantifiable, and retains both the biological activity of the antibody and the cytotoxicity of the photosensitizer. Prelimi_nary steps involve linking BPD-MA to a modified polyvinyl alcohol (PVA) backbone, followed by conjugation to the antibody using heterobifunc_tional-linking technology.[42]

Specific binding to human ovarian adenocarcinomas of a drug-antibody conjugate (daunorubicin DNR-OC-125) made from a new analog (PIPP-DNR) of daunorubicin that chemically links the drug to monoclonal antibodies has been studied. Immunofluorescence data show that the DNR-OC-125 conjugate has high affinity and specificity for proliferating malignant cells from human ovarian tumors. The results further demonstrate that the DNR-OC-125 conjugate retains specific binding to CA-125 antigenic sites characteristic of the OC-125 monoclonal antibody moiety. The DNR-OC-125 conjugate selectively binds to CA-125 antigen-positive ovarian cancerous tissue in both cryostat and paraffin-embedded tissue sections. These results indicate that the OC-125 monoclonal antibody can serve as a cancer-targeting carrier for daunorubicin and its analogs.[43] Cis-diamine di-chloro platinum (II) (Cis-Pt) has been complexed to a carboxymethyl dextran-avidin conjugate and targeted to biotin-monoclonal antibody 108(b-MAb108). This MAb recognizes the extracellular domain of the epidermal growth-factor receptor. The results presented in this prelimi_nary investigation suggest that Pt-dex-Av is specifically removed from the circulation by b-MAb108 concentrated at the tumor site.[44] 5-Fluorouridine (FUR), an antineoplastic agent, has been conjugated to the carbohydrate moiety of an anticarcinoembryonic antigen (CEA) MAb by using amino-dextran as the intermediate carrier. In the GW-39/nude mouse model, the conjugate remains efficient in targeting the human colonic tumor and possesses greater inhibitory growth effects on this subcutaneous tumor than free FUR or an irrelevant antibody conjugate. In addition, reduced host toxicity of the conjugate may permit its use in a high-dose therapy of this tumor system. [45]

Polyethylene glycol (PEG) modification of the MAb A7 has been found to enhance tumor localization. The F(ab')2 fragment of murine MAb A7 has been covalently bonded. PEG and the conjugate have been compared to the parent F(ab')2 fragment in in vitro and in vivo studies. PEG-conjugated antibody fragment was found to retain its antigen-binding activity in a competitive radioimmunoassay. The conjugate had a longer half-life and showed increased accumulation in tumors. Although the tumor:blood ratio for the parent F(ab')2 fragment was higher than that for the conjugate, it later showed a higher value than the whole MAb A7. Tissue:blood ratios were kept low with the conjugate,

indicating that it was taken up in normal organs to a lesser extent as compared with the parent F(ab')2 fragment. These findings indicate that the PEG-conjugated F(ab')2 fragment may be a prom_ising carrier for use in targeting cancer chemotherapy[46] The pharmacokinetics of a disulfide-linked conjugate of a murine mono_clonal antibody A7 with neocarcinostatin (A7-NCS) has been studied follow_ing its intravenous administration to nude mice. The conjugate was removed from the blood circulation with a half-life of 12 hr, showing nearly the same kinetics as the free antibody. A7-NCS remained stable in the circulation and able to reach the target tumor without releasing significant free NCS.[47]

N-(2-Hydroxypropyl)methacrylamide (HMPA) copolymers have seen extensive development as lysosomotropic drug carriers. They can be used for site-specific drug delivery by incorporation of appropriate targeting groups. Specifically, they have been conjugated to antitumor MAbs murine IgG, antibody 872.3, and its F(ab') and F(ab')2 fragments. Conjugates were synthesized containing an average of 5 copolymer units (MW 20kD) per antibody molecule and achieved prolonged circulation in the bloodstream.[48]Three novel prodrugs have been designed for use as anticancer agents. Each is a bifunctional alkylating agent that has been protected to form arelatively inactive prodrug. These prodrugs are designed to be activated to their corresponding alkylating agents at a tumor site by prior administration of an antitumor antibody conjugated to the bacterial enzyme carboxypeptidase G2 (CPG2) in a two-phase system called antibody-directed enzyme prodrug therapy (ADEPT). The potential of a tumor-localized bacterial enzyme to activate protected alkylating agents in order to eradicate an established human xenograft has been demonstrated.[49]

Murine MAb A7 directed against human colon cancer has been chemically modified using methoxypolyethylene glycol (MPEG). A high substitution of PEG molecules on MAb A7 produces a progressive reduction in antibody-binding activity. The pharmacokinetic and immunological properties of MPEG-modified MAb A7 and the MPEG-modified F(ab')2 fragment, which retained their antibody-binding activity, have been compared with parent MAb A7 and the F(ab')2 fragment. Blood clearance of MPEG-modified antibodies appears to be diminished by MPEG modification and fits a two-compartment model. Low MPEG-substituted MAb A7 showed less organ uptake in the liver and spleen and similar uptake in the lung and kidney when compared with the parent MAb A7. Both preparations exhibited less tissue:blood ratios in all respective organs as compared with parent antibodies. Tumor localization was enhanced by MPEG modification of the F(ab')2 fragment, but not by MPEG modification for the whole MAb A7. Multiple intravenous administrations of MPEG-modified antibody to rabbits did not appear to elicit a measurable immune response. In conclusion, MPEG-modified antibodies are promising reagents as drug carriers to the target tumor.[50]

Two murine MAbs have been produced to losartan (DuP 753), a nonpeptide angiotensin II receptor antagonist. Using a solid-phase competitive enzyme-linked immunosorbent assay (ELISA), each antibody was examined for its ability to bind to a set of losartan analogs that differ structurally to varying degrees. Both antibodies distinguished fine structural changes in the analogs, particularly at the R5 position of the imidazole ring. No cross-reactivity toward either antibody was observed with the natural ligand angiotensin II, the peptide antagonist saralsin, or the AT2 selective nonpep_tide antagonist.[51]

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