Oral presentation

An in-depth structural and dynamic look at the specific enzymatic characteristics of TREX1 unveils its varied functions in processing both RNA and DNA/RNA hybrids.

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TREX1(Three prime Repair Exonuclease 1) and TREX 2 are the most abundant 3' to 5' exonucleases in mammalian cells and are involved in various DNA metabolism progresses [1, 2]. Dysfunctional TREX1 leads to various autoimmune diseases with accumulation of endogenous ssDNA, dsDNA, and DNA/RNA hybrids in the cytoplasm that trigger immune activation through the cGAS-STING pathway. Although inhibition of TREX1 could be a valuable cancer immunotherapy strategy, profiling cellular functions in terms of its potential substrates is a crucial prerequisite. The intricate workings of TREX1 in DNA processing have been unveiled [1], with a particular emphasis now placed on its vital role in processing DNA/RNA hybrids and RNA substrates. The nuclease activity measurements here establish that TREX1 can digest both ssRNA and DNA/RNA hybrids but not dsRNA. The newly solved structures of TREX1-RNA product and TREX1-nucleotide complexes show that 2'-OH does not impose steric hindrance or specific interactions to distinguish RNA and DNA substrates. Through all-atom molecular dynamics (MD) simulations, we illustrate that the 2'-OH-mediated intra-chain hydrogen bonding in RNA substrates would affect the binding with TREX1 and thereby reduce the exonuclease activity. This notion of higher conformational rigidity in RNA leading TREX1 to exhibit weaker catalytic cleavage is further validated by the binding affinity measurements with various synthetic DNA-RNA junctions. The results of this work thus provide new insights into the mechanism of TREX1 processing RNA and DNA/RNA hybrids and contribute to a better molecular- level understanding of TREX1's complex cellular functions as an exonuclease [3].

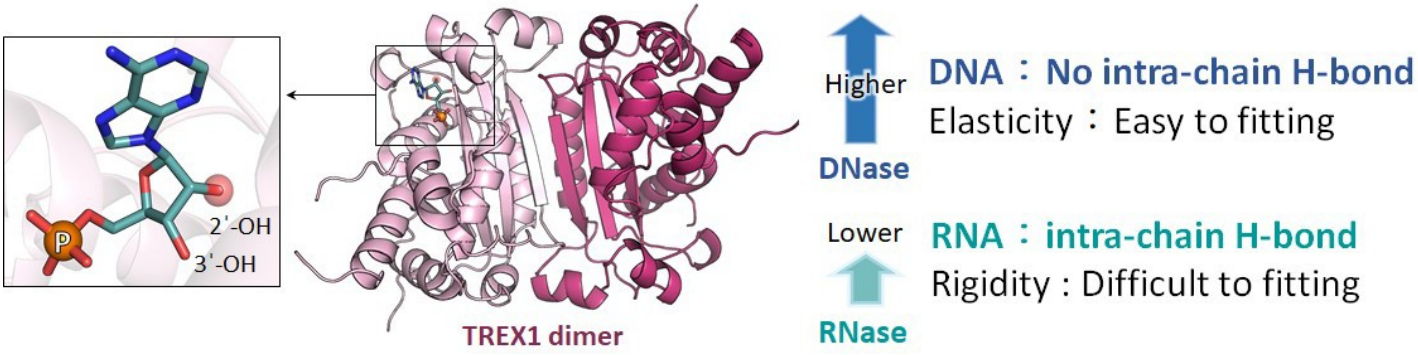

Figure 1. TREX1 are DNase and RNase with a preference for DNA. This is due to the intra-chain hydrogen bonds formed on the RNA substrate, increasing its rigidity. RNA with higher rigidity is more challenging to bind and digest by TREX1.

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[2] Cheng, H. Lo.; Lin, C.T.; Huang, K.W.; Wang, S.; Lin, Y. T.; Toh, S. I.; Hsiao, Y.Y.* (2018). Nucleic Acids Res. 46(22):12166-12176

[3] Huang, K.W.; Wu, C.Y.; Toh, S.I.; Liu, T.C.; Tu, C.I; Lin, Y.H.; Cheng, A.J.; Kao, Y.T.; Chu, J.W.* & Hsiao, Y.Y.* (2023). Nucleic Acids Res., 51(21): 11927–11940.