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Nanoparticle-inhibited neutrophil elastase prevents neutrophil extracellular trap and alleviates rheumatoid arthritis in C57BL/6 mice

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ABSTRACT

Rheumatoid arthritis (RA) is characterized by inflammation outbreak and joint destruction. As the main culprit of RA, neutrophils firstly migrated to inflamed joints and aggravate inflammatory reaction by release excess neutrophil extracellular traps (NETs). However, it remains unsatisfactory efficiency to prevent NETs formation. Emerging evidence indicated that inhibition of neutrophil elastase (NE) could prevent NETs production. Here, we established a method in which sivelestat (ST, a low molecular specific inhibitor of NE)–conjugated bovine serum albumin nanoparticles (BTST NPs) could specifically target inflamed neutrophils for delivery of ST, which could selectively inhibit NE and prevent NETs production. Moreover, BTST NPs were also loaded with dexamethasone palmitate (DP), a classic glucocorticoid drug for RA, to deliver DP to the inflammatory site to achieve synergistically treatment of RA. It was identified that activated neutrophil could selectively internalize DP/BTST NPs. The release of ST and DP were depending on ROS environments in neutrophils at inflamed joints, subsequently could hinder NETs generation. In collagen-induced arthritis (CIA) models, DP/BTST NPs significantly improved targeting effect, alleviated RA symptoms, and enhanced prominent biological safety. We pioneer proved that this novel ST-conjugated BSA NPs holds a promising approach to improve treatment of RA and various NET-mediated inflammatory diseases.

Introduction

Rheumatoid arthritis (RA) is a potentially devastating and influential chronic inflammatory disorder, burden approximately 1% population worldwide, but still lacks a significant treatment thus far [1,2]. Characterized by synovial inflammation and progressive joint destruction, RA is incurable and causes disability with significant morbidity and increased mortality during the disease progression [3,4]. Current clinical treatment uses mainly three traditional types of medications: non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), and glucocorticoids (GCs) [5–8]. However, although these conventional approaches can ameliorate RA symptoms, low half-life and frequent dosage administration are usually accompanied to retard the progression, which unavoidable lead to irreversible outcomes [9,10]. Therefore, it's urgently warranted to exploit novel therapeutic agents for RA treatment.

As the first responders to inflammation, neutrophils play an indispensable role during the occurrence and development of RA [11,12]. Activated neutrophils produce excess neutrophil extracellular traps (NETs), which can persist the development of RA by enriching sources of citrullinated proteins and promoting more cytokine production [13–16]. Hence, preventing NETs formation might be a potential approach to treat RA. Neutrophil elastase (NE) belongs to serine proteases and usually stored in neutrophil azurophilic granules. Recently, evidence have supported that NE could lead to NETs release by translocating from granules to nucleus and processing histones, which was initiated by reactive oxygen species (ROS) [17–19]. Consequently, inhibiting NE activity might be a feasible way for eliminating NETs.

Sivelestat (ST) is recognized as a specific NE inhibitor and used to treat acute lung injury accompanied by systemic inflammatory response syndrome [20,21]. However, its practical application was hindered owing to low bioavailability and plasma half-life [22–24]. Thus, there is an urgent need for a new approach to prolong systemic circulation of the medication and increase bioavailability of ST. What's more, considering the complexity and diversity of cytokine of

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