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REVIEW OPEN ACCESS

Novel Techniques for Small Molecule-Based Drug Delivery in Cancerous Tissue: A Literature Review

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Abstract

Introduction: Small molecule cancer drugs target rapidly growing cancerous and healthy cells, leading to negative side effects. Due to the broad effects of small molecule drugs (SMDs), particularly on healthy cells, researchers have established methods such as altering lipophilicity, introducing drug conjugates, and nano-based drug delivery methods to diminish side effects.

Methods: Relevant biomedical literature between 1991 to 2021 was obtained using Medline PubMed. Search terms were "physicochemical properties", "nanotubes", "liposomes", and "small molecule drug conjugates". Literature was selected based on pertinency after assessing the abstracts.

Results: Properties such as a drug's lipophilicity influence most SMD's promiscuity. Controlling the hydrophobic features of lipophilic drugs within optimal ranges increases their specificity, half-life, and aqueous solubility. However, the narrow optimal range of lipophilicity makes it challenging to observe noticeable effects without reducing therapeutic effects. SMD conjugates improve drug delivery using a targeting ligand, and a therapeutic payload. The targeting ligand ensures greater binding to receptors on target tissues, such that a lower dose of a drug is required, thereby decreasing toxicity. SMD conjugates are non-immunogenic and have lower molecular weights, allowing for greater entry into solid tumours. Several nanomedical approaches have been developed to improve drug delivery. Carbon nanotubes, which exploit the enhanced permeability and retention effect, increase the accumulation of the drug at the cancerous tissue. Another method involves the use of liposomes, which exhibit high biocompatibility with cell membranes, low toxicity, and capability to carry hydrophobic as well as hydrophilic molecules.

Discussion: While said novel therapies show increased targeting effects and decreased toxicity, notable limitations exist. Some SMD chemotherapeutics with high lipophilicity has been linked to adverse side effects. Conversely, lower lipophilicity ranges may reduce the permeability and potency of the drug. Alternatively, select SMD conjugates display poorer bioavailability, quick clearance, and multidrug resistance. Moreover, the toxicity of carbon nanotubes is not entirely deduced which may be associated with negative side effects.

Conclusion: This systematic review emphasizes the importance of novel drug delivery systems to mitigate the toxic effects of small molecule cancer drugs through changes in lipophilicity, the introduction of drug conjugates, and nano-based drug delivery methods.

Keywords: lipophilicity; pro-drug; liposome; physicochemical properties; small molecule-drug conjugates; drug-nanotubes; drug design; cancer-targeted

Introduction

Currently, cancer is the second most prevalent disease in all of North America [1]. This group of diseases is characterized by rapid and uncontrollable cell growth and resistance to death [2]. At present, the primary treatment of metastatic cancers involves the administration of anti-cancer drugs such as chemotherapy, hormone-based, and biologics therapy [1]. One of the most traditional cancer treatments is small molecule drugs, which are generally defined as synthetic compounds with a molecular weight below 1-1.5 kDa [3,4]. Due to their size and simple chemical structures, these compounds have more predictable pharmacokinetics and pharmacodynamics when compared to treatments like biologics [4]. However, SMDs are associated with a range of off-target effects which decrease efficacy and are associated with numerous side effects [5]. One approach to increase the efficacy of these drugs is to increase their delivery to target sites. The most notable progress in the development of

SMDs and targeted drug delivery involves the modifications to drug lipophilicity, small molecule drug conjugates (SMDCs), and nanomedicine.

Lipophilicity, which is defined as the compound's affinity for nonpolar environments, has been shown to greatly influence the target specificity and selectivity of SMDs [5]. Lipophilicity contributes, among other things, to a drug's absorption, distribution, metabolism, excretion, and toxicity (ADMET) profile [5,6]. This is important as the ADMET profile deals with pharmacokinetics of a proposed drug candidate and ultimately helps scientists evaluate its efficacy and safety [7].

Furthermore, research in precision medicine has led to the development of SMDCs, an alternative and more modern approach to antibody drug conjugates (ADCs) [8-10]. SMDCs are composed of a targeting ligand, a linker, and a therapeutic payload [11]. The targeting ligand works to bind to specific elements of target tissues, often with very high affinities, allowing for the therapeutic payload to be delivered directly to the tumour [12-15]. The low molecular weight of SMDCs allows for greater penetration into cancerous tissue to yield greater therapeutic effects and mitigate the negative effects of cancer chemotherapeutics due to the nature of the specific delivery [16,17].

Since their development in 1991, carbon nanotubes have increasingly gained research interest as small-molecule drug carriers. Several properties have distinguished carbon nanotubes from other small-molecule drug carriers. Carbon nanotubes appear in two forms which cater to different applications. Carbon nanotubes can either be single walled, consisting of a single cylindrical graphene sheet, or be multi-walled tubes, consisting of several cylindrical graphene sheets [18]. Their high surface areas make them perfect candidates for targeted drug carriers [19]. The highly efficient translocation mechanisms of carbon nanotubes across the plasma membrane equip them with the advantage of overcoming the low permeability of the plasma membrane to many drugs [19,20].

This work presents a brief literature review on the various techniques by which drug delivery systems have been altered to increase the efficacy of small-molecule drugs for cancer treatment, including altering lipophilicity, introducing drug conjugates, and utilizing nano-based drug delivery methods to diminish side effects of chemotherapeutic agents.

Methods

Search Strategy

Relevant publications published between 1991 to 2021 were obtained through a computerized search through MEDLINE PubMed. Search terms included "small molecule drugs" followed by "lipophilicity" OR "physicochemical properties," OR "nanotubes," OR "liposomes," OR "conjugates". In doing so, 4551 results were obtained, however using the selection criteria, 3367 results were excluded. Literature was selected based on relevance following abstract screening.

Selection Criteria

The selection criteria for the included articles were as follows:

- The full report was published in English.
- Only full reports were selected. Letters, abstracts, books, conference proceedings and posters were excluded.
- Both primary and review articles were selected.

Results

General Overview of Lipophilicity

Many new drug candidates have poor water solubility, selectivity, and bioavailability. In fact, it is often one of the main barriers preventing drugs from reaching the market [21]. There are a variety of techniques employed by scientists to circumvent this issue, one of which is altering the characteristics of a drug's physicochemical profile, such as its lipophilicity. There is strong evidence to suggest that controlling for a drug's lipophilicity can improve its selectivity and potency [5]. Moreover, this physicochemical parameter is of particular importance, especially in the early stages of drug design. Lipophilicity contributes to the ADMET profile of a drug, thus selecting drug candidates with favorable ADMET profiles can increase the likelihood of therapeutic success [5].

Measuring Lipophilicity

Typically, lipophilicity is measured by its partition coefficient (logP) or distribution coefficient (logD), that is its disbursement between two immiscible solvents. There is an optimum region of lipophilicity [21-23]. A drug with high lipophilicity exhibits poor solubility and absorption, whereas drugs with low lipophilicity exhibit poor potency and selectivity [24]. It is believed that the optimal region of lipophilicity is between the narrow range of 1-3 for logD and 0-3 for logP [5]. Alternatively, lipophilicity predictive models, such as the shake flask method, can be used in lieu of experimental determination [21,22].

Strategies Used to Improve Lipophilicity

There exists a strong correlation between a drug's lipophilicity and promiscuity, which is why the development of lipophilic compounds for cancer treatment has been widely studied over the past several decades. The use of lipophilic pro-drugs is an example of this strategy. A pro-drug is a small targeting moiety added to a drug of interest, which allows it to be selectively activated in a given environment [25]. The pro-drugs undergo a process called biotransformation mainly in the liver, where they are transformed, by chemical or enzymatic cleavage, whereby the active form is released [25]. Pro-drugs are typically used to improve target specificity and selectivity [25]. Over the years, many lipophilic pro-drugs have been developed to

treat different types of cancers more effectively. An example of this includes chemotherapeutic drugs developed by Mattarei et al (2018) [26]. This group of researchers were attempting to target cancer cells by exploiting one of its intrinsic features: an elevated level of reactive oxygen species (ROS). The researchers were attempting to stress the cancer cells to death by inhibiting mtKv.13, a mitochondrial potassium channel, which has been shown to contribute to apoptosis in various cancer cell lines [26]. To do so, they combined triphenylphosphonium (TPP), a lipophilic pro-drug, to several PAP-1 (5-[4-phenoxybutoxy] psoralen) derivatives [26]. The drug becomes active after its carbamate group is hydrolyzed in a physiological environment [26]. The synthesized drugs in question were permeable to the mitochondrial membrane in both *in vitro* and *in vivo* cell models [26]. Moreover, they induced a cytotoxic effect in cancer cells, whilst leaving no significant impact on healthy human and mouse cells [26].

Liposomal drug delivery systems are another method employed by scientists to improve the lipophilicity. Liposomes themselves consist of an amphipathic bilayer lipid membrane [27]. Scientists encapsulate the hydrophilic/hydrophobic drugs into the liposomes, and the liposomes themselves facilitate the entry into the target cells by fusing with their membranes [27]. An example of this includes curcumin nanoliposomes. Curcumin is a natural anti-inflammatory compound, but by itself, curcumin has low water solubility and low bioavailability [28]. To circumvent this issue, Chen et al. (2015) employed the use of nanoliposomes, which are nanoscale bilayer lipid membranes [28]. The drug derivatives' stability, cellular antioxidant activities and cellular uptake capacity were evaluated against different ionic conditions [28]. The stability of the encapsulated curcumin improved and exhibited similar cellular antioxidant activity compared to its free form. In sum, lipophilic carriers such as liposomes and nanoliposomes have proven themselves to be effective agents to assist in the cellular and tissue uptake of a given drug.

General Overview of SMDCs

Traditional chemotherapeutic drugs often lack tumour specificity which contributes to toxicity in normal cells [1]. As such, novel cancer drug discovery has heavily emphasized the importance of selective agents with high tumour specificity to mitigate these negative effects [29]. Specifically, many research groups are focused on developing therapeutic drugs tethered via a releasable linker to a targeting ligand, allowing the drug to accumulate and act solely in the tumour [29]. Since 2000, ADCs have dominated the pharmaceutical industry as a new class of highly potent drugs [30]. This is largely attributed to their specificity due to the presence of a monoclonal antibody that effectively targets tumor cell-surface proteins [30]. Despite their praise, said drugs still have several side effects as many of the targeted tumor cell-surface proteins are also expressed in normal cells [31]. Since then, SMDCs have emerged as a new, less established class of drugs to improve targeted delivery in cancer cells [32]. Much like ADCs, a typical SMDC contains a targeting ligand, a spacer, a cleavable bridge, and a therapeutic payload [32]. However, SMDCs utilize small molecule targeting in place of an antibody's Fab region. This site-specific technology is non-immunogenic, and lower in molecular weight when compared to ADCs [33]. These characteristics allow for greater tumor penetration [33]. Due to the novelty of such drugs, recent studies have concentrated their efforts on altering these targeted conjugates to improve pharmacodynamic and pharmacokinetic parameters and increase the variability of the targeting ligand [32].

Targeting Ligand Selection and Design

The targeting ligand of an SMDC is the equivalent of the antibody in an ADC [30]. This ensures that cytotoxic agents, such as chemotherapeutic drugs, can be selectively released in the tumor [32]. Firstly, when selecting a target receptor, it must be overexpressed on the tumor tissue when compared to normal cells and it must be present in sufficient quantities to be able to deliver appropriate amounts of drug through receptor-mediated endocytosis [29]. Thus, when examining SMDC design, the binding affinity, the target specificity, and the size of the molecule must be heavily considered to ensure this high efficacy [32]. By maintaining a high binding affinity and target specificity, the therapeutic payload can be decreased without sacrificing high drug efficacy in the tumour [32,33]. Therefore, SMDC drug design is focused on ensuring that such characteristics are maintained to decrease the concentration of cytotoxic drugs required for therapeutic effects.

Folate-Targeted Small Molecule Drug Conjugates

Currently, targeting ligands similar in structure to molecules, proteins, or ligands involved in cancer-related pathways are rapidly emerging [32,33]. These SMDCs, such as the use of folic acid as a ligand, selectively bind to receptors in said pathways and thereby inhibit tumor growth [32]. Notable research has been done on the use of folic acid as a targeting ligand for the folate receptor [29]. Under normal conditions, folic acid is crucial for the proliferation of cells; however, cancer cells have a high degree of folate receptor expression [29,32,33]. Therefore, when such SMDCs bind to the folate receptors (FRα, FRβ and FRγ), a glycosyl phosphatidylinositol-anchored glycoprotein on the cell surface endocytoses the folate-conjugated compound into the tumour cell [29,30]. One example is *Vintafolide*, composed of a folic acid targeting ligand, disulfide linker, and the drug DAVLBH [33-35]. The folic acid binds to the folate receptors on the tumour cells, and enters the cell by endocytosis [29,35]. The SMDC is then sequestered in an endosome with low pH [35]. The acidic environment causes the release of the SMDC from the folate receptors, while the reductive capacity in the endosome cleaves the linker and

releases the active drug [35]. The drug then leaves the endosome and enters the tumour cell, while the folate receptor is recycled [35].

Using the *Vintafolide* example, it becomes evident that SMDCs share similar characteristics to prodrugs [29, 35]. Namely, the design of a releasable linker that responds to the acidic environment of the endosome ensures that cytotoxic drugs are only released in the tumour. This further allows for greater potency and cytotoxic effects within the tumour without the negative side effects of traditional chemotherapeutic agents [35].

Despite success in clinical trials, studies reveal major side effects such as constipation, due to unwarranted actions in of vintafolide in the liver [33-35]. Namely, the drug transferred into the bile duct and inhibited the gut's peristaltic actions [29]. However, changes to the spacer of the SMDC, specifically modifying the oligopeptide spacer into a peptidoglycan spacer, resulted in significantly less clearance in the bile duct, while still maintaining drug potency [29].

Overview of Carbon Nanotubes and Their Applications

Like other targeted drug delivery methods, carbon nanotubes provide the advantage of cell-specific drug delivery, thereby reducing the toxicity of drugs to healthy tissue [36]. However, carbon nanotubes also possess some distinguishing qualities. Carbon nanotubes exhibit ultrahigh surface areas, high cellular internalization, incredibly stable and stiff structures, and high biocompatibility [37]. In addition, carbon nanotubes are subjected to the enhanced permeability and retention effect, which allows for high permeability across cell membranes and a lower clearance rate by the lymphatic system, resulting in accumulation at target sites for longer durations [37]. These qualities, amongst others, allow carbon nanotubes to present themselves as excellent candidates for applications in cancer therapy.

Types of Carbon Nanotubes

Single- and multi-walled nanotubes have been gaining research interest as nanotechnology methods for delivering chemotherapeutic agents to tumors. Carbon nanotubes owe their stable and biocompatible structures to the versatile bonding properties of carbon atoms. Single-walled carbon nanotubes (SWCNTs) are developed using single-atom thick carbon sheets rolled into cylindrical structures [18]. Multi-walled nanotubes consist of several of these graphene sheets bonded together and rolled into cylindrical structures [38]. The type and size of carbon nanotubes administered for drug delivery significantly affect cellular uptake. Larger nanotubes with larger diameters experience higher cellular uptake than smaller nanotubes [39]. However, this comes at the cost of increased cytotoxicity, as will be discussed in coming sections in this paper.

Translocation Mechanisms of Carbon Nanotubes and Methods of Drug Delivery

Translocation mechanisms, or the methods by which nanotubes enter the cell, are not fully understood [37]. However, SWCNTs, along with other forms of nanotubes, enter cells through various endocytic processes [37]. Carbon nanotubes are hydrophobic, insoluble structures, which require modifications to enhance their biocompatibility and permeability [37]. Covalent and non-covalent functionalizations have been popular methods of modifying carbon nanotubes into a soluble form [40]. These processes involve non-covalently coupling SWCNTs with amphiphilic macromolecules or polymers, or covalently coupling them with hydrophilic functional groups [37]. Most popularly, nanotubes have been coupled with polyethylene glycol (PEG), as this method results in low *in vivo* toxicity rates and low accumulation in the liver and spleen, while exhibiting higher accumulation in tumors [37]. Non-covalent functionalization methods have also demonstrated low accumulation in the liver and spleen and high blood clearance rates, resulting in low *in vivo* toxicity, compared to non-functionalized SWCNTs [37]. To increase SWCNTs' targeting capabilities, nanotubes can also be conjugated with small targeting molecules that will increase the SWCNTs' affinity to overexpressed receptors in cancer cells [37].

Toxicity

The cytotoxic effects of carbon naotubes to healthy tissue remain a controversial topic. This is largely due to the inconsistencies in the toxicology studies conducted to date. Toxicity rates depend on several factors. Studies have shown that SWCNTs appear to result in higher rates of cell apoptosis in comparison to multi-walled nanotubes [41]. It has been suggested that this observation can be attributed to transition metal contaminants in the SWCNTs that accumulated during their manufacturing [41]. However, several studies have also observed that multi-walled carbon nanotubes may induce carcinogenic effects, such as the development of mesothelioma [39]. These conflicting observations indicate that the toxicity of carbon nanotubes remains a complex issue that requires further investigation.

Discussion

Limitations of Lipophilicity

The studies highlighted in this review showcase how a drug's lipophilicity can be altered in a variety of ways to obtain promising new drug candidates. While these alterations have improved efficacy, selectivity, and specificity of the treatments, it is important to note that no one physicochemical property can be relied upon to achieve the desired ADMET profiling criteria. In this review, a single parameter was examined, however, physicochemical properties such as a drug's pKa and water solubility are important to consider in drug design and discovery. As such, a more extensive summary of how these various elements can influence the ADMET profile is required.

Limitations of Small Molecule Drug Conjugate Therapies

Perhaps one of the greatest advantages of SMDCs is the variability in each of the structural components. Namely, the tremendous variation in targeting ligands ensures that therapies can be generated for specific cancer types [32]. Their specificity combined with site-specific release, and low molecular weight, allows for greater tumour penetration and establishes higher drug potency in tumour cells [32]. As of right now, only a select few ligands have been analyzed systematically as potential drug candidates for cancer chemotherapeutics. Currently, folate-targeted small molecule drug conjugates are the most established SMDC therapy, but said drugs are not without their faults. Specifically, SMDCs rely on overexpression of specific receptors on tumours, rather than honing on the discovery of unique receptors. While this significantly improves the off-target effects of traditional chemotherapeutics, SMDCs can still target healthy cells and exhibit negative side effects. As such, this paper largely reports the successes and limitations of folate-targeted small molecule drug conjugates. Future research should continue to examine novel studies and ongoing clinical trials to emphasize advancements to said drugs.

Advantages and Limitations of Carbon Nanotubes

An advantage of utilizing carbon nanotubes in cancer therapy is administering combination therapy, which involves the loading of several drugs into each nanotube to avoid multi-drug resistance [37]. Various studies have confirmed the efficacy of conjugating carbon nanotubes with chemotherapeutic agents. Conjugated drug-nanotube complexes have demonstrated high cytotoxicity to cancer cells. Liu et al. (2008) conjugated paclitaxel (PTX), a common chemotherapeutic drug, to SWCNT's to create a water-soluble drug-nanotube conjugate [43]. Liu et al. (2008) observed a significant reduction in mice tumour size in comparison to the use of clinical Taxol® [43]. Similarly, Lay et. al (2010) conducted experiments to validate the efficacy of PTX-nanotube conjugates in cancer therapy, with their results indicating high efficacy in targeting cancer cells and exhibiting low toxicity to healthy tissue [44].

However, despite the potential SWCNTs possess in terms of cancer drug delivery, there has been little to no application of their use in clinical settings. This is largely due to inconsistent toxicity reports from studies in the literature. Factors influencing toxicity include the length and diameter of the nanotubes used. Longer carbon nanotubes have been observed to exhibit more cell death than shorter ones [37]. The larger diameters encourage higher cellular uptake by healthy tissue, increasing cytotoxicity [39]. Nonetheless, various measures have been investigated to address these toxicity concerns. The shortening of nanotubes has been shown to reduce their aggregation in the bloodstream and increase urinary excretion; hence reducing accumulation of nanotubes in healthy tissue, specifically the liver, and reducing toxicity [45]. In addition, the coatings used to functionalize the nanotubes play a role in reducing nanotube toxicity. Acid-based coatings have been shown to increase toxicity of nanotubes by inducing a high inflammatory response [46]. Hence avoiding acid-based functionalization of nanotubes is another method of interest to reduce their toxicity. It is important to note that this literature review primarily discussed single-walled carbon nanotubes as potential drug carriers with limited exploration of other nanomedical approaches for enhancing drug delivery. Other promising nanocarriers include polymeric nanoparticles, dendrimers, and magnetic nanocarriers [47].

Conclusion

In sum, this review paper presents novel approaches from the literature to improve small-molecule drug delivery in various cancer types. Firstly, the alteration of a drug candidate's lipophilicity can circumvent undesirable characteristics of its physicochemical profile. Ultimately, this can help scientists avoid rejecting promising SMDs. Moreover, small molecule drug conjugates show tremendous promise in their ability to improve tumor tissue selectivity and eliminate off-target effects. As an increasing number of SMDCs are being tested in clinical trials, said drugs are becoming more established as potential cancer therapies. Finally, while carbon nanotubes have exhibited promising results, their clinical use remains unexplored due to a lack of experimental data confirming their safety for prolonged use as a drug delivery method. Further toxicology studies are crucial for clinical advancements using carbon nanotubes in cancer therapy. Together, the discussed methods for targeted drug delivery provide alternatives to traditional chemotherapeutic drug delivery methods.

List of Abbreviations Used:

SMD: small molecule drug
SMDC: small molecule drug conjugate
ADMET: absorption, distribution, metabolism, excretion, toxicity
ADC: antibody drug conjugate
logP: partition coefficient
logD: distribution coefficient
ROS: reactive oxygen species
TPP: triphenyl phosphonium
PAP-1: 5-[4-phenoxybutoxy] psoralen
FRα: folate receptor alpha
FRβ: folate receptor beta
FRγ: folate receptor gamma
DAVLBH: desacetylvinblastine monohydrazide
SWCNT: single-walled carbon nanotube
PEG: polyethylene glycol
PTX: paclitaxel

Conflicts of Interest

The authors declare that they have no conflict of interest.

Ethics Approval and/or Participant Consent
This study did not require ethics approval or participant consent since it is a literature review and did not involve humans, animals, or tissues in its completion.

Authors' Contributions
AS: Contributed to the research, drafting, and editing of the manuscript from start to finish.
RM: Contributed to the research, drafting, and editing of the manuscript from start to finish.
AZ: Contributed to the research, drafting, and editing of the manuscript from start to finish.

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