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Melittin based nano drug delivery system for cancer therapy

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Abstract

Melittin is a 26 amino acid polypeptide with a wide range of toxicological and pharmacological effect. It constitutes 40%-60% of dry honeybee (*Apis melifera)* venom. It has significant antitumor characteristics surface activityon cell lipid membranes, including potent hemolytic activity. It creates pores on the targeted cell membrane. Melittin has shown variety of anticancer effects in preclinical cell culture and animal model system. MEL has tremendous antifungal, antibacterial, anti-inflammatory and antitumor properties. Practical application of melittin in oncology is hampered by its strong, nonspecific hemolytic activity and intrinsic instability. To address these shortcomings, delivery systems are used to overcome the drawbacks of melittin and facilitate its safe delivery. To accomplish stable loading, side effect shielding, and tumor-targeted delivery, many nanocarrier systems—such as liposomes, cationicpolymers, etc. have been created. To increase its toxic effect, carbon nanoparticles were used as carriers of melittin to breast cancer cells. Melittin complexed with nanographene oxide has a more harmful effect on breast cancer cells than melittin alone. Furthermore, nanodiamonds can shield cells from melittin's lytic effects. As a result of the findings, carbon nanoparticles as melittin carriers may find value in medicine in the future. PI3K/Akt and NF-kB signaling pathways are typically activated in P-gp-mediated MDR-related pathways, however melittin inhibits these processes. To overcome anticancer resistance and improve chemotherapy effectiveness, a polymersome based on a poly (lactic acid) (PLA)-hyaluronic acid (HA) di-block copolymer and encapsulating melittin and doxorubicin was created. By controlling P-gp overexpression pathways, a polymersome containing an anticancer medication and melittin might overcome.

Keywords: carbon nanoparticles, Haemolysis, Melittin, Nano-Delivery System, Stable loading, Tumor-targeted delivery.

Introduction

Melittin (MEL) basically a positively charged, amphipathic peptide consisting of 26 amino acids that associate with phospholipids of the membrane bilayer causing cell death forming 4.4nm diameter transmembrane pores that may enable the internalization of cytotoxic elements that can kill the cell. One of the primary ways that melittin works as an anticancer drug is by disrupting the cell membrane of cancer cells. Melittin is able to penetrate the cell membrane of cancer cells, causing it to become destabilized and leading to the formation of

pores. These pores allow the uncontrolled influx of Ca^{2+} ion and activates PLA2 resulting in the cell death. Melittin binds non-competitively with phospholipase A2 (PLA2) to inhibit its enzymatic activity, and thus can be used for the treatment of inflammation caused by the production or enhanced activity of secreted PLA2. There are various ways that can be used to deliver melittin as a drug to the targeted site. Nano drug delivery system is widely applicable in melittin based drug delivery system. Melittin has high cytotoxicity and can create pores on the cell membrane and can mediate cell death to any cell.

Types of nano particles used in cancer therapy

There are few nanocarrier which is used to carry the melittin and can reduces the cytotoxicity of the melittin thus provide the possibility of targeting to the intendent cell. The possible ways we can use MEL in targeted drug deliverysystems are as follows:

Doxorubicin which is a significant anti-cancer drug derived from *Streptomyces peucetius* and melittin are loaded to citric acid Fe_3O_4 magnetic nanoparticle can be used in magnetically targeted cancer therapy (Hematyar *et al.*, 2018).

Melittin mixed with perfluorocarbon can show a significant effect in cancer cells. It can inhibit MDA – MB – 435 human breast cancer by 24.68 %. MEL derivative peptide was incubated with PFC nanoparticles is activated by matrix metalloproteinase-9(MMP-9), a protease overexpressed in many tumour cells. In addition, treatment of PFC nanoparticles resulted in ~54% reduction in melanoma tumour size *in vivo* (Soman, et al, 2008). The EGF-targeted lipo disks binded specifically to A-431 tumour cells, and resulted in a improved cell-killing effect, as cell viability decreased 20% compared to free MEL MEL was loaded in PEGylated anti-HER2 immunoliposomes decreased cancer cells viability in a dose–response manner (Soman, et al, 2008).

Mechanism of Melittin using doxorubicin

Multi drug resistance is one of the major barriers in cancer therapy. There is a special type of receptor in cancer therapy called Peg p receptors. During the time of tumor formation, the cell receptors are over expressed. When the receptors are overexpressed the chemotherapeutic drugs which enters inside the cell releases out. Verapamil, gallopamil can inhibits the MDR modulator for the over expression of pump receptors. But over expression of Multi drug resistance (MDR) not only inhibits the elicit toxic effects of the drugs but also inhibits the intracellular influx of co-delivered anticancer drugs. Doxorubicin is commonly used as an anticancer agent. However, it is resisted by cancer cell and it has also toxic effect on other healthy cells. Melittin also cause hemolysis of blood. To overcome this problem scientists form Dox-ml-pl (***Fig 1***), which is a polymersome, composed of Polylactic acid (PLA), Hyaluronic acid (HA) di-block of co-polymers loaded with melittin and doxorubicin. P13k/Akt pathway promotes the proliferation of cancer cells. The NFkB (Kappa factor) binds with the promoter of MDR gene to initiate transcription and expression of Pgp pump (Lee *et al.*, 2013). Thus, NFkB pathway is involved in regulation of the MDR expression in cancer cell ***(Fig 2)***. Thus, down regulation the P13k/Akt and NF – kB pathway can improve the efficiency of chemotherapy (Deng, et. al, 2014)

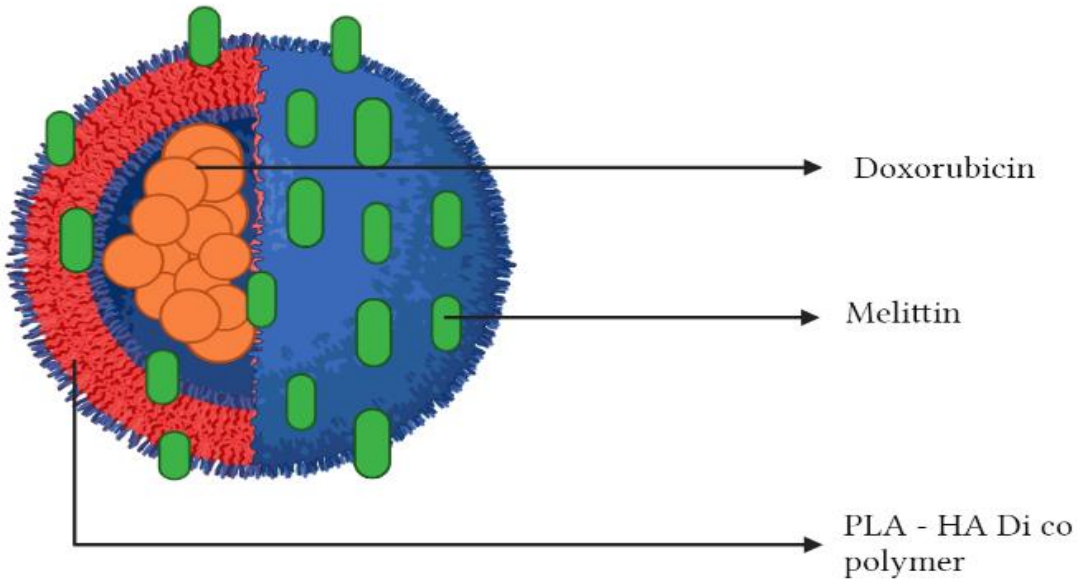

Fig. 1: *Structure of Dox-ml-pl composed of Polylactic acid, Hyaluronic acid di-block of co polymers loaded with melittin and doxorubicin.*

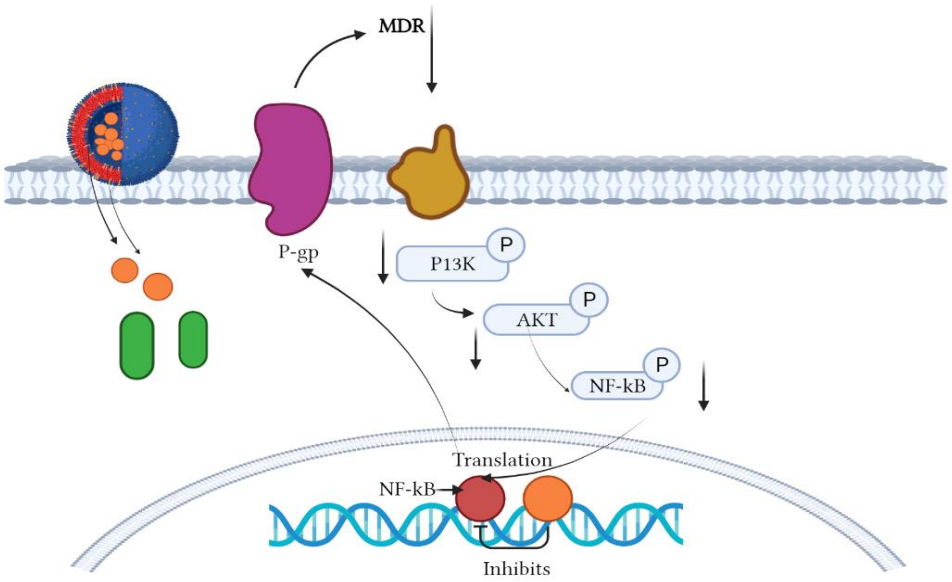

Fig. 2: *Schematic of Dox-Mel PL demonstrating the co-delivery of melittin and doxorubicin via a PLA-HA polymersome to downregulate PI3K/Akt and NF-κB pathways, consequently overcoming multidrug resistance and enhancing chemotherapeutic efficacy*

Intracellular uptake of Dox – Mel – PL

The developed PLA-HA polymersome encapsulating doxorubicin and mellittin was confirmed through dynamic light scattering and transmission electron microscope (TEM). A PLA-HA polymersome encapsulating doxorubicin and melittin (Dox-Mel PL) was formed through the self-assembly of a PLA-HA copolymer, with an average size of 293.9 ± 17.53 nm. The TEM image of Dox-Mel PL shows spherical polymersomes, indicating the successful self-assembly of an amphiphilic PLA-HA copolymer. The loading efficiencies of doxorubicin and melittin in Dox-Mel PL were 54.05% and 84.25%, respectively.

Development of D-melittin polymeric nanoparticles for anti-cancer treatment

Melittin, the major peptide component of bee venom, is a very effective cytolytic anti-cancer peptide with well-documented anti-tumour efficacy. However, melittin's nonspecific hemolytic activity and inherent instability make it difficult to use in cancer. To solve these flaws, delivery mechanisms are utilised to overcome melittin's limitations and ease its safe distribution. Nonetheless, a recent study found that encapsulated melittin is immunogenic and may be used as an adjuvant to generate a deadly antibody immunological response against the delivery carrier. D-melittin nano formulations greatly reduce immunological response, resulting in high safety without reducing cytolytic capacity. The first use of D-melittin and its micellar formulations in cancer therapy. D-melittin was supplied via a pH-sensitive polymer carrier that (i) forms micellar nanoparticles under normal physiological circumstances, encapsulating melittin, and (ii) dissociates at endosomal pH, restoring melittin activity. D-melittin micelles (DMM) are cytotoxic and cause hemolysis in a pH-dependent way. DMM causes immunogenic cell death, indicating its potential for cancer immunotherapy. Indeed, *in vivo* investigations confirmed DMM's enhanced safety profile over free peptide and increased effectiveness in inhibiting tumor development. These findings reveal a novel technique for safe, systemic melittin administration.

To promote intracellular melittin delivery, a polymer platform called virus inspired polymer for endosomal release (VIPER) is used. D-melittin was conjugated to an extremely pH-sensitive polymer, which shields melittin at physiological pH but quickly unsheathes melittin at endosomal pH. At physiological pH, the polymer-peptide conjugate self-assembles into micellar nanoparticles and dissociates after entering the cells (Kurrikoff *et al., 2019).*

Future Prospects

The future prospects for melittin-based nano drug delivery systems in cancertherapy are promising. Here are some potential future directions and advancements:

***Improved targeting strategies*:** Further refinement of targeting strategiescan enhance the specificity of melittin-based nano drug delivery systems. This includes the development of more efficient targeting ligands, such as

antibodies or peptides, that can selectively recognize cancer-specific markers and improve the accumulation of melittin in tumor tissues.

Combination therapy approaches: The combination of melittin with other therapeutic agents, such as chemotherapy drugs, immunotherapies, or gene therapies, can lead to synergistic effects and improved treatment outcomes. Future research may focus on identifying optimal combinationtherapies and developing innovative nano drug delivery systems to deliver multiple agents simultaneously.

Overcoming drug resistance: Resistance to chemotherapy is a significant challenge in cancer treatment. Melittin-based nano drug delivery systems can potentially overcome drug resistance by directlytargeting cancer cells and bypassing the mechanisms of resistance. Additionally, the combination of melittin with other agents that can reverse drug resistance may further enhance treatment efficacy.

Advanced imaging and diagnostics:
Integration of imaging agents ordiagnostic probes into melittin-based nano drug delivery systems can enable real-time monitoring of treatment response and provide valuableinsights into the delivery and distribution of therapeutic payloads. This can facilitate personalized treatment approaches and optimize treatmentregimens.

Conclusion

In conclusion, the melittin-based nano drug delivery system holds immense potential as a targeted and efficient approach for therapeutic interventions. By encapsulating melittin within nano carriers, such as liposomes or nanoparticles, this innovative method offers several advantages. These include enhanced targeting specificity, reduced off-target effects, controlled release profiles, and the potential for combination therapies.
The melittin peptide's inherent cytotoxicity can be harnessed to selectively eliminate cancer cells, while the nano delivery system minimizes its impact on healthy cells, thereby addressing a significant challenge in cancer treatment. This approach not only improves the therapeutic index but also paves the way for personalized medicine strategies, tailoring treatments to individual patients and cancer types.

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Conflicts of Interest:

The authors declare no conflict of interest.

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