New technique reveals how Zika virus interacts inside our cells

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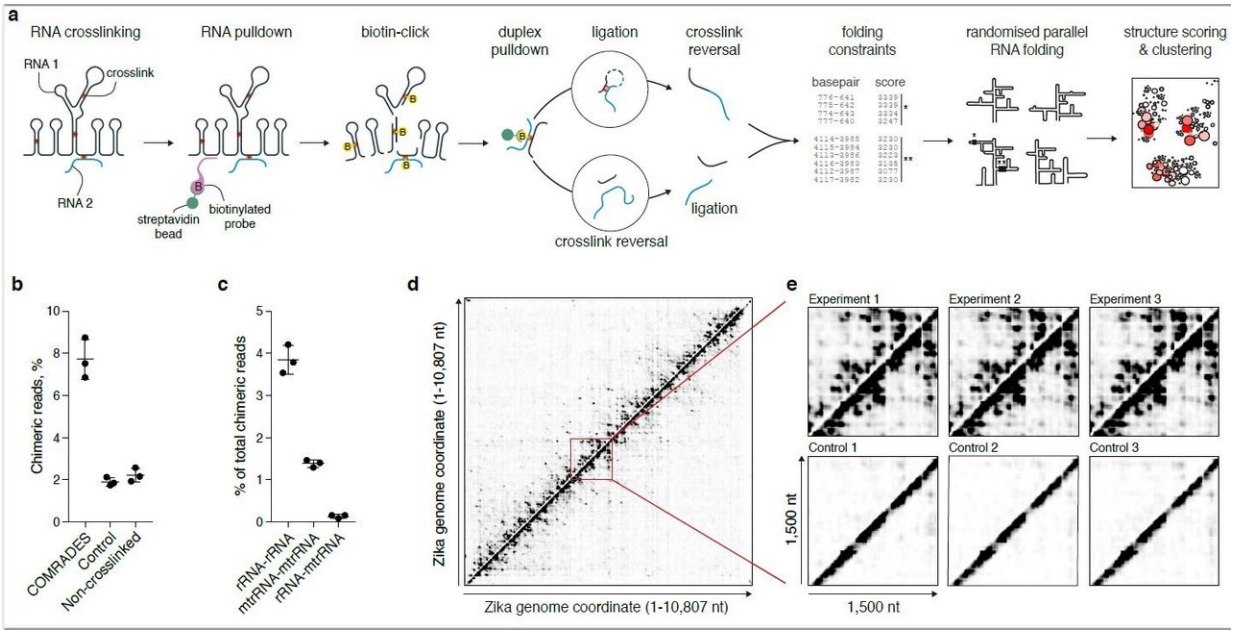

Credit: *Nature Methods* (2018). DOI: 10.1038/s41592-018-0121-0

Scientists have developed a new technique that can determine how viruses interact with a host's own RNA. As well as providing insight into how viruses direct the host cell to create new virus particles, this technique, published today in *Nature Methods*, could allow researchers to design artificial molecules capable of blocking the virus replication process and preventing the virus spreading.

RNA viruses are often considered to present the highest threat for triggering a worldwide pandemic. In the absence of effective and available vaccines or medicines, the diseases caused by RNA viruses such as Ebola virus, Zika virus and SARS coronavirus, exert a significant public health impact, while viruses attacking swine cause heavy losses to the pig farming industry. Meanwhile new RNA viruses continue to emerge, due to their rapid evolution.

RNA viruses are so-called because they use RNA instead of DNA to represent their genetic code. Their genome codes for proteins, and interacts with the host cell machinery. However, until now, the structure of viral RNA genomes while inside the host cell was largely unknown.

Scientists at the University of Cambridge have developed a new technique to determine the structure and interactions of the Zika virus genome inside human cells. The technique is called COMRADES (Crosslink Of Matched RNAs And DEep Sequencing) and, importantly, it can be applied to any RNA virus in any host cell. The detailed information derived from COMRADES offers the potential to design a new generation of medicines that work by blocking virus-host RNA interactions or interfering with essential structures in the viral genome.

Our own cells also contain RNA, whether these are 'messenger RNAs' coding for proteins or 'non-coding RNAs' that regulate diverse aspects of cell function. The infection cycle of RNA viruses takes place mainly in the cell cytoplasm, where many of our RNAs reside. Virus and host RNA molecules can interact directly by 'base-pairing' along parts of their structure—in other words, making a series of bonds to zip the two molecules together. These interactions offer potential targets for anti-viral therapies, and indeed an anti-hepatitis C virus drug that targets such host-virus RNA interaction, Miraversen, is currently in advanced clinical trials.

However, the prevalence of naturally occurring host-virus RNA base-pairing is unknown, and discoveries of new interactions are rare. The novel COMRADES technique, developed by Dr. Omer Ziv at the Wellcome Trust/ Cancer Research UK Gurdon Institute with an international team of colleagues, can screen for host-virus RNA base-pairing and reveal the interacting sequences of RNA in a single experiment.

Dr. Ziv and his collaborators have applied the COMRADES method to investigate the Zika virus genome inside human cells, revealing its structure as well as multiple interactions with human regulatory non-coding RNAs such as micro RNAs, transfer RNAs and small nuclear RNAs. With the new technique, both the identity and the position of every base-pair are revealed, supplying the necessary and sufficient information for designing complementary sequences that could interfere and block each interaction, with potential clinical effects. The COMRADES method therefore opens the door to designing a new generation of RNA-based antiviral medicines for a diverse range of RNA viruses in any host cell.

Dr. Ziv, a postdoc in Professor Eric Miska's lab at the Gurdon Institute, said: "With the COMRADES technique we can explore the detailed molecular interactions between virus and host RNA. This would allow us to design short RNA or DNA sequences that can be administered to interfere with those interactions—potentially preventing the virus' ability to replicate and infect further cells. The information we get from COMRADES opens the door to a whole new way of tackling these viruses. Given the wide applicability of this technique to any RNA virus and any host cell, both human and animal RNA viral diseases can be a target for such research."

More information: Omer Ziv et al, COMRADES determines in vivo RNA structures and interactions, *Nature Methods* (2018). DOI:

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