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A Method for Suppressing Innate Immune Responses to RNA Therapy

Stanford researchers have developed a method to suppress immune responses to RNA therapy by chemically treating the RNA with an acylating reagent.

RNA therapy, which uses RNA-based molecules to modulate biological pathways, is a versatile and specific approach with the potential to treat a wide range of diseases. One of major hurdles to advancing RNA therapy is immunogenicity; injected or administered RNAs can be recognized by the immune system as foreign entities, triggering an innate immune response that might reduce the therapeutic efficacy and possibly cause side effects. There have been efforts to address this by modifying the structure or sequence of RNA nucleotides, suppressing the immune system, and packaging RNA within a shielding delivery system.

Researchers at the Kool Lab in Stanford have identified a novel method to mitigate the immunogenicity problem. They used an acylating reagent to add acyl groups to the 2'-hydroxyl (OH) groups on RNAs. Lipofecting cells with the resulting polyacylated RNAs prevented recognition by toll-like receptors (TLRs) that typically trigger the immune response. Consequently, this led to a reduction in inflammatory responses without affecting translation. This approach is beneficial in that the RNA can be from any source and be of any length.

Stage of Development
In vitro data in cultured cells. They are expanding the *in vitro* research to test in a wider range of cell types, including primary cells.

Applications

- mRNA vaccines
- mRNA therapeutics
- RNA interference

- CRISPR therapies and diagnostics
- siRNA
- RNA aptamers
- Anti-sense oligonucleotides

Advantages

- Can address a wide range of diseases:
  - Genetic disorders
  - Cancer
  - Neurological disorders
  - Infectious diseases
- Allows for targeted therapy
- Could be personalized
- Post-transcriptional method
- Can apply to RNAs of any length and origin
- Reversible
- Immune system not altered
- Translation is not compromised
- Rapid and simple modifications

Publications

- Kadina, A., Kietrys, A. M., et al. (2018). RNA Cloaking by Reversible Acylation. *Angewandte Chemie (International ed. in English), 57*(12), 3059–3063.
- Habibian, M., McKinlay, C., et al. (2019). Reversible RNA acylation for control of CRISPR-Cas9 gene editing. *Chemical science, 11*(4), 1011–1016.
- Fang, L., Xiao, L., et al. (2023). Reversible 2'-OH acylation enhances RNA stability. *Nature Chemistry, 15*(9), 1296–1305.
- Fang, L., Velema, W. A., et al. (2023). Pervasive transcriptome interactions of protein-targeted drugs. *Nature chemistry, 15*(10), 1374–1383.

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