Morphology-Dependent HIV-Enhancing Effect of Semen-Derived Enhancer of Viral Infection

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Introduction

PAP is a 39-residue peptide derived from the protease cleavage of Prostatic Acidic Phosphatase (PAP) in semen. It forms amyloid fibrils that enhance HIV infection up to 100,000 times and these fibrils are called semen-derived enhancer of viral infection (SEVI) [1]. It is believed that the strong cationic charges carried by the peptide bestow the viral enhancing efficacy I [2], however, the fact that the HIV-enhancing capability requires fibrillization [1] indicates the molecular conformation is also implicated. Due to its nature of insolubility and non-crystallization, no structural model is available for SEVI. In this report, we correlate the fibril morphology with its HIV-enhancing efficacy to show that the HIV-enhancing potency of SEVI is morphology dependent.

Experimental

The morphology of SEVI fibrils was characterized by bright-field TEM imaging. Selectively ^{13}C and ^{15}N labeled PAP peptide was used to prepare SEVI fibrils for solid state NMR (ssNMR) measurements to identify the local structural conformation and molecular arrangements. Thioflavin-T and Tyr fluorescence assays were used to track the fibrillization kinetics and conformational transients during the fibrillization process. TZM-bl reporter assays were used to test the HIV-enhancing potency of SEVI at different concentrations. SsNMR spectra were acquired on a 600 MHz Bruker system at the NHMFL.

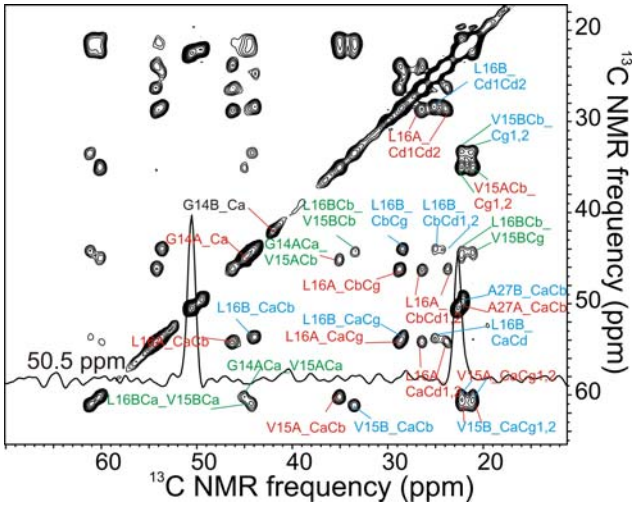

Figure 1. 2D ^{13}C-^{13}C correlation spectrum with 13.5 kHz magic angle spinning and 100 ms DARR mixing. Two sets of signals are present for each carbon sites, signals arisen from carbon sites within the same residues are colored in red and blue for meshed and straight SEVI fibrils, respectively. Signals arisen from carbon sites within different residues are colored in green.

Results and Discussion

We show that PAP peptides form amyloid fibrils of two distinct morphologies under TEM, straight and meshed fibrils. Consistently, two sets of signals were observed in ssNMR spectra of SEVI fibrils that are ^{13}C and ^{15}N labeled at G14, V15, L16 and A27. As is shown in Fig. 1, the chemical shifts of both types of fibrils are characteristic of β-strand conformation and the sharp linewidth suggests that they are in well-ordered states. Distinct inter-residue cross peaks in ssNMR spectrum as well as well as Tyr fluorescence indicate PAP peptides assume distinct molecular packing in the two SEVI fibrils. Thioflavin-T fluorescence assays show that straight and meshed fibrils are formed following two distinct pathways. Additionally, they exhibit different HIV enhancing potency in TZM-bl reporter assays.

Conclusions

Our investigation report for the first time the HIV-enhancing potency of SEVI is morphology dependent. Our data reveal the structural basis for the variations of the potency of SEVI fibrils to enhance HIV-infection and provide a molecular explanation for the observed donor-dependent HIV-enhancing efficacy of semen.

Acknowledgements

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References

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[2] Roan, N.R., *et al.*, Journal of Virology, **83(1)**, 73-80 (2009).