Plausible implications of targeted inhibition of Notch and in cystic fibrosis using nano-lipid-drug conjugates

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ABSTRACT

Cystic fibrosis (CF) is a genetic disorder characterized by the accumulation of thick, sticky mucus in the lungs and other organs. Current treatment options focus on managing symptoms, but there is a need for therapies that modify the underlying disease process. The Signal Transducer and Activator of Transcription 3 (STAT3) and Notch signaling pathways have been implicated in CF pathogenesis. Activation of STAT3 contributes to chronic inflammation and tissue damage, while Notch signaling promotes fibrosis and fibroproliferative diseases. Niclosamide, an anthelmintic drug, has shown inhibitory effects on these pathways but has limited clinical utility. Lipid-Drug Conjugate nanoparticles (LDCs) offer a promising drug delivery system for enhancing the bioavailability and targeting of therapeutic compounds. In this study, we propose the preparation of Niclosamide LDCs (Niclo-LDCs) using Octadecylamine as a lipid. We hypothesize that Niclo-LDCs have the potential to inhibit Notch and STAT3 activation, thereby reducing inflammation in the lungs of CF patients. By specifically targeting the cross talk between these pathways, Niclo-LDCs may represent a promising therapeutic strategy for CF treatment. Further investigation and validation of this hypothesis could lead to the development of novel treatments for CF that modify the underlying disease process.

KEY WORDS: Cystic fibrosis, CFTR protein, STAT3 signaling pathway, Notch signaling pathway, Niclosamide-LDCs

INTRODUCTION

Cystic fibrosis (CF) is a genetic disorder that affects the lungs, pancreas, and other organs. It is caused by a mutation in the gene that codes for the cystic fibrosis transmembrane conductance regulator (CFTR) protein[1, 2]. The CFTR protein is a chloride channel that regulates the flow of ions across cell membranes. In individuals with CF, the defective CFTR protein leads to an accumulation of thick, sticky mucus in the lungs, pancreas, and other organs[3]. Treatment options for CF include include, Antibiotics, to treat and prevent lung infections, Mucus-thinning agents, to help clear the airways, Airway clearance techniques, such as chest physical therapy and inhaled medications, Nutrition support, CFTR modulators, which help to improve the function of the defective CFTR protein[4-6]. While current treatments primarily focus on managing the symptoms and complications of CF, there is a growing interest in developing drugs that can modify the underlying disease process.

The Signal Transducer and Activator of Transcription 3 (STAT3) signaling pathway is a cell signaling pathway that plays a role in the regulation of inflammation and tissue repair[7, 8]. Research has shown that the STAT3 signaling pathway is activated in the lungs of individuals with CF. Activation of STAT3 is thought to contribute to the chronic inflammation and tissue damage seen in CF. Studies have suggested that targeting STAT3 may be a potential therapeutic strategy for treating CF[9, 10]. The exact mechanisms by which STAT3 contributes to CF are not fully understood, but research has suggested that it may play a role in the inflammatory response in the lungs of CF patients. Some studies have shown that targeting STAT3 using small molecule inhibitors or siRNA can reduce inflammation and improve lung function in CF animal models. Studies have shown that STAT3 activation leads to the production of pro-inflammatory molecules, such as TNF-alpha and IL-6, which contribute to inflammation and tissue damage. Additionally, activated STAT3 has been shown to inhibit the activity of the Nrf2 pathway, which is a protective pathway that helps to reduce inflammation and oxidative stress[11-14].

Notch signaling pathway has been recognized as a highly conserved and versatile signaling network that plays essential roles in various cellular processes and functions. While its involvement in development and tissue homeostasis has been extensively studied, emerging evidence indicates that Notch signaling also plays a significant role in fibrosis and the pathogenesis of chronic fibroproliferative diseases in different organs and tissues[15]. The effects of Notch activation can vary depending on the cellular and tissue context, as well as the physiological or pathological state. In some situations, Notch signaling promotes fibrosis by stimulating fibroblast activation, extracellular matrix deposition, and myofibroblast differentiation[16, 17]. It can induce the production of profibrotic factors, such as transforming growth factor-beta (TGF-β), connective tissue growth factor (CTGF), and platelet-derived growth factor (PDGF), which contribute to fibrotic processes. Additionally, Notch signaling can enhance the survival and resistance to apoptosis of fibroblasts, allowing for their persistence in fibrotic lesions[18].

Niclosamide (Niclo) is an anthelmintic drug that has been found to have inhibitory effects on the Notch signaling pathway, and more recently it has been found to have some inhibitory effects on the STAT3 and Notch signaling pathways. However, the clinical limitations of Niclo are low bioavailability, solubility and off-target effects[19-24].

Lipid-Drug conjugate (LDC) nanoparticles (NPs) are a class of drug delivery systems in which therapeutic compounds are conjugated or incorporated into lipid-based carriers. These carriers can include liposomes, lipid nanoparticles, or other lipid-based formulations. LDCs offer several advantages for drug delivery, including enhanced solubility, improved stability, prolonged circulation time, and targeted delivery to specific tissues or cells. In LDCs, the drug is typically conjugated to or encapsulated within lipid molecules[25, 26]. This conjugation or encapsulation allows for improved drug solubility, which can enhance bioavailability and absorption. Moreover, the lipid carriers can protect the drug from degradation and facilitate its delivery to the target site. In the present study we propose to prepare LDCs of Niclo (Niclo-LDCs) using Octadecylamine as a lipid.

HYPOTHESIS

Niclo-LDCs have the potential to inhibit the activation of Notch signaling and STAT3, which are key players in the development and progression of cystic fibrosis (CF). By specifically targeting the cross talk between Notch and STAT3 pathways, Niclosamide LDCs may effectively reduce inflammation in the lungs of CF patients. This hypothesis is based on the understanding that Notch signaling and STAT3 cross talk play critical roles in CF pathogenesis and that utilizing Niclosamide LDCs could represent a promising therapeutic strategy for CF treatment.

EVALUATION OF HYPOTHESIS

The hypothesis builds upon existing evidence supporting the inhibition of Notch signaling and STAT3 as potential therapeutic approaches for CF. Niclosamide, a known inhibitor of both Notch signaling and STAT3, can be conjugated with lipids to form Niclosamide LDCs, which could enhance drug delivery and targeted action in the lungs. By encapsulating Niclosamide within a lipid formulation, its bioavailability and pharmacokinetic properties may be improved, leading to enhanced efficacy in inhibiting Notch signaling and STAT3 activation[8, 13, 14, 27, 28]. Studies have demonstrated the critical involvement of Notch signaling and STAT3 in CF, including their contribution to inflammation and tissue damage. The hypothesis posits that by inhibiting the cross talk between Notch and STAT3 pathways, Niclosamide LDCs may effectively modulate the inflammatory response in CF lungs, ultimately reducing inflammation and mitigating disease progression[29-33].

Further, the formulation of Niclo-LDCs offers several advantages. Lipid conjugation can improve drug solubility, stability, and tissue penetration, allowing for targeted delivery to the lungs, which are the primary site of CF pathology. Additionally, lipid-based drug delivery systems can provide sustained release of the therapeutic agent, potentially prolonging the duration of action and reducing dosing frequency. The formulation of Niclo-LDCs represents a novel approach in CF therapeutics, combining the known inhibitory effects of Niclosamide on Notch signaling and STAT3 with the advantages of lipid-based drug delivery.

CONCLUSION

In conclusion, the hypothesis suggests that Niclo-LDCs, which are lipid-based formulations of Niclosamide, have the potential to inhibit Notch signaling and STAT3 activation in cystic fibrosis (CF). By targeting the cross talk between these pathways, Niclo-LDCs may effectively reduce inflammation in CF lungs, offering a

promising therapeutic strategy for CF treatment. The formulation of Niclo-LDCs combines the known inhibitory effects of Niclosamide with the advantages of lipid-based drug delivery, such as improved solubility, stability, and targeted delivery to the lungs.

CONFLICT OF INTEREST: None to declare

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