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Editorial

Second-Generation SARS-CoV-2 Recombinants: Lessons from Other Viruses

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RNA viruses have developed notable strategies to evolve and escape host immunity. For non-segmented viruses, which represent most viral species, cumulative mutations (antigenic drift) are the main way of evolution. However, when two different RNA viruses infect the same cell, they can undergo two forms of recombination, both leading to antigenic shifts: RNA recombination and reassortment, with the latter restricted to viruses with segmented genomes [1]. For example, homologous recombination plays only a very minor role in the evolution of human influenzavirus A [2], which instead can reassort the RNA segments of its genome (intra- or inter-subtypic reassortment), as well as undergo intragenic recombination between different RNA segments (commonly referred to as nonhomologous recombination [3–5]), as well as intragenic recombination between viral RNA and exogenous RNA [6].

Despite being theoretically possible in any RNA virus, the rates of recombination vary markedly among RNA viruses. Some viruses, particularly those with negative-sense single-stranded genomes, exhibit such low rates of recombination that they are effectively clonal. Although recombination is often represented as a form of sexual reproduction, there is little evidence that recombination in RNA viruses evolved as a way of creating advantageous genotypes or removing deleterious mutations. In particular, there is no association between recombination frequency and the burden of a deleterious mutation. Similarly, there is little evidence that recombination could have been selected as a form of genetic repair.

Some retroviruses such as HIV recombine rapidly because their virions contain two genome copies and template switching between these copies is unavoidable during the viral replication cycle. Recombination in RNA viruses is hence likely a mechanistic by-product of the processivity of the viral polymerase that is used in replication, and it varies with genome structure. Negative-sense single-stranded RNA viruses may recombine at low rates because of the restrictive association of genomic RNA in a ribonucleoprotein complex, as well as a lack of substrates for template switching. Some positive-sense single-stranded RNA viruses exhibit high rates of recombination that can exceed the rates of single nucleotide variations. Comparison across multiple viruses suggests an inverse correlation between genome length and recombination rate. Patino-Galindo et al. detected high levels of recombination in Sarbecoviruses, HBV, HEV, Rhinovirus A, and HIV. Noteworthy recombination hotspots are found in MERS-CoV and Sarbecoviruses (at Spike, Nucleocapsid and ORF8) [7]. Of interest, recombination has also been recently reported for DNA viruses, in particular, Anelloviridae [8].

Second-generation recombinants are defined as recombinants of (first-generation) recombinant lineages. To have second-generation recombinants, several conditions are needed:

- Different sublineages should exist, including a growing share of first-generation recombinants;

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- Different sublineages should circulate at high levels (syndemic) to facilitate co-infection in different lineages;
- High levels of viral surveillance (genome sequencing), making detection and tree reconstruction feasible.

Second-generation recombinants have been so far documented for several viruses:

- Retroviruses:
  - HIV-1: at present, 106 circulating recombinant forms (CRFs) have been identified worldwide, with many more unique recombinant forms (URF). URFs are responsible for at least 20% of HIV-1 infections worldwide—a proportion that reaches 40% in some African countries [9]. Inter-subtype recombinant viruses, especially CRF01_AE and CRF07_BC, have become the predominant strains of the HIV-1 epidemic in China [10]. The double infection between CRFs established more optimal conditions for the second-generation recombination, and many second-generation recombinants were represented by the recombination of CRF01_AE and CRF07_BC fragments, such as CRF79_0107 [11], CRF80_0107 [12], CRF102_01075 [13], CRF109_0107 [14], CR125_0107 [15], and others [16–24]. Other instances include CRF01_AE x CRF08_BC [25], CRF01_AE x subtype B [26], CRF07_BC x CRF83_cpx [27], and CRF86_BC x a URF [28] also from in China.
  - HTLV [29].
- HBV X/C [30] and complex A/C/G recombinants [31].
- ssRNA viruses.
  - Enterovirus [29].
  - Alphacoronavirus: Clade B (Serotype II) Feline coronavirus (Alphacoronavirus 1) [32].
  - Betacoronavirus:
    - SARS-CoV-2 [33,34]: when it comes to SARS-CoV-2, the nomenclature of recombinants is managed so far only by the PANGOLIN phylogeny, which ante poses the "X" prefix. With 2372 sublineages designated as of 14 April 2023 (including 920 labeled as Omicron by the WHO), there have been 58 recombinant lineages (excluding designated progenies). The diversification of progenies has led to fourth-level descendants, which, according to PANGOLIN rules, should be shortened using aliases: the point here is that rules impose the next available alias without the X prefix, preventing the immediate understanding of whether the originating lineage was or not a recombinant [35].
- XBL is an XBB.1* where part of ORF1a has been replaced with BA.2.75.* [36].
- XBY is XBF x BR.2.1.
- XBW is XBB.1.5 x BQ.1.14.
- XBV is XBB.1 x CR.1.

In conclusion, while reconstructing, further-generation recombination might sound like a mere style exercise, but it has huge implications for vaccine preparedness and seroepidemiology, recombination being a key driver of immune escape. With widespread endemic circulation, more and more second- and further-generation SARS-CoV-2 recombinant lineages are expected, with some of them posing a theoretical concern for increased disease severity and vaccine efficacy.

Conflicts of Interest: We declare that we have no conflict of interest related to this manuscript.

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