

Melittin-Based Cancer Therapy Delivery Strategies

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Abstract

Melittin (MLT) is a bee venom-derived natural cytolytic peptide that has been studied in preclinical animal models for the treatment of inflammatory disorders such as arthritis, rheumatism, chronic pain, and others. MLT has been widely used as an anticancer drug in recent years. MLT causes cancer cells and drug-resistant cells to die by attaching to phospholipids and generating pores in plasma and organelle membranes. 8 MLT has also emerged as a promising immunotherapeutic drug that stimulates the release of tumor-associated antigens and endogenous danger markers, as well as the activation of cytotoxic T cells and natural killer (NK) cells. Furthermore, MLT enhances antitumor immune responses by promoting the release of antitumor cytokines such as IL-2, INF-, and TNF-.

Introduction

MLT, in particular, has the ability to reverse the Immunosuppressive Tumour Microenvironment (TME) by inducing TAM reprogramming and differentiation into immunostimulatory M1-polarized TAMs. MLT's therapeutic application is hampered by inadequate tissue distribution, hemolysis, quick metabolism, limited specificity, and toxicity, despite accumulating evidence of its powerful anticancer effects. As a result, developing novel MLT delivery systems could be critical for better application of MLT in anticancer therapy while avoiding ionising radiation. Furthermore, given the extremely changeable physiology of tumours, such as the aberrant vascular system within the TME, MLT delivery systems that enable trigger-based (physiology-dependent or external stimuli-dependent) targeting and release may aid in delivering maximum payload to the targeted region. Recent improvements in MLT and its delivery tactics have been presented in many studies, either as a summary of material-based delivery systems or as a focus on general aspects of MLT membrane contacts and anti proliferative molecular mechanisms from a biological perspective. However, material-assisted MLT delivery vehicles deserve special consideration in terms of applied biotechnology and mechanistic features, immunomodulatory effects, and translational aspects. Various carriers have been used in MLT delivery schemes in recent years. These carriers are well-suited to carry MLT to tumour locations and boost antitumor efficiency by regulating the TME, a complex system that includes tumour cells, fibroblasts, endothelial cells, and immune cells. pH-responsive polymeric nanoparticles, magnetic field responsive nanoparticles, pH/near-infrared (NIR) laser responsive nanocomposites, thermosensitive hydrogels, and peptide-responsive carbon nanomaterials are just a few of the multistimuli-responsive carriers that have been produced. Multiple carrier-based MLT delivery techniques for cancer therapy are outlined here. MLT is a poisonous component of *Apis mellifera* bee venom that can be employed as an antibacterial and cytolytic peptide. It is made up of 26 amino acids (NH₂-GIGAVLKVLTGTPALISWIKRKRQQ), with a hydrophobic amino-

terminal region (residues 120) and a hydrophilic carboxy-terminal region (residues 2126). 18 MLT is a cationic peptide with a net charge of +6, with four charges in the C-terminal area and the remaining two in the N-terminal region, in addition to its amphiphilic nature. As a result, MLT is a suitable model peptide for lipid interaction. MLT is normally monomeric and has a random coil structure; however, when it is injected into a lipid membrane, it converges into a tetramer and assumes a α -helical conformation. Temperature, pH, salt concentration, and peptide concentration can all affect MLT's conformation. MLT establishes electrostatic connections with negatively charged cell membrane surfaces in milliseconds, resulting in pore creation, cellular content leakage, and eventually cell death.