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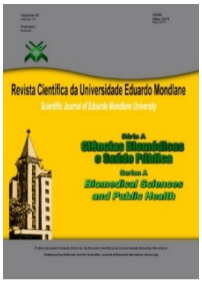

MINI REVIEW: the role of homologous recombination in emergence of SARS-CoV-2

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Artigo de revisão

MINI REVIEW: the role of homologous recombination in emergence of SARS-CoV-2

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ABSTRACT: During viral recombination, new genetic combinations are generated from the mixing or crossover of two or more nucleic acids from different origins. This process, therefore, requires that more than one virus infects the same cell in order to generate combinations of new viral sequences or chimeric molecules. This process is thought to have an impact in epidemiology, emergence and evolution of RNA viruses. In this mini-review, we highlight the homologous recombination and explain how it might have contributed in the emergence of SARS-CoV-2.

Keywords: Homologous recombination, SARS-CoV-2, recombination in RNA viruses.

MINI-REVISÃO: o papel da recombinação homóloga na emergência de SARS-CoV-2

RESUMO: Durante a recombinação viral, novas combinações genéticas são geradas a partir da mistura ou cruzamento de dois ou mais ácidos nucleicos de diferentes origens. Esse processo, portanto, exige que mais de um vírus infecte a mesma célula a fim de gerar combinações de novas sequências virais ou moléculas quiméricas. Pensa-se que este processo tenha um impacto na epidemiologia, emergência e evolução dos vírus RNA. Nesta revisão, realçamos a recombinação homóloga e elucidamos como ela pode ter influenciado no surgimento do SARS-CoV-2.

Palavras-chave: Recombinação homóloga, SARS-CoV-2, recombinação em vírus RNA.

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RECOMBINATION IN RNA VIRUSES

Viral recombination requires that more than one virus infects the same cell in order to generate combinations of a new viral sequences or chimeric molecules (PÉREZ-LOSADA *et al.*, 2015; SIMON and HOLMES, 2011). This is usually different from mutations, wherein changes occur at the nucleotide level and new variants of the same virus are generated (SIMON and HOLMES, 2011). In addition, the exchange of genetic material between viruses is usually non-reciprocal, meaning that the recipient of genome portion does not act as donor of the replaced portion in the original source. In this regard, the term recombination does not have the same meaning in viruses that it does in diploid, sexually reproducing organisms wherein the exchange of genetic material between chromatidis in the first meiosis division is reciprocal (PÉREZ-LOSADA *et al.*, 2015).

Recombination events are much more frequent in viruses with ribonucleic acid material (RNA) than in viruses with deoxyribonucleic acid(DNA), and hence, most disease outbreaks to date are associated with RNA viruses. Even though, studieshave demonstrated that the recombination

rate is different within the major groups of RNA viruses. Those with a minus (-) single-stranded RNA genome show the lowest recombination rate, whereas those with plus (+) single-stranded RNA genome (e.g. human immunodeficiency virus (HIV), Coronavirus) show the highest recombination rate (TAUCHER *et al.*, 2010). However, there were some exceptions to this general pattern. For instance, in Zika virus with (+)ssRNA recombination is rarely observed, whereas in Influenza with (-)ssRNA recombination (re-assortment) is very frequent (RABADAN *et al.*, 2008). A further way in which genetic changes can occur is viral re-assortment; in which new strains emerge through whole gene replacement from another related virus (AUSTERMANN-BUSCH and BECKER, 2012; SCHEEL *et al.*, 2013). RNA recombination occurs in all RNA viruses whereas re-assortment only occurs in RNA viruses with a segmented genome such as Influenza A virus (SIMON and HOLMES, 2011). Albeit the two types of recombination are different in terms of occurrence, they both require that two or more viruses infect the same host cell (PÉREZ-LOSADA *et al.*, 2015). In other words, these types of recombination only take place in co-infected host cells.

HOMOLOGOUS RECOMBINATION AND ITS ROLE IN THE EMERGENCE OF SARS-COV-2

Generally, different models have been proposed to explain how a hybrid RNA sequence is formed after an intermolecular exchange of genetic information between different nucleotide sequences in a co-infected host (PÉREZ-LOSADA *et al.*, 2015; SIMON and HOLMES, 2011). The most widely accepted model is "copy choice" (SIMON and HOLMES, 2011), wherein the viral replication enzyme RNA polymerase switches from one template (the donor) to another (the receptor) during replication whilst remaining bound to the growing RNA nucleic acid chain. The result is generation of an RNA molecule (viral sequence) with mixed origins.

An alternative way is that the template switching between RNA molecules from different origins is driven by sequence similarities (i.e., it only occurs between regions with high sequence similarities). This process is called "homologous recombination" (ZHANG and TEMIN, 1994; PÉREZ-LOSADA *et al.*, 2015). This process is well-known and occur in many viruses including viral hepatitis (B and C), Dengue virus and HIV. In fact, the best example of homologous recombination is that exhibited by the HIV (SIMON and HOLMES, 2011). To date, HIV is the only Retrovirus shown to have high recombination rates; ranging from 1.38 x 10-4 to 1.4 x 10-5 s/s/y (per site per year) (PÉREZ-LOSADA *et al.*, 2015).

Homologous recombination is the type of RNA recombination common in *Coronaviridae* family and may have contributed to the SARS-CoV-2 cross-species transmission. A recent study has shown that homologous recombination may have occurred within the viral spike protein which the virus uses to recognize the host cell receptor (Ji *et al.*, 2020). Sequence analysis carried out in the same study revealed that SARS-CoV-2 is recombinant virus between the bat coronavirus and an origin-unknown coronavirus (for more details see Ji *et al.*, 2020).

CONCLUSION

Most RNA viruses that cause diseases in humans have "jumped" from animals to humans and for those that do not have a clear zoonotic path there is evidence to suggest that they have zoonotic origins in evolutionary terms. Recombination events might have allowed these viruses to effectively adapt in humans and cause apparent or unapparent diseases. SARS-CoV-2 is recombinant virus between the bat coronavirus and an origin-unknown coronavirus.

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