Modulating macrophage plasticity for the treatment of disease

RCSI UNIVERSITY OF MEDICINE AND HEALTH SCIENCES

Researchers in RCSI have discovered that enhancing the expression of a particular enzyme maintains macrophages in an anti-inflammatory and tissue regenerative state. They have developed a target site blocker which up-regulates the expression of this enzyme and can be incorporated within biocompatible nanoparticles for targeted drug delivery. This disruptive technology can be exploited as a therapy for a range of autoimmune, inflammatory, and neurological diseases associated with an inflammatory burden mediated by macrophages.

BACKGROUND

Macrophages are a sub-type of immune cells that are critical for fighting infection in the body through the release of inflammatory and toxic mediators. However, if inflammation persists, they can also become destructive. This can lead to the severe tissue damage observed in variety of inflammatory and autoimmune diseases such as rheumatoid arthritis (RA), colitis, and multiple sclerosis (MS), diseases for which there are currently no cure. Treatments for managing such diseases include the use of drugs which limit inflammation and immune cell replication. Indeed, the global drug market for RA alone has been estimated to be $25 billion. However, these treatments are characterised by multiple side-effects, including systemic immune suppression which leaves an individual susceptible to opportunistic infections and cancer. Furthermore, while the current treatment regimens limit inflammation in the early stages of disease, the underlying tissue damage continues to progress irrespectively.

VALUE PROPOSITION

There is an unmet clinical need for the identification of novel targets which both limit inflammation and promote repair. Researchers in RCSI have recently identified that enhancing the expression of a particular enzyme is essential for maintaining macrophages in an anti-inflammatory and tissue regenerative state. This in turn has led to the invention of a target site blocker (TSB) capable of promoting an anti-inflammatory and reparative phenotype in macrophages which potentially could be exploited as a therapy for a range of macrophage-associated autoimmune/inflammatory and neurological diseases.

TECHNOLOGY

A microRNA (miRNA) binds its target mRNA via sequence-specific miRNA responsive elements, impeding its translation and leading to low quantity of the protein product. TSBs are locked-nucleic acid antisense oligonucleotides that specifically compete with miRNAs for binding to these responsive elements, hence preventing them from gaining access to those sites. In this invention, the TSB interferes with individual miRNA binding sites (for example miR-155) within the target mRNA, thereby preventing the binding of endogenous miRNAs and increasing the expression of the protein encoded by the targeted mRNA (Fig. 1). Furthermore, other TSBs that may block the binding of an array of miRNAs on the target mRNA have been designed that capitalise on the potential of the therapeutic. These TSBs have also been incorporated into biocompatible nanoparticles for specific drug delivery to macrophages.

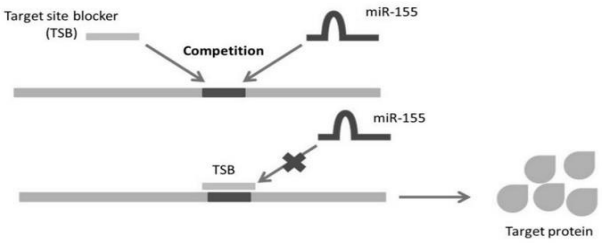

Fig 1. TSB competes with miR-155 for binding to the target mRNA thereby increasing the expression of the target protein.

FEATURES	BENEFITS
Maintains macrophages in anti-inflammatory state	Applicable to a range of diseases (RA, colitis, MS)
Blocks binding of an array of miRNAs	Enhances the potential of therapeutic TSBs
Incorporation of TSBs within nanoparticles	Enhanced drug delivery to macrophages

TECHNOLOGY READINESS LEVEL

- Patent application filed
- In vivo proof of concept

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