Defecting 2'-O Methyltransferase as a Novel Strategy for Live Attenuated Vaccine Development

Editorial

Volume 3 Issue 1 - 2016

Hui Cai*

The Ohio State University, USA

***Corresponding author:** Hui Cai, The Ohio State University, 1925 Coffey Road, Rm 219, Columbus, OH 43210, USA, Tel: 469-766-1765; Email: chncaihui@gmail.com

Received: January 12, 2016 | **Published:** January 13, 2016

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 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-methylatransferase activity induced higher expression of type I interferon [9].

With this in mind, targeting viral 2'-O-methylatransferase 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'-methylatransferase by replacing critical residues within the conserved catalytic KDKE motif. Interesting, 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.

References

1. Filipowicz W, Furuichi Y, Sierra JM, Muthukrishnan S, Shatkin AJ, et al. (1976) A protein binding the methylated 5'-terminal sequence, m7GpppN, of eukaryotic messenger RNA. Proc Natl Acad Sci U S A 73(5): 1559-1563.
2. Schibler U, Perry RP (1977) The 5'-termini of heterogeneous nuclear RNA: a comparison among molecules of different sizes and ages. Nucleic Acids Res 4(12): 4133-4149.
3. Darnell JE (1979) Transcription units for mRNA production in eukaryotic cells and their DNA viruses. Prog Nucleic Acid Res Mol Biol 22: 327-353.
4. Weber F, Haller O, Kochs G (1996) Nucleoprotein viral RNA and mRNA of Thogoto virus: a novel cap-stealing mechanism in tick-borne orthomyxoviruses? J Virol 70(12): 8361-8367.
5. Vasiljeva L, Merits A, Auvinen P, Kääriäinen L (2000) Identification of a novel function of the alphavirus capping apparatus. RNA 5'-triphosphatase activity of Nsp2. J Biol Chem 275(23): 17281-17287.
6. Liu L, Dong H, Chen H, Zhang J, Ling H, et al. (2010) Flavivirus RNA cap methyltransferase: structure, function, and inhibition. Front Biol (Beijing) 5(4): 286-303.
7. Decroly E, Ferron F, Lescar J, Canard B (2012) Conventional and unconventional mechanisms for capping viral mRNA. Nat Rev Microbiol 10(1): 51-65.

8. Ogino T, Banerjee AK (2011) An unconventional pathway of mRNA cap formation by vesiculoviruses. Virus Res 162(1-2): 100-109.

9. Züst R, Cervantes-Barragan L, Habjan M, Maier R, Neuman BW, et al. (2011) Ribose 2'-O-methylation provides a molecular signature for the distinction of self and non-self mRNA dependent on the RNA sensor Mda5. Nat Immunol 12(2): 137-143.

10. Züst R, Dong H, Li XF, Chang DC, Zhang B, et al. (2013) Rational design of a live attenuated dengue vaccine: 2'-o-methyltransferase mutants are highly attenuated and immunogenic in mice and macaques. PLoS Pathog 9(8): e1003521.

11. Menachery VD, Yount BL, Josset L, Gralinski LE, Scobey T, et al. (2014) Attenuation and restoration of severe acute respiratory syndrome coronavirus mutant lacking 2'-o-methyltransferase activity. J Virol 88(8): 4251-4264.

Citation: Cai H (2016) Defecting 2'-O Methyltransferase as a Novel Strategy for Live Attenuated Vaccine Development. J Hum Virol Retrovirol 3(1): 00078. DOI: 10.15406/jhvrv.2016.03.00078