

Defecting 2'-O methyltransferase as a novel strategy for live attenuated vaccine development

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Editorial

The 5' ends of almost eukaryotic cellular mRNAs possess Cap 0 structure with an N-7 methyl-guanosine moiety linked to the first nucleotide of the nascent mRNA via a 5'-5' inverted triphosphate bridge. And in higher eukaryotes, Methylation of cellular mRNA occurs additionally at the 2'-O position of the penultimate to form the Cap1 structure (7mGpppNm-) and antepenultimate to form Cap2 structure (7mGpppNmNm-).

The cap structure ensures the transcript to escape a variety of cellular 5'-3' exonucleases and promote recognition of eIF4E for translation. Besides, RNA capping was also involved in other cellular processes such as RNA splicing and exports.¹⁻³ Vast majority of viruses replicate in the cytoplasm, and also they failed to access the host capping machinery in the nucleus. Therefore, they evolved their own capping apparatus, and a diversity of mechanisms which leads to the same RNA cap structure are being deciphered.⁴⁻⁸

In the conventional pathway, the cap structure is added to the nascent 5'-triphosphate mRNA in a series of reactions. First, the 5'-triphosphate of the nascent RNA is hydrolyzed the RNA triphosphatase (RTPase), and the γ -phosphate will be removed to leave 5'-diphosphate RNA; Second, an RNA guanylyltransferase (GTase) transfer a GMP moiety to ppN- to yield the cap core structure GpppN- in 5'-5' orientation. Third, the core cap structure is methylated on the N-7 position of its guanine by an RNA guanine N7 methyltransferase (N7-MTase) to generate the minimal Cap 1 structure. Lastly, further Methylation by ribose 2'-O methyltransferase occurs at the 2'-position of the first transcript nucleoside (Cap 1) and the second nucleotide (Cap 2).

Recently, Zust R, et al.⁹ demonstrated the 2'-O-methylation of mRNA protected viral RNA from recognition by Mda5 and thus prevented production of type I interferon in virus infected cells, and also 2'-O-methylation of viral mRNA contributes to evasion of the interferon-mediated restriction of viral replication. Therefore, the human and mouse coronavirus mutants lacking 2'-O-methyltransferase activity induced higher expression of type I interferon.⁹

With this in mind, targeting viral 2'-O-methyltransferase might provide a new and valid rational approach for a live attenuated vaccine design. In 2013, dengue virus mutants lacking 2'-O-methyltransferase activity are attenuated in mice and rhesus monkeys, but elicit a strong adaptive immune response. Monkeys immunized with a single dose of the mutant virus showed 100% sero-conversion even when a dose as low as 1,000 plaque forming units. Animals were fully protected against a homologous challenge.¹⁰ Very recently, Menachery V, et al.¹¹ generated mutants in SARS-CoV 2'-O-methyltransferase by replacing critical residues within the conserved catalytic KDKE motif. Interestingly, the mutants remained replication competent, but

these mutants were attenuated in IFN competent cells, had reduced pathogenesis and complete protected mice from lethal challenge in vivo.¹¹

Whether the balance between low virulence and high immunogenicity is achieved in humans by 2'-O-MTase mutants remains to be elucidated. However, current data demonstrated that targeting viral 2'-O-methyltransferase as a valid strategy for rapid, rational vaccine design for majority viruses encoding their own 2'-O-methyltransferase.

Acknowledgments

None.

Conflicts of interest

None.

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