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RESEARCH ARTICLE

Peptide-Assisted Delivery And Anti-cancer Action In The Chemotherapeutic Treatment Of Small-cell Lung Cancer

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ABSTRACT: Small cell lung cancer (SCLC) is a variant of lung cancer, which, as opposed to non-small cell lung cancer, is more aggressive and undergoes earlier metastasis. This makes SCLC treatment difficult, with modern treatment often entailing severe side effects. With chemotherapy being the most commonly utilised method of treatment, a wide range of combination drugs incorporate a variety of anti-cancer mechanisms. Prolonged treatment results in off-target toxicity of therapeutics, encompassing numerous side effects. Anti-cancer peptides (ACPs) and cancer-targeting peptides (ATPs) offer promising solutions in reducing the aftereffect of treatment, allowing for more tumour-targeted therapeutic action. Additionally, this is achieved by specific peptides that can bind to overexpressed receptors on SCLC cells, as well as the electrostatic attraction between ATPs and SCLC cell membranes. ACPs also exercise a range of mechanisms that directly target SCLC, disrupting the membranal stability of tumour cells and exhibiting anti-cancer action. Overall, the use of peptides is promising in future chemotherapeutic innovation, reducing the harms of treatment and increasing the efficacy of drug action.

KEYWORDS: Biomedical Engineering; Biomaterials and Regenerative Medicine; Drug Delivery; Overexpressed Cancer Receptor; Cancer Membranal Destabilisation.

Introduction

Small cell lung cancer (SCLC) has developed to be a challenging illness to treat, even in modern medicine. Carrying a 5-year survival rate of 8% for women and 6% for men while translating to 30,000 annual cases in the United States alone, SCLC remains a problem for cancer researchers and doctors around the globe.[1,2] SCLC primarily originates from damage to cells lining the bronchi and bronchioles of the lungs, caused by a variety of factors.[3] SCLC is extremely difficult to treat, as the disease is often characterised by rapid tumour development and late-stage diagnosis due to a more gradual onset of symptoms when compared to other forms of cancer. Due to this late diagnosis, SCLC has a higher mortality rate, again, relative to other forms of cancer, such as non-small cell lung cancer.[4,5]

Cigarette smoking, as standard to other forms of lung cancer, is the most common exposure factor that leads to the development of SCLC. Tobacco smoke is known to contain a range of carcinogens: aromatic hydrocarbons, nitrosamines, and aldehydes are common cancer-causing compounds.[6] The prolonged inhalation of asbestos has also been shown to be a significant factor in causing SCLC. When asbestos fibres reach the bronchus and bronchioles, this can cause tissue damage on a cellular level, affecting the DNA of cells in the lungs.[6] In 2023, Curiel-García *et al*. found that exposure to asbestos had the potential to increase the risk of development of SCLC up to five times in some cases.[7]

Recent advancements in interventions involve utilising immunotherapy techniques. Medications like pembrolizumab, atezolizumab and nivolumab have shown promising improvements in survival rates.[6] These drugs block the immune checkpoint proteins that stop the immune system from attacking healthy cells. SCLC incorporates mechanisms that mimic healthy cells, blocking these immune checkpoint proteins that help the immune system recognise and attack cancer cells.[8] Another promising approach for the treatment of SCLC is the use of combination therapies and Chemotherapy.

Chemotherapy is the most prevalent treatment for almost all cancers that uses therapeutic drugs to kill cancer cells. These drugs can be administered in different ways, including through injection, orally, or by direct application.[9] As described previously, SCLC is a highly aggressive form of lung cancer that often avoids detection until after metastasis. This makes it challenging to treat with surgery or radiation alone, which are two other common treatment modalities. Still, chemotherapy is commonly used as the primary treatment for SCLC due to its high response rates and ability to control the spread of the cancer.[10]

While chemotherapy is one of the most effective methods of treatment for SCLC, there are many limitations involving significant side effects throughout treatment.[11] Such symptoms include fatigue, nausea and vomiting, hair loss, mouth sores, diarrhoea, constipation, low blood counts, and nerve damage, among many other severe adverse effects.[11] As chemotherapeutic drugs function on fast-growing cells, cancer cells that undergo rapid mitosis can be targeted. Unfortunately, other cells, in addition to cancer cells, are affected.[11] For example, tissue lining the digestive tract, bone marrow, and hair follicles are affected. This non-cancer-cell toxicity is the cause of the most noticeable symptoms of chemotherapy, such as low blood counts resulting in fatigue, gastrointestinal problems, and hair loss.[11]

Radiotherapy is also related to significant side effects for the patient. Common symptoms after treatment include fatigue, skin problems and, in some cases, difficulty breathing.[12]

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Patients with health conditions could experience more severe side effects such as radiation pneumonitis causing lung inflammation or cardio-toxicity, damaging the heart. Overall, radiotherapy has limited effectiveness in treating SCLC, as treatment can only occur if the cancer is detected before metastasis.[12]

A promising approach to solving some of the limitations of chemotherapeutic treatments for SCLC is to incorporate a therapeutic drug with a peptide delivery platform. Peptides are short chains of amino acids held together by peptide bonds. They combine to form complex proteins and have specific sequences that dictate their behavior; therefore, they can be modified for functional uses. One of the uses is for the treatment of cancer to target a predetermined cell type. Controlled drug delivery (CDD) is an important concept that can be used to deliver such peptides to the cancer site. The use of CDD allows for the release of a drug at a predetermined rate and, more importantly, in a specified area. This is specialised, in contrast to standard drug delivery, which is either orally or intravenously. These CDDs aim to improve the effectiveness of the treatment and reduce the toxicity of the relevant chemotherapeutic drugs. This paper will continue to review the literature on chemotherapeutic therapy with the aid of peptide delivery platforms.

Discussion

Existing chemotherapeutic treatments for lung cancer:

Commonly common combination drugs in the chemotherapeutic treatment of SCLC are cisplatin and etoposide, carboplatin and etoposide, cisplatin and irinotecan, and carboplatin and irinotecan.[5] Other common drugs are topotecan and lurbinectedin.[5] This paper will continue to explore the mechanisms of action for the most frequently used chemotherapeutics – Etoposide, Cisplatin and Carboplatin – in treating SCLC and analyse each drug's advantages and side effects.[5]

Etoposide:

There are many developed chemotherapeutic combination treatments for SCLS. One of these is etoposide and cisplatin.[13] Etoposide functions by inhibiting the activity of the enzyme topoisomerase II, acting in cell cycle phases S and G2, in which

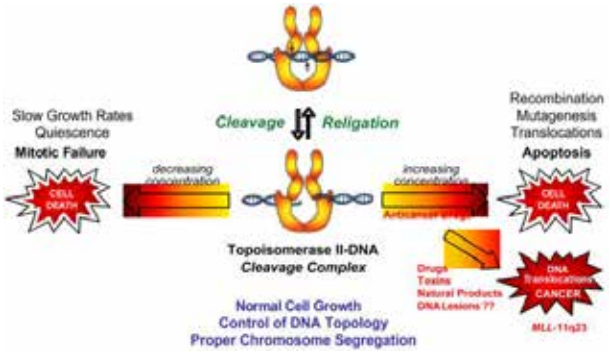

Figure 1: A diagram of the Topoisomerase Cleavage Complex.[49] This figure is reproduced with permission from ElSEVIER From "DNA topoisomerase II, genotoxicity, and cancer" by McClendon *et al.* 2007.

the cancer cell undergoes DNA replication. Topoisomerase functions to untangle DNA strands during replication, ensur replication, ensuring separation and the rejoining of DNA strands[14] (Figure 1).As etoposide binds with the DNA-topoisomerase complex, a stabilised cleavage complex is formed. As a result, this complex cannot complete the normal function of topoisomerase II. The usual process of controlled cleavage of DNA strands, followed by re-ligation to form an intact double helix, is disrupted.[15] In a stabilised cleavage complex, the enzyme cannot re-ligate the DNA strands, resulting in broken DNA strands. Subsequently, broken DNA strands accumulate, leading to increased DNA damage, eventually causing cancer cell death.[15]

Etoposide is an effective drug in chemotherapeutic treatment for SCLC, as response rates have been shown to be up to 80% with a structured intake schedule over five days of treatment.[16]

Overall, etoposide is hugely valuable for the therapeutic treatment of SCLC.[16] However, the drug entails side effects that vary from mild to more significant.

While etoposide primarily targets cancer cells, other rapidly dividing cells are also affected.[15,16] This results in a range of side effects. For example, one common side effect is bone marrow suppression, in which the drug interferes with stem cell division and growth, causing a decrease in red blood cells, white blood cells and platelets in the blood. As a result, symptoms include fatigue, weakness and shortness of breath.[15] Patients are also more susceptible to infection and bleeding during the chemotherapeutic treatment process caused by reduced counts of white blood cells and platelets, respectively (Table 1).

Table 1: Classes of chemotherapeutics.

Drug Class	Example	Mechanisms	Advantages	Side effects
Topoisomerase II inhibitor, plant alkaloid.	Etoposide	• Disrupting cancer cell replication	• High effectiveness • Dosage dependant • Convenient administration	• Bone marrow suppression • Gastrointestinal effects • Hair loss • Fatigue
Alkylating agent	Cisplatin	• Inducing DNA crosslinking • Causing DNA damage • Inhibiting DNA repair	• High initial response rates • Dosage dependent • Effective in combination treatments • Convenient administration	• Gastrointestinal disorders • Fever, weight loss, appetite loss. • Anaemia, leukopenia. • Itchiness, skin rash, swelling. • Speech impairment, lipothymia (near-fainting syndrome), convulsions, panic. • Cough, shortness of breath, chest pain.
Alkylating agent	Carboplatin	• DNA crosslinking • Inducing DNA damage • Inhibiting DNA repair • Cell cycle arrest • Initiation of apoptosis	• Convenient administration • Dosage dependant • Effective in combination treatments • Lower likelihood of nausea • Lower neurotoxicity • Lower renal toxicity	• More likely to develop anaemia • More platelet toxicity • More severe neutropenia • Other general side-effects

Cisplatin:

Cisplatin is generally used as a chemotherapeutic drug, delivered as a combination treatment with Etoposide. Cisplatin incorporates a variety of mechanisms that exhibit anticancer effects.[18] Such mechanisms are DNA cross-linking, inducing DNA damage, creating reactive oxygen species, and inhibit

ing DNA repair. Cisplatin causes DNA cross-linking, forming additional bonds with DNA molecules at adenine and guanine bases. This initiates the creation of inter-strand linkages between the binding sections of DNA chains, finally forming intrastrand crosslinks between two cancer cell DNA strands. These DNA crosslinks disrupt DNA transcription, inhibiting cancer cell replication.[18]

Cisplatin is rarely the only drug given to a patient in a chemotherapeutic dose; hence, data on the action of cisplatin alone is limited. However, a study in 2018 demonstrated that initial doses of the mixture of cisplatin and etoposide have shown high response rates of up to 60% to 70%.[19] Accordingly, cisplatin is also effective in combination treatments, allowing for more effective doses. Like etoposide, cisplatin involves significant side effects during treatment, generally classified as gastrointestinal problems, fever, weight loss, haematological disorders, dermatological disorders, problems with the peripheral nervous system and respiratory disorders[20] (Table 1).[19]

Carboplatin:

Carboplatin is commonly used in combination with etoposide or paclitaxel for treating SCLC. Many mechanisms observed in the anti-cancer action of carboplatin are similar to those of cisplatin as they are in the same drug class. Similar mechanisms are DNA crosslinking, causing DNA damage, inhibiting DNA repair, inducing cell cycle arrest and initiating apoptosis.[21] Carboplatin treatment activates cell cycle checkpoint proteins, such as p53 and ATM, which trigger cell cycle arrest in a normal cell. This temporary arrest allows time for DNA repair and prevents the replication of damaged DNA.[21]However, SCLC cells often have dysfunctional p53 pathways, resulting in compromised cell cycle arrest and a higher chance for damaged DNA to be ignored. Damaged DNA is then replicated, generating more frequent errors in DNA sequencing, eventually causing cell death.[21]

As carboplatin and cisplatin are platinum-based chemotherapeutic drugs and are classified in the same drug class, they share advantages in treatment. These benefits include being easily administered, dosage dependent, and showing solid results in combination treatments.[19] However, a study in 2012 on the treatment of SCLC involving cisplatin compared to carboplatin in a group of 328 patients showed minimal evidence for a difference in the overall survival rate of patients.[22] The paper, instead, highlighted that cisplatin was associated with more nausea, neurotoxicity and renal toxicity, with 95% of patients displaying these symptoms. It is important to note that carboplatin was associated with more anaemia, platelet toxicity and severe neutropenia, all at 95% frequency (Table 1).[22] Even though the study involved a limited statistical group of patients, general symptoms and statistics can be reliable. This conclusion demonstrates that different drug combinations should be diagnosed for patients who are more vulnerable to varying side effects of chemotherapeutic drugs, lowering the risk of developing more significant symptoms.

Mechanisms of cancer targeting peptides:

Mechanisms of membrane destabilisation:

Cancer-targeting peptides (CTPs) are short amino acid chains that can specifically bind to cancer cells or tissues. Their small size, charge and specificity allow them to interact with cancer tissue more effectively than larger molecules, acting as a promising approach to chemotherapeutic drug delivery. CTPs are designed to adapt to the characteristics of cancer cells, such as specialised receptors and membrane proteins. By targeting these specific molecules, CTPs can selectively bind with cancer cells. CTPs can also either directly damage cancer cells by utilising a variety of mechanisms, or deliver payloads of chemotherapeutic agents.

As membrane-destabilising peptides bind specifically to the membrane of cancer cells, they exhibit a variety of mechanisms which break down the membrane, ultimately causing cell lysis and cancer cell death.[23] As membrane-destabilising peptides interact specifically with the outer layer of cancer cells, they exhibit a variety of mechanisms which break down the membrane, ultimately causing cell lysis and cancer cell death.[22] A range of phospholipid types make up the bilayer of cancer cells, the most common being Phosphatidylserine (PS), Phosphatidylethanolamine (PE), Phosphatidylcholine (PC), Phosphatidic Acid, Phosphatidylinositol, Phosphatidylglycerol, Glycosphingolipids, Membrane Cholesterol, Sphingolipids, Lysophosphatidylcholine, and lysophosphatidylethanolamine.[23] When comparing the lipid composition of a cancer cell to that of a mammalian cell, PS and PE proteins appear more frequently (Figure 2).[24]

Some lipids, namely Phosphatidylserine (PS) and Phosphatidylethanolamine (PE), are classified as negatively charged lipids, with cell membrane abundances of 6 mol% and 15-25 mol%, respectively.[25]

Recent studies have confirmed that most CTPs are positively charged. A paper from 2021 claimed that over 85% of anti-cancer peptides have a charge of at least +2.[26] Based on the difference in polarity of CTPs and the cancer cell membrane, studies have hypothesised that the anti-cancer activity of CTPs is likely due to the abundance of negatively charged molecules on the cancel cell membrane.[27] This theory helps explain the preferential interaction of CTPs to the cancer cell membrane.

During peptide-cancer cell interaction, CTPs are adsorbed onto the cell surface membrane, most commonly forming Barrel-stave pores, Toroidal pores, Carpet and Detergent-like models or Shai-Huang-Matsuzaki unifying models.[28] In developing a Barrel-stave pore, peptides interact with phospholipid chains in the cell surface membrane (Figure 3). They rotate to form helical, hollow bundles that fit vertically between membrane phospholipids.[27] This insertion of peptides creates circular pores in the cancer cell's membrane, causing cell lysis. Toroidal pores are formed, instead, when peptides bond in a parallel direction to the cell membrane.[27] In these structures, peptides induce a curvature of the membrane, forming a layer of peptides that interact with the phospholipid heads of the bi-layer membrane (Figure 3). Pores are created from the disruption of membrane structure. Similarly, Carpet and Detergent-like models involve the build-up of parallel peptides on the bilayer membrane of the cancer cell.[28] As peptide concentration reaches a threshold, the cell membrane is broken down. Detergent-like models propose membrane blebbing

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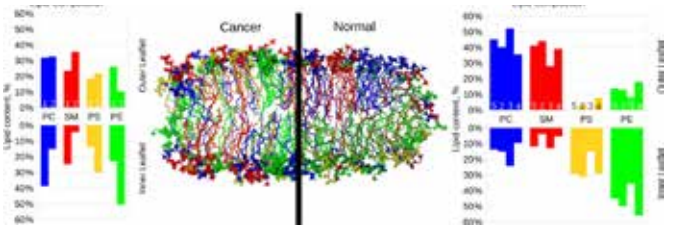

Figure 2: Lipid concentration on cancer cells compared to that of normal mammalian cells.[24] PC, SM, PS and PE stand for Phosphatidylcholine, Sphingomyelin, Phosphatidylserine and Phosphatidylethanolamine, respectively. This figure is reproduced with permission under Creative Commons Attribution 4.0 international. From "The asymmetry of plasma membranes and their cholesterol content influence the uptake of cisplatin" by Rivel *et al.* 2019.

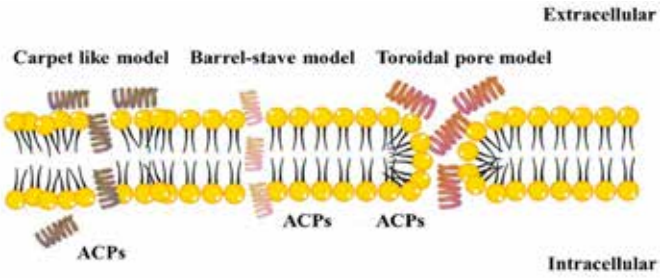

Figure 3: Diagram of the mechanisms of anti-cancer peptide (APCs) membrane destabilisation.[29] This figure is reproduced with permission from Creative Commons Attribution 4.0 international. From "Anti-Cancer Peptides: Status and Future Prospects" by Ghaly *et al.* 2023.

that creates mi-cellar structures.[30] The Shai-Huang-Matsuzaki (SHM) unifying model suggests that the initial parallel peptide interaction with the cell membrane forms the Carpet mechanism, followed by the formation of Toroidal pores, unifying Carpet and Toroidal pore formation. The SHM model explains the existence of multiple pore formations and offers a theory for anticancer peptide action.[31]

Specificity of anti-cancer peptides:

CTPs can act as ligands to be recognised by the cancer cell and to bind to cancer cell receptors on the outer membrane. This process aims to either cause a response from the cancer cell that allows for a liposome to be attached to the membrane, releasing chemotherapeutic drugs, or to signal the process of endocytosis, in which the cancer cell engulfs the liposome.[32] Also, suppose a peptide is successfully recognised by the cancer cell. In that case, it can then be adsorbed onto the cell surface membrane, forming membranal pores through the abovementioned mechanisms, killing the cancer cell.[32]

The most common membrane proteins with overexpressed receptors in SCLC cells include CD24 receptors, Bombesin receptors, Neurotensin receptor 1, and CCKR2 receptors.[32,33]

CD24 proteins are frequently expressed in SCLC but rarely found on the surface membrane of Non-Small Cell lung cancer. CD24 is a glycosyl phosphatidylinositol-anchor molecule, resulting in its specificity for Src family protein kinases. These peptides include c-for, lyn and lck proteins. [33, 34] Bombesin receptors consist of BB1, BB2 and BB3 receptors, with BB2 receptors most commonly found on SCLC cells.[35] Peptide ligands neuromedin B and gastrin-releasing peptides are complementary for BB1 and BB2, respectively, while 14-mer peptide homolog Bn binds with all Bombesin receptors.[32] Alternatively, Neurotensin receptors respond to Hexapeptide Neurotensin(8-13) proteins, while CCKR2 receptors respond to natural peptide ligands cholecystokinin and gastrin.[32] The design of CTPs for the treatment of SCLC should mimic the structure of these proteins to maximise cancer cell binding selectivity.

Overall, the specificity of protein receptors present on SCLC cells and cancer cells in general allows for the adsorption of CTPs onto the membrane of cancer cells. This allows for more effective on-target cancer treatment, particularly when CTPs also deliver chemotherapeutic drugs.

Peptide-Assisted Chemotherapeutic Delivery:

Mechanisms of Peptide-assisted Chemotherapeutic delivery:

Ilangala *et al.* discusses the usefulness of peptides in chemotherapy. Provided that the most critical problem in chemotherapeutic treatment is off-target toxicity, peptides offer a method of selective binding to cancer cells. The paper divides anticancer peptides (ACPs) into three main categories: peptides that disrupt cellular signalling pathways, tumour-homing peptides, and cell-penetrating peptides (Figure 4).[36] Pro-apoptotic and necrosis-inducing peptides are classified as peptides that disrupt cellular signalling pathways. They are most commonly small, negatively charged structures that allow them to be attracted to the negatively charged surface membrane of cancer cells, causing cell death. Pro-apoptotic peptides disrupt mitochondrial membranes, inducing apoptotic factors such as cytochrome C.[36]

The presence of specific antigens on the surfaces of cancer cells has allowed for the existence of tumour-homing peptides. This allows a particular peptide to bind with an antigen or protein present more frequently on cancer cell membranes. This paper emphasises that tumour cells have over-expressed peptide receptors relative to body cells, in a ratio of 3:1.[36] Ultimately, this highlights the potential binding selectivity of anti-cancer peptides, justifying their ability in reducing the off-target toxicity of chemotherapeutic treatment.

Overall, Ilangala *et al.* summarise peptides' potential when used to attack tumour cells directly and as a specialised delivery mechanism for chemotherapeutic drugs. This paper describes the mechanisms by which anticancer peptides can act, conclusively explaining how tumour-targeting peptides can increase the efficacy of chemotherapeutic treatment while effectively reducing off-target toxicity.

Worm *et al.* (2020) begin by discussing the utilisation of peptide-binding receptors as targets for anti-cancer drug delivery, as opposed to the anti-cancer abilities of peptides themselves.[32] The paper considers integrin receptors, Epidermal growth factor receptors, Somatostatin receptors, Gonadotropin-releasing hormone receptors, bombesin receptors (see section 2) and other less common cancer cell membrane receptors.

Integrin receptors are "a family of transmembrane receptors that appear as heterodimers of variably and noncovalently associated alpha and beta subunits".[32] As the integrin receptor facilitates many cellular processes such as cell adhesion, migration and proliferation, they are frequently overexpressed on

cancer cells, particularly on SCLC cells and non-small cell lung cancer cells.[32,37,38] The paper states that the most attractive target of the integrin pseptide receptor is the alpha-v-beta-3 receptor. The paper emphasises that RGD peptide-integrin binding is not yet fully understood. However, complementary peptides that bind to this receptor include the arginine-glycine-aspartic acid (RGD) motif protein.

Despite the epidermal growth factor receptor (EGFR) being rarely found on SCLC cells, it is still commonly found in glioblastoma, melanoma, breast and prostate cancer tumour cells, making EGFR a significant receptor to conduct further research on.[32,39] Provided the four most common EGFR proteins all found in cancer cells are EGFR/HER1, HER2/neu, HER3, and HER4, the paper explains that inhibition of EGFR receptors quickly results in cell death shown in clinics with monoclonal antibodies and small molecule inhibitors. Complementary proteins for EGFR include GE11 proteins and various antibodies.[32]

Somatostatin receptors (SSTR) consist of SSTR1, SSTR2, SSTR3, SSTR4 and SSTR5, with SSTR2 being commonly found in breast, ovarian and lung cancer, particularly being over-expressed in SCLC. [32,40] The most common natural ligand complementary to SSTR is neuropeptide somatostatin, with other artificial proteins such as octreotide, octreotide and lanreotide having high affinity for SSTR.[32]

Gonadotropin-releasing hormone receptors (GnRH-R) are commonly over-expressed on ovarian, prostate, breast, and lung cancer tumour cells.[32,41] GnRH-R is naturally activated by the ligands GnRH-I and GnRH-III, while modified proteins such as [D-Lys6]-GnRH-I and [Lys4]-GnRH-III are often used as binding peptides.

This work continues by discussing new G-protein coupled receptors, the human Y1 receptor, chemotherapeutic agents, and radionuclides as possible forms of treatment. In summary, this paper lists and describes the most significant peptide-binding receptors that are over-expressed on cells of various cancer types. This provides valuable insight on which peptides and receptors to utilise for maximum tumour-site accuracy in future research.

Zhang and colleagues explore the potential of the bombesin (Bn) receptor for use as both a peptide receptor for targeted chemotherapy in the treatment of SCLC and as a diagnosis tool in identifying early-stage SCLC.[42] The paper explains that in the US, the United States Preventive Services Task Force (USPSTF) encourages smokers who "had more than a 20-pack-year smoking history, who are currently smokers, or recently quit within the last 15 years" from ages 50 to 80 have an annual chest CT scan to check for lung cancer.[42,43] However, many have ignored testing guidelines due to the typical absence of noticeable symptoms within the first stages of lung cancer. The author continues by emphasising the problems of modern lung cancer detection methods, such as describing the use of a chest radiograph scan to have "poor sensitivity for detection for SCLC, unless the neoplasm has already developed to extensive stages".[42,44] Zhang *et al.* explain that the only way to confidently diagnose SCLC is by undergoing a lung tissue biopsy followed by a microscopic examination to confirm the presence of SCLC cells. This can be a lengthy process, detrimental when late diagnosis is one of the most

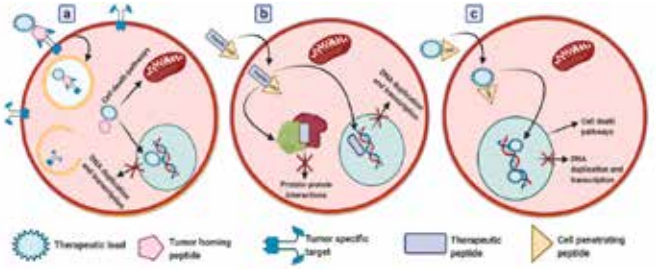

Figure 4: (a) Mechanism of tumour-homing peptides, (b) Mechanism of peptides that disrupt cell signalling, (c) Mechanism of cell penetrating peptides.[34] This figure is reproduced with permission from ELSEVIER.

significant problems in SCLC treatment. The paper explores the possible use of Bn receptors in *in vivo* cancer imaging to identify SCLC in its early stages. Doctors can use a positron emission tomography (PET) scan to identify Bn-radioisotope conjugates that attach to tumour cells allowing for early identification of SCLC and other forms of cancer.[42]

Zhang *et al.* mention that Bn receptors are over-expressed in 85% of SCLC cells; therefore, Bn is a viable receptor to investigate further as a target for chemotherapeutic delivery .[45]A promising Bn-drug conjugate model labelled "scorpion" involves a polyethene cross-linked paclitaxel as a therapeutic with attached peptides. This model showed more significant cytotoxicity in tumour cells with Gastro-releasing peptide (GRP) receptors and BB2, a variation of Bn receptors, compared to paclitaxel alone.[42,45]

The paper also discusses the potential of other targeting molecules, such as ligands and antibodies, for more efficient chemotherapeutic delivery. Overall, Zhang *et al.* summarise the usefulness of Bn receptors in treating and diagnosing SCLC, acting as an overexpressed receptor found on numerous types of cancer cells.

Limitations and challenges of Peptide-Assisted Chemotherapeutic Delivery:

Ilangala and colleagues (2021) explored the limitations that oppose the introduction of peptide-assisted delivery mechanisms into modern cancer treatments, explaining that peptides only comprise 2% of the global drug market.[36] These limitations include their tendency to aggregate and being vulnerable to hydrolysis and oxidation. Other factors are the peptides' metabolic degradation, the reticuloendothelial system's activity, and fast kidney filtration. Low membranal permeability can also affect the effectiveness of peptide delivery.[36] Methods of improvement of these peptides are split into two categories of innovation: Medicinal Chemistry, to adjust the molecular structure of peptides while improving their efficacy, and formulation strategies, focusing on the physical method and process of a patient intake.[36]

Conclusion

With modern chemotherapy entailing significant side effects caused by off-target toxicity, peptide-assisted delivery of therapeutics offers a promising solution to both mitigate symptoms and increase the efficacy of drug activity. The three

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most common drugs used in the chemotherapeutic treatment of SCLC are etoposide, cisplatin and carboplatin. These drugs utilise a variety of anti-cancer mechanisms, including disrupting cancer cell replication, inducing DNA cross-linking, causing DNA damage, inhibiting DNA repair, inducing cell cycle arrest, and causing apoptosis. Cancer-targeting peptides are used and can potentially be attached to various chemotherapeutic drugs to deliver therapeutics. CTPs most commonly carry a positive charge, which would likely bind more efficiently to different negatively charged membrane lipids found on cancer cells, including Phosphatidylserine (PS) and Phosphatidylethanolamine (PE). Anti-cancer peptides (ACP) bind to the membrane of cancer cells, forming a range of structures such as the carpet-like model, the barrel stave model, and the toroidal pore model. This action destabilizes the membrane, ultimately causing lysis and cell death. Cancer cells also have attached membrane proteins, allowing for complementary peptide binding. Membrane receptors such as the Bombesin receptor, namely the BB2 receptor, are over-expressed in SCLC cells; this allows for high binding selectivity for peptides and their attached therapeutic, decreasing off-target toxicity. The main issues in modern applications of peptide delivery systems are peptides' tendency to aggregate and their vulnerability to hydrolysis and oxidation. These issues can be solved by altering the molecular structure of these delivery peptides. Further research is warranted in constructing peptides more resistant to chemical breakdown. Receptors commonly found on tumour cells include the integrin receptor, EGFR, SSTR, and GnRH-R. For SCLC, the bombesin receptor is over-expressed in SCLC cells, making the Bn receptor an excellent target for future SCLC peptide treatment. The use of CTPs and ACPs as a therapeutic delivery mechanism is one of many promising innovations in the improvement of cancer treatment efficacy. They offer non-invasive solutions to minimize or even eliminate numerous side-effects of chemotherapeutical treatments. Modern research should be focused on methods of hydrolysis-resistance of CTPs, and their potential in improving patient experience. Further study should also be conducted on the potential utilisation of the Bn-radioisotope as a method of early-stage SCLC detection.

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