History of PseudoUridine

BOC Sciences® PseudoUridine

PseudoUridine (abbreviated by the Greek letter psi-Ψ) is the C5-glycoside isomer of uridine that contains a C-C bond between C1 of the ribose sugar and C5 of uracil, rather than the usual C1-N1 bond found in uridine. The C-C bond supports more rotational freedom and conformational flexibility. In addition, PseudoUridine has an extra hydrogen bond donor at the N1 position, making it the most abundant RNA modification in cellular RNA.

1951

The first modified nucleoside was found in the RNA hydrolysis product, which soon became known as the fifth nucleoside.

1957

It was identified as the 5-ribosyluracil and named PseudoUridine (Ψ).

1965

A study by Naylor *et al.* demonstrated that Ψ-containing dinucleotides were more resistant to degradation from snake venom and spleen phosphodiesterases than their U-containing counterparts.

1995

Ψ was proposed to perform the same stabilizing function in most structural contexts.

2000

Pseudouridylation of RNA conferred an important selective advantage in a natural biological context.

2001-2002

Ψ altered RNA structure in a relatively significant way, and RNA pseudouridylation was used for RNA stabilization.

2005

The addition of Ψ to IVT mRNA as a substitute for uridine suppressed the immune response mechanism.

2008

Karikó *et al.* confirmed that unmodified mRNA, compared to Ψ-modified mRNA, was more immunogenic in mice. However, they have also suggested that while Ψ-modified mRNA could be preferable for mRNA vaccines, it would eventually require the co-administration of an adjuvant such as lipopolysaccharide or an immunostimulatory oligo.

2010

It was reported that Ψ-modified transcripts, coding for four transcription factors (KLF4, c-MYC, OCT4, and SOX2), were successfully used to reprogram human cells to pluripotency with great efficiencies.

2011

Work from the Karikó/Weissman lab suggested that Ψ-modified mRNA could be more resistant to RNase L-mediated degradation, which could be achieved by limiting the activation of 2′-5′-oligoadenylate synthetase, an important enzyme in the innate antiviral response that is usually activated by double-stranded RNA. Because RNase L is a 2′-5′-oligoadenylate synthetase-dependent ribonuclease, the ability of pseudouridylated mRNA to limit the activity of 2′-5′-oligoadenylate synthetase could provide an advantage to Ψ-modified mRNA over unmodified mRNA.

2013

Ψ was incorporated into RNA transcripts via *in vitro* transcription, where UTP is replaced by ΨTP.

2014

Ψ has been found in tRNA, rRNA, snRNA, mRNA, and other types of RNA.

2019

It was reported that Ψ is also capable of modulating the translatability or sense codon decoding.

2021

Clinical trial test results ultimately revealed that only 48% of efficacy against the symptomatic disease was achieved using the unmodified mRNA vaccine, suggesting that both modified Ψ and the use of LNP technology were critical success factors for platform validation of mRNA.

Conclusion

Whereas the existence of Ψ has been known for several decades, its contributions to various cellular processes are just beginning to be understood.

Undoubtedly, developments in biology and chemistry of RNA modification (Ψ) will be game-changing in defining an end to the pandemic.

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