

SERINC5: not all splice variants work against HIV

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The battle between viruses and their host is armed by cellular defences, often referred to as restriction factors, on one side, and by the counteracting measures expressed by viral genomes, on the other side. The presence of cell-derived barriers which interfere with virus replication was first revealed for retroviruses in the 70s. Since the description of FV1 (1), a cytoplasmic murine factor inhibiting MLV replication, several blocks that impair replication of viruses on the cell surface, in the cytoplasm, and in the nucleus have later been discovered. The latest addition to the list is SERINC5, a cellular protein which was recently found to block retrovirus delivery into target cells (2,3). SERINC5 belongs to a family of transmembrane proteins which in mammals includes five members. Another member, SERINC3, also acts as a retrovirus inhibitor, but possesses a much lower potency than SERINC5. Collectively, these proteins share a similar topology by crossing the membrane with 9 or 10 transmembrane domains and are incorporated into nascent retroviral particles. It was recently suggested that SERINC5 interferes with the process of virus-cell fusion to impair capsid delivery into target cells (2,3). Retroviruses, such as HIV, MLV and EIAV have developed factors that are capable of antagonizing SERINC5 (2-4). Primate lentiviruses (HIV and SIV) achieve this goal with the protein Nef, a well-known regulator of vesicle intracellular trafficking, which engages the endocytic machinery to relocalize SERINC5 from the cell surface into the late endosomal compartment. This discovery has solved a longstanding mystery

(20-year long) on the ability of Nef, a crucial pathogenic factor, to enhance the infectivity of HIV-1. Being highly conserved and different viruses having developed counteracting tools independently, SERINC5 is likely to play a fundamental role in retroviral pathogenesis. A very recent study emphasizes also that in addition to impairing HIV fusion to target cells, the host factor is crucial for sensitizing the virus to neutralizing antibodies (5). However, how SERINC5 acts on the virus particles remains unknown. SERINC proteins were thought to function as a facilitator of serine incorporation into phospholipid, but this activity remains controversial, and an inhibition of the virion infectivity as a consequence of an alteration of the virion lipidome by SERINC5 has been recently ruled out (6). Therefore the mechanism of the antiviral activity of the restriction factor, as well as its role *in vivo* remains to be understood. Given the potent activity of SERINC5 against HIV-1, one fascinating hypothesis is to use this protein as an antiviral agent, for example for gene therapy applications. To this end, as well as for a better understanding of the antiviral activity of the protein, it is important to evaluate the presence, distribution, and function of different SERINC5 isoforms.

For most genes of higher eukaryotes, alternative RNA splicing generates a significant variability in the end-product of the same gene. Alternative splicing may originate transcripts encoding protein isoforms with different intracellular localization or activity, but most often the function of different isoforms remains unknown.

Different splice isoforms are detected also for SERINC5, generating transcripts encoding for proteins which differ only at the C-terminus. The studies published so far have focused solely on the antiviral activity of the SERINC5 isoform (SERINC5-001) encoding for a 461 aa-long protein, which contains 10 transmembrane domains and the carboxyl terminus located in the cytoplasm. Whether other SERINC5 splice isoforms are equally expressed and can similarly inhibit retroviruses remains to be demonstrated. The work from Zhang *et al.* (7) now clarifies this issue and establishes that not all splice isoforms are equally expressed while only one is capable of encoding a protein which potently inhibits HIV-1.

While RNAseq provides a powerful tool to detect mRNA variants present even at low copy number, retrieving solid evidence for the existence of splice isoforms is often difficult. The Ensembl genome browser indicates the existence of six SERINC5 splice isoforms. Given that for one isoform, no solid evidence supports its existence, the authors focused on five isoforms (SERINC5-001, -004, -005, -008a, and -008b), which differ only at the C-terminus. While the authors confirm the strong anti-HIV activity of SERINC5-001, they reveal that ectopic expression of any of the remaining five isoforms causes no inhibition of HIV. Interestingly, with the exception of SERINC5-001, which is the longest isoform, all other isoforms lack the last transmembrane helix, encoding for proteins with only nine transmembrane domains and a predicted C-terminus located extracellularly. The study shows that the proteins encoded by the shorter isoforms are detected at a much lower steady-state level compared to the longest isoform, suggesting that the C-terminus of SERINC5-001 plays a critical role for sustained protein expression. Such effect could be due to an altered stability of the encoded protein, given that agents which impair the functionality of the proteasome and the lysosomal system can rescue the expression level. Such defective expression correlates with a different intracellular localization of the shorter splice isoforms, which in contrast to SERINC5-001, accumulate intracellularly rather than at the cell surface, further suggesting that the 10th transmembrane domain may regulate localization to the plasma membrane, which is ultimately required for the inhibitory effect on HIV infectivity. As speculated by the authors, it remains possible that the SERINC5 isoforms lacking the 10th transmembrane domain accumulate in the intracellular compartment and are rapidly degraded as a consequence of misfolding, further indicating that the predominantly functional splice isoform is SERINC5-001.

Given that only SERINC5-001 functions as HIV inhibitor, one important issue is to evaluate whether it is also expressed in cells that are the natural target of HIV-1 infection. Indeed, Zhang *et al.* quantified the abundance of the alternatively spliced isoforms in primary macrophages derived from monocytes (MDM) and peripheral blood mononuclear cells (PBMC) revealing a significantly higher expression level for SERINC5-001 compared to the remaining isoforms. The evidence that the strongly HIV-inhibiting SERINC5 isoform is also the variant with the highest expression in the primary cell types relevant for HIV replication further indicates that the host factor plays a significant role in controlling retrovirus replication *in vivo*.

Since SERINC5 was shown to alter also the susceptibility of HIV to neutralizing antibodies, it will be interesting to assess whether the differential effect of the alternatively spliced isoforms on infectivity is mirrored by a similarly different effect on neutralization, which would indicate a possible functional relationship between the two antiviral activities.

Now that the most active SERINC5 splice isoform has been identified, it would be fascinating to propose this gene product, or a molecule inspired by its structure, for therapeutic purposes. Further studies will certainly be needed to identify the mechanism of action and the determinants required for SERINC5 activity. However, since it has been shown that the ability of Nef to counteract SERINC5 can be readily saturated when the host factor is artificially overexpressed, the prospect of generating a gene product with powerful anti-HIV activity for *in vivo* delivery remains compelling. Accordingly, Zhang *et al.* show that SERINC5 expression by vectors commonly used in the laboratory is sufficient to overwhelm the ability of HIV-1 Nef to overcome the host restriction factor. Given that it has been shown that the potency of the ability to counteract SERINC5 varies among Nef alleles derived from different HIV-1 isolates (2,3,8), whether all Nef proteins can be saturated with ectopic expression of SERINC5 and whether the virus can eventually evolve more powerful tools to overcome the inhibition remain now to be verified. Of note, retroviral Env is another important determinant which modulate the susceptibility of virus particle to SERINC5-mediated inhibition, since the envelope glycoproteins derived from some primary HIV-1 isolates have been shown to significantly lower the susceptibility of the virus to inhibition by SERINC5 (9).

Altogether, with their work, Zhang and colleagues added one significant step in deciphering the interaction between

the virus and its host.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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