Kill or corrupt: the mode of action of nucleotide analogues against SARS-CoV2

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Réplicases virales: Structures, mécanismes, et drug-design

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Understanding how the CoV replication/transcription complex (RTC) works is central to design antiviral drug therapies as well as to the understanding of the emergence of variants. The SARS-CoV2 RTC is blatantly more 'active' than any other viral RdRp known. It possesses both unusually high nucleotide incorporation rates and high-error rates allowing facile insertion of mispaired nucleotides ('errors') but also nucleotide analogues used as antiviral drugs.

However, the SARS-CoV2 is 'naturally' resistant to many NAs because the RTC coopts nsp14, a 3'-to-5' exonuclease (ExoN) adjacent to the nsp12 polymerase, to excise chain-terminating NAs.

Unlike for HCV and other (+)RNA viruses, 2'-ribose-modified NAs are surprisingly more discriminated relative to other viral polymerases. Likewise, 1'-cyano or 2'-F, 2'-methyl modifications only modestly decrease their removal by the CoV-specific RNA repair system nsp14-ExoN.

With this in mind, we propose to sort NAs according to their mechanism-of-action on the RTC.

NAs can be RNA synthesis 'killers' by chain-termination (either immediate or delayed), or RNA 'corruptors'. In the latter case, chemical modifications can translate into either chemical or genetic corruption of the viral RNA message.

Understanding the specifics of NAs (Remdesivir, Molnupiravir, Ribavirin, Bemnifosbuvir, Favipiravir,...) in these mechanisms is essential to prevent drug-resistance, emergence of variant, and access to powerful combination therapies. In the long run, this knowledge should efficiently guide the synthesis of much awaited orally available, wide spectrum drugs finding their use in prophylaxis and therapeutics against COVID-19 and other coronavirus diseases.