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Targeting the Weakness of Hyper Expression of Phosphatidylethanolamine (PE) on the Cancer Cell Membrane Surface using Cyclotide Peptides, A Potential Pathway in the Cancer Cure

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Abstract

Cancer mortality and morbidity are projected to increase significantly over the coming decades. Modern molecularly targeted therapies have generally proven to be less selectively toxic to cancer cells than anticipated, and they are undoubtedly associated with a range of unusual, and sometimes debilitating, side effects. This is largely because conventional cancer therapies primarily target the strengths of cancer, which are difficult to overcome. Therefore, identifying weaknesses in cancer cells that can be more easily targeted is crucial. In our research, we have identified one such weakness: the overexpression of the phospholipid molecule Phosphatidylethanolamine (PE) on the outer surface of all cancer cell membranes. We aim to explore various therapeutic options for targeting this membrane phospholipid using well-studied cyclotide peptides.

Keywords: Cancer Weakness; Phosphatidylethanolamine; Cyclotide Peptides; Cancer therapy

Introduction

Despite the 50-year-long fight against cancer, initiated by former U.S. President Richard Nixon in 1971, the global incidence of cancer continues to rise. Although using the metaphor of war to describe cancer treatment has been criticized [1], the principles of warfare can still apply to the battle against cancer. One key rule in warfare is: "Strike at the enemy's weakness and avoid the enemy's strength" [2]. However, current cancer therapies predominantly target cancer's inherent strengths, particularly its ability to proliferate-an attribute shared by all cells and deeply embedded in their genomes. As a result, modern molecularly targeted therapies have not been as selectively toxic to cancer cells as hoped.

Moreover, these therapies are often associated with unusual and debilitating side effects and, disappointingly, offer only temporary benefits before resistance develops [3]. To effectively combat cancer, it is essential to identify its weaknesses. Unfortunately, a review of the literature reveals very little useful information on this subject. Therefore, we have undertaken the task of identifying vulnerabilities in cancer cells by analysing their structural and physiological characteristics in comparison to normal cells. After identifying these weaknesses, we will explore suitable and effective therapeutic agents from existing research to target them.

Identifying the weakness of cancer

The following criteria may be considered for detecting the weakness of the cancer cells:

The character or molecular structure:

a). which is unique to cancer cells and not found in normal cells.

b). factors which are crucial for the survival of cancer cells.

c). such cancerous cells are specifically targeted while the normal cells are left safe and unaffected or least affected.

d). ensure the cancer cells do not develop resistance.

e). should not lead to serious side effects and

f). should be positively responding to prescribed therapies and treatment.

Identification and selection of the character / structure: PE is a strong candidate

Taking into consideration of the above criteria and based on the existing knowledge about the unique features and molecular structures, scientists have identified one particular phospholipid namely, Phosphatidylethanolamine (PE) present in the peripheral area of the cancer cell membranes. PE is considered as a strong candidate to be explored and treated as a potential molecular target for membrane targeted novel anticancer therapy [4].

Why do we consider PE as the cancer cells' weakness?

a). Uniqueness in expression and distribution: Phosphatidylethanolamine (PE), a lipid membrane component which exists only in the inner layers of cell membrane under normal circumstances, increases and gets over expressed on the outer membrane of tumour cells resulting in disrupted membrane asymmetry [5-7]. Therefore, this is one of the unique features of cancer cells.

b). Importance for survival: Calzada et al. [8] in their review listed out the importance of PE in various metabolic and functional activities such as protein biogenesis, oxidative phosphorylation, autophagy, oxidative phosphorylation, membrane fusion, mitochondrial stability and is a significant precursor of various other lipids. Further this is the second most abundant phospholipid in the mammalian cell, comprising 15-25% of total phospholipids. Thus, targeting this molecule will definitely have its impact on the very survival of the cell.

c). Not showing resistance: Peptide-based agents often disrupt PE without binding to the target protein. Instead, they interact with potential binding partners of the target protein and bypass a major cause of drug resistance [9]. Therefore, targeting PE does not lead to resistance.

d). Less toxic and easy target: Therapeutic peptides acting on PE have the advantages of target specificity and low toxicity [9] with reduced side effects to normal cells [10]. Thus, the toxicity and side-effects factors can be taken care of.

e). Targeted by many therapeutics: Wide availability of small molecules and peptides from various plant and animal products as the effective therapeutic agents targeting for PE of the cancer cells have been reported [10,11]. This provides wide scope for selecting some effective therapeutics to target cancer cells.

Identification of effective therapeutic candidates: Peptides as the potential Therapeutic candidates

Following are the qualities that make the peptide molecules as the potential therapeutic candidate

a. Unique feature and stability: Cyclotide peptides' unique and unusual features of a head-to-tail cyclized backbone and a cystine knot core contribute to their exceptional stability [12,13].

b. Specific targeting: Troeira HS et al. [14] and Troeira HS, and Craik DJ [15] highlighted the unique molecular structures of cyclotides which are responsible for specific targeting of phosphatidylethanolamine (PE) phospholipids in the cell membrane and their efficacy depending on the level of concentration of the PE.

c. Easy availability: Most drawbacks of using antibodies can be eliminated by using smaller biomolecules like peptides. Peptides with up to 50 amino acids can be easily synthesized on a larger scale to a reasonable price [7].

d. Drug Resistant: Peptide-based agents often disrupt protein–protein interactions (PPIs) without binding to the target protein. Instead, they interact with potential binding partners of the target protein and bypass a major cause of drug resistance [9]. It has been experimentally shown that some of the peptide molecules which are used to target the PE molecule cause a therapeutic effect through direct binding with their target [5,7].

e. Unique action: On disturbance by the peptides PE significantly increases the susceptibility of the membrane and causes an order-of-magnitude increase in membrane permeability by facilitating the formation of larger transmembrane pores leading to cell necrosis [16].

f. Non-toxic: Peptides are generally considered safe, since they feature low immunogenicity and produce non-toxic metabolites [17].

Discussion

Anticancer peptides (ACPs), derived from naturally occurring and modified peptides, have received great attention in the recent years and emerged as novel therapeutic and diagnostic candidates for cancer therapies, because of several advantages over the present treatment modalities [9,10,17-22]. Among the ACPs, the Disulfide-rich Cyclic peptides are superior in terms of their exceptional stability, particularly in resistance to extreme pH and temperature [23]. Targeting the specific membrane components of the cancer cells is proved to be a safer and effective means of killing cancer cells as it involves minimal off-target effects [22]. In this respect, use of cyclotides targeting the PE molecule that gets expressed high, in cancer cells is widely studied in respect of their application in cancer therapy [10,11,13,19,23-29].

The mechanism of some specific Cyclotide peptides that target PE molecule of the cell membranes have been studied and explained [9,14,30,31]. Troeira HS and Craik DJ [15] further characterised the cyclotides and reported that the cyclotides which belong to the Mobius, and bracelet subfamilies in particular have been found to harbour lipid-binding domains, which allow for the specific recognition of over expressed PE phospholipids in cancer cell membranes. Among the various mechanisms which kill the cancer cells, permeabilization and pore formation mechanism

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is considered as more effective and safer because, it enables selective cell killing with minimal off-target effects [16,22,30-35].

Peptides which affect cancer cells by targeting overexpressed receptors are very challenging [36]. One of the challenges is that the over expressed receptors in cancer cells should be higher in concentration in comparison with normal cells, usually 3-fold or higher in comparison with normal cells [37]. As far as the PE in cancer cells' outer membrane is concerned, it always remains highly expressed than in the normal cells. Among the various important roles played by PE in cellular functions [8], PE's role in cell division is vital one [38,35]. Hence it is presumed that any damage or disturbance to the PE in the cancer cell membrane may also affect the cell division process which is a vital character of all cancer cells. In this connection Lehmann et al. [32] reported that the Magainin II peptide exerts cytotoxic as well as antiproliferative efficacy by pore formation in bladder cancer cells. Further research is needed to understand how far the vital functions performed by the PE would be affected while targeting the PE in cancer cells.

Another adaptive role the increased PE content in cancer cell membrane is that it leads to the activation of PE Binding Protein (PEBP) which desensitizes the cells from the proapoptotic signals [39]. Therefore, it is presumed that targeting PE may enable the cancer cells sensitising proapoptotic signals thereby leading to apoptosis form of cell death. This calls for further research. The significant aspect of cell death via membrane disruption is that it can result regardless of growth rate or multidrug resistance mechanisms, conditions that often foil conventional chemotherapy approaches, while cationic residues in the peptide can enable preferential targeting of the peptide to the relatively anionic cell membrane of cancer cells [9]. Although using peptides as therapeutics has many advantages, peptides have the disadvantage of being easily degraded by proteases once administered and, depending on the mode of administration, often have difficulty being adsorbed into the blood stream [9] and quickly cleared from the blood circulation by liver and kidney [7].

However, recently, various strategies have been developed to overcome these obstacles of peptide delivery and bioavailability [7,9,40]. One of the most known concepts of peptide stabilization is lipidation, which involves the incorporation of fatty acids into the peptide [41]. Molecular grafting is one approach to stabilizing and constraining peptides that involves melding a bioactive peptide sequence onto a suitable molecular scaffold. This method has the benefit of improving the stability of the bioactive peptide lead and potentially expanding its functionality [42]. The construction of anticancer peptide nano systems using biomedical engineering techniques is also a promising approach [19].

Conclusion and Recommendation

Specific addressing of tumour cells without affecting healthy tissue is currently a major desire in cancer therapy. This may require identification of weakness of the cancer cells, targeting of which may less likely affect the healthy cells but, will affect effectively the cancer cells in particular. In that respect, the surface receptor PE, which binds peptides is frequently overexpressed on cancer cells and may be considered as the weakness of the Cancer cells. It is therefore be considered as the most promising target for selective killing of tumour cells. The significant aspect of cell death via PE targeted membrane disruption by peptides is that it can result regardless of growth rate or multidrug resistance mechanisms.

Cyclotide peptides which belong to the Möbius, and bracelet subfamilies in particular may be the most favorable therapeutic candidate which kill cancer cells without creating resistance and side-effects. Recently, various strategies have been developed to overcome the obstacles involved in delivery and bioavailability of peptides. Presently, various peptide therapies are being tested in various cancer cell lines. Finding out the more effective cyclotides for fighting against the above said weakness of the cancer cells, will be a more promising way to end the war against cancer.

Conflicts of Interest

The Author declares that he has no conflicts of interest.

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