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Sialic acid-conjugate modified doxorubicin nanoplatform for treating neutrophil-related inflammation

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ABSTRACT

Neutrophils, the most abundant leukocytes in human peripheral blood, are important effector cells that mediate the inflammatory response. During neutrophil dysfunction, excessive activation and uncontrolled infiltration are the core processes in the progression of inflammation-related diseases, including severe coronavirus disease-19 (COVID-19), sepsis, etc. Herein, we used sialic acid-modified liposomal doxorubicin (DOX-SAL) to selectively target inflammatory neutrophils in the peripheral blood and deliver DOX intracellularly, inducing neutrophil apoptosis, blocking neutrophil migration, and inhibiting the inflammatory response. Strong selectivity resulted from the specific affinity between SA and L-selectin, which is highly expressed on inflammatory neutrophil membranes. In inflammation models of acute lung inflammation/injury (ALI), sepsis, and rheumatoid arthritis (RA), DOX-SAL suppressed the inflammatory response, increased the survival of mice, and delayed disease progression, respectively. Moreover, DOX-SAL restored immune homeostasis in the body, without side effects. We have presented a targeted nanocarrier drug delivery system that can block the recruitment of inflammatory neutrophils, enabling specific inhibition of the core disease process and the potential to treat multiple diseases with a single drug. This represents a revolutionary treatment strategy for inflammatory diseases caused by inappropriate neutrophil activation.

1. Introduction

Neutrophils, the most abundant innate immune effector cells in human circulating leukocytes (accounting for 50%–70% of leukocytes) [1,2], are the first line of defense against bacterial and fungal infections and play an important role in various immune and inflammatory processes [3–5]. It has been shown that if neutrophils are dysregulated, the defense mechanisms involved in neutrophil infiltration and pro-inflammatory responses are potentially harmful to the host [6–8]. Excessive activation and uncontrolled infiltration of neutrophils are the main reasons for the continued deterioration of various diseases, including severe coronavirus disease-19 (COVID-19) [9–11]; sepsis [12,13]; pulmonary diseases [14–20], such as adult respiratory distress syndrome (ARDS), acute lung inflammation/injury (ALI), cystic fibrosis lung disease, and asthma; cardiovascular diseases [21,22], such as atherosclerosis, ischemia-induced tissue damage in myocardial infarction and stroke and thrombosis; autoimmune diseases [23–26], such as systemic lupus erythematosus, rheumatoid arthritis (RA), small-vessel vasculitis, and psoriasis; neuroinflammation and neurodegenerative diseases [27–29], such as multiple sclerosis (MS) and Alzheimer's disease; and cancer [30].

Many ongoing studies have attempted to manipulate all neutrophils to treat some of these diseases; therapeutic approaches have included targeting the neutrophil development and production and interfering with the accumulation of neutrophils at the inflammatory sites. Some of these treatment strategies have begun to enter clinical testing. For example, CXCR2 antagonists have been tested in clinical studies. In a phase II study, the CXCR2-blocking AZD5069 (ClinicalTrials.gov Identifier: NCT01890148) reduced the number of neutrophils in the sputum of patients with asthma. Phase II clinical trials of the anti-GM-CFS receptor antibody mavrilimumab (ClinicalTrials.gov Identifier: NCT01712399), which treats RA by inhibiting the development and/or function of neutrophils, have been successfully completed. These results indicate the onset of an exciting era in which neutrophil targeting is used for the treatment of human diseases.

However, although the strategy of targeting neutrophils to treat

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