Modified siRNAs for silencing TNF-α gene expression to treat inflammatory diseases

CSIC, the Universitat de Barcelona and the Universitat Autónoma de Barcelona have developed new small interfering RNAs (siRNA) chemically modified for treatment of inflammatory diseases, particularly intestinal diseases, through TNF-α gene expression silencing. These compounds show high inhibitory activity and reduce the non-specific immune response triggered by other synthetic siRNAs.

An offer for Patent Licensing and/or R+D collaboration

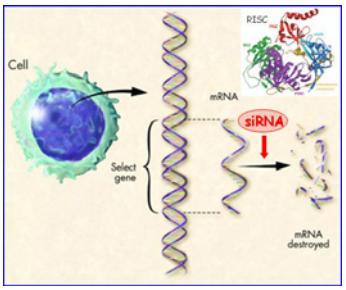
Treatment of inflammatory diseases through the gene expression silencing therapy

RNA interference (RNAi) is an important post-transcriptional mechanism that induces silencing of a specific gene expression through the action of small interfering RNAs duplexes (siRNA) that inhibit translation of messenger RNA (mRNA) to protein. Such inhibition is triggered when the antisense or guide strand of a siRNA binds to a protein named RISC, and the complex formed is able to cleave the complementary mRNA sequence so that the corresponding protein is not formed.

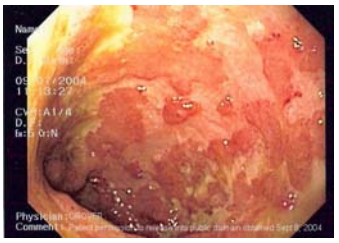
New siRNA with small modifications have been developed, based on the addition, through a phosphodiester bond, of a propanediol group at the 3'-end of either of the strands of a siRNA that also contains some 2'-OMe groups. These slight modifications in the siRNA, when introduced jointly, show a great capacity to inhibit gene expression of tumor necrosis factor-α (TNF-α), a pro-inflammatory cytokine that plays an important role in inflammatory processes, but avoiding immune response stimulation triggered as an innate defense mechanism when synthetic siARN are introduced in the cell.

Efficacy of these compounds has been proved both *in vitro*, in cultured cells and primary macrophages and *in vivo*, in a chronic colitis mouse model, with an observed reduction of 50% in all disease markers in relation to the use of unmodified siRNAs.

These new siRNA molecules developed may have use for treatment of diseases caused by gene overexpression such as inflammatory diseases, irritable bowel syndrome, Crohn disease, ulcerative colitis, or rheumatoid arthritis.



RNA interference mechanism for gene regulation therapy



These modified siRNA have shown 50% higher efficiency during treatment of mice with ulcerative colitis as compared to treatment with unmodified siRNA. Picture by Samir at English Wikipedia, reproduced under a Creative Commons BY-SA 3.0 license.

Main advantages

These siRNA show high efficacy compared to other siRNA described due to:

- Modifications introduced increase stability to nucleases action, conferring a prolonged inhibitory effect.
- Enhance cell administration and distribution, acting directly on the target tissue or organ, in this case the intestine.
- No secondary effects of non-specific stimulation of the immune response associated to treatments with siRNAs.
- Clear clinical outcome: Topical treatment (rectal administration) in mice gave clear decrease of inflammation by improving clinical markers.

Higher silencing capacity of TNF-α expression than that achieved by unmodified siRNAs or modified with other synthetic modifications, both *in vitro* and *in vivo*, and at nanomolar concentrations.

Patent Status

Spanish application filed

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