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Magic angle spinning NMR of viruses

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ABSTRACT

Viruses, relatively simple pathogens, are able to replicate in many living organisms and to adapt to various environments. Conventional atomic-resolution structural biology techniques, X-ray crystallography and solution NMR spectroscopy provided abundant information on the structures of individual proteins and nucleic acids comprising viruses; however, viral assemblies are not amenable to analysis by these techniques because of their large size, insolubility, and inherent lack of long-range order. In this article, we review the recent advances in magic angle spinning NMR spectroscopy that enabled atomic-resolution analysis of structure and dynamics of large viral systems and give examples of several exciting case studies.

Contents

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1. Introduction

Viruses are relatively simple pathogens that are intimately linked with all forms of life. They are adept at replicating in bacteria, archea, protists, fungi, plants, and animals while adapting to a variety of environmental conditions, some of which are extremely abrasive [1–5]. Once a virus penetrates a host cell and releases its genetic material, it is wholly reliant on the infected host to carry out its viral life cycle. Viruses seize control of their host cell machinery to replicate and assemble new virus particles for release and propagation. This leads to infections that can have a significantly negative impact on the health of the host cell and eventually lead to cell death [6].

In contrast to the generally negative perception of viruses, they do possess many potentially beneficial applications [7,8]. Although viruses and living beings share a close relationship, there are still many questions regarding their structure and function. There are a variety of different methods for studying viruses at different levels of spatial and temporal resolution, including: transmission electron microscopy (TEM) [9], cryo-electron microscopy (cryo-EM) [10], cryo-electron tomography (cryo-ET) [11], X-ray crystallography [12], solution-state NMR [13], atomic force microscopy (AFM) [14], mass spectrometry (MS) [15], circular dichroism (CD) [16], optical tweezers [17], molecular dynamics (MD) [18], and solid-state NMR [19–21]. Of these, only X-ray crystallography, solution-state NMR, and solid-state NMR yield atomic level resolution, with recent exciting advances in cryo-EM bringing the resolution close to atomic for that technique as well [22].

X-ray crystallography is limited to samples that can be crystallized. Solution NMR requires that samples be soluble and is limited to relatively small systems. In contrast, solid-state NMR (SSNMR) has no requirement with respect to long-range order, solubility, or the molecular weight of the system under analysis. SSNMR has therefore found an important role in the structural biology of viruses. The rich information content of the experiments, including insights into structure and dynamics as well as interactions with host cell factors and small-molecule inhibitors, coupled with a wide range of sample conditions amenable for characterization,

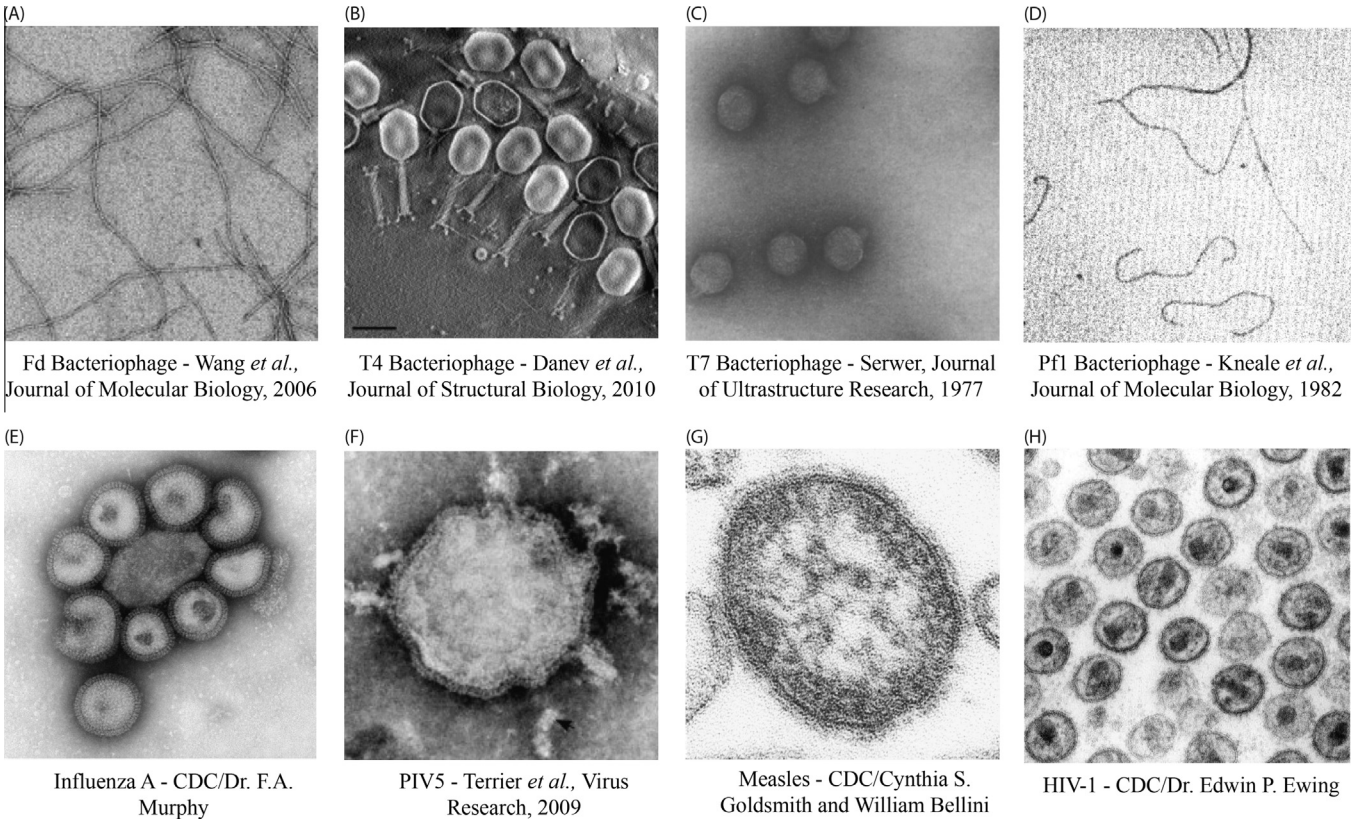

Fig. 1. Images of viral systems that contain individual protein domains, peptides, or entire assemblies that have been investigated by solid-state MAS NMR. (A) fd bacteriophage, (B) the T4 bacteriophage, (C) the T7 bacteriophage, (D) the Pf1 bacteriophage, (E) influenza A, (F) parainfluenza PIV5, (G) measles, (H) HIV-1. (A) Reprinted with permission from Wang et al., *J. Mol. Biol.*, **2006**, *361* (2), pp. 209–215. Copyright 2006 Elsevier. (B) Reprinted with permission from Danev et al., *J. Struct. Biol.*, **2010**, *171* (2), pp. 174–181. Copyright 2010 Elsevier. (C) Reprinted with permission from Serwer, *J. Ultra Mol. Struct. R.*, **1977**, *58* (3), pp. 235–243. Copyright 1977 Elsevier. (D) Reprinted with permission from Kneale et al., *J. Mol. Biol.*, **1982**, *156* (2) pp. 279–292. Copyright 1982 Elsevier. (E) From Centers for Disease Control and Prevention (CDC) Public Health Image Library (PHIL), content provided by CDC and Dr. F.A. Murphy. (F) Reprinted with permission from Terrier et al., *Virus Res.*, **2009**, *142* (1) pp. 200–203. Copyright Elsevier 2009. (G) From Centers for Disease Control and Prevention (CDC) Public Health Image Library (PHIL), content provided by CDC, Cynthia S. Goldsmith, and William Bellini, Ph.D. (H) From Centers for Disease Control and Prevention (CDC) Public Health Image Library (PHIL), content provided by CDC and Dr. Edwin P. Ewing.