

PRESS RELEASE

In defence mode: this is how Zika virus protects key parts of its genome

New research by SISSA explains how the virus succeeds in protecting important parts of its genome from the defence mechanisms of the infected cell. A simple and ingenious strategy discovered thanks to computer simulations



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To fight viruses, cells can deploy defence enzymes that progressively destroy viral genome strands starting from one of the two strand ends. However, this degradation mechanism is not effective against epidemic viruses such as Zika. In fact, the defence enzyme jams at precise points of the viral genome, which put up a strenuous resistance by assuming a “defensive” conformation. This is how the virus succeeds at protecting important pieces of its RNA inside infected cells, as demonstrated by a recent study coordinated by SISSA of Trieste and published in the journal *Nature Communications*.

Although the capability of some viruses, such as those responsible for Zika infection, dengue or yellow fever, to generate RNAs resistant to the attack from the cellular machinery was already known, the scientists have discovered and explained in this study the mechanistic rationale behind the phenomenon using computer simulations. Some parts of the viral RNA strand react to the

progressive enzymatic degradation, which starts from one particular end of the strand, by assuming an extremely compact form. The degradation process is thus blocked and eluded. At the same time, if the same RNA strand is approached from the other end, the one engaged by the enzymes that copy it, the molecule does not oppose as strongly, allowing the virus to replicate itself efficiently. The defence mechanism, in short, starts where the attack begins. The new study opens new perspectives for the use of computer simulations to discover heretofore unimagined properties of viral RNAs and thus providing, in perspective, possible mechanistic clues for novel therapeutic approaches. Furthermore, the unusual properties found in Zika RNA, which are the product of the long evolutionary race between the virus and the infected organisms, could be exploitable for designing new meta-materials endowed with directional mechanical resistance.

Virtual experiments to study viral genome resistance

“Lab experiments had already discovered that sizeable portions of the Zika genome could successfully resist to the attack of degrading enzymes. How exactly this occurred, however, was unclear and beyond reach of direct probing with current experimental techniques”, explains Cristian Micheletti of SISSA, who coordinated the study. To shed light on the issue, the scientists have used computer simulations, reproducing in a sort of virtual experiment what happens inside the cell when the viral RNA is engaged at its two ends. “The research has allowed us to understand how the degradation resistance of these viral RNA is encoded in their intricate structure and how the latter, in turn, causes the mechanical resistance to be so different at the two ends. The uncovered mechanical rationale is as simple as it is elegant and at the same time very efficient.”

Like an automatic umbrella

Micheletti explains it using the metaphor of an automatic umbrella: “if we put our automatic umbrella into the holder and we inadvertently press the button, the umbrella will get stuck and will resist our attempts to pull it out. This is more or less what happens when the defence enzymes interact with special spots of the viral RNA strand: they trigger a tightening process of the strand which prevents them from proceeding any further”. By contrast, the enzymes that read or copy the same viral RNA work from the opposite end of the strand, and do not trigger a significant resistance, allowing the pathogen to replicate and spread the infection. In short, by taking the umbrella from the other end, there is no risk of triggering the switch.

From biology to nanotechnology: new research perspectives

Antonio Suma, lead author of the study, explains: “By using modelling and simulations we have shed light on the unusual mechanical properties of Zika genome and complemented experiments by providing a detailed description of the underpinning atomistic processes.”

“It will be very interesting” continues Micheletti, “to investigate whether these surprising mechanical properties can be found in other viral and non-viral RNA. We also hope our findings will inspire the realization of new types of meta-materials, for example supra-molecular strands that, thanks to a judicious design of their conformation, might acquire the same directional mechanical strength found in Zika RNA.”

USEFUL LINKS

Full paper:

<https://rdcu.be/b5RN1>

IMAGE

“Representation of the Zika RNA fragment considered in the study”

Credit: Cristian Micheletti

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