Lecture 2

The structural biology of HIV-1 assembly

Adelajda Zorba
Removal of Arginine 332 Allows Human TRIM5α To Bind Human Immunodeficiency Virus Capsids and To Restrict Infection

Yuan Li,¹ Xing Li,¹ Matthew Stremiau,¹ Mark Lee,¹ and Joseph Sodroski¹,²∗

What are those?
Cryo-Electron Microscopy

http://people.csail.mit.edu/gdp/cryoem.html
X-Ray Crystallography


http://www.websters-dictionary-online.com/definitions/X-ray+crystallography?cx=partner-pub-0939450753529744%3Av0qd01-tdlq&cof=FORID%3A9&ie=UTF-8&q=X-ray+crystallography&sa=Search#920
Nuclear Magnetic Resonance (NMR)

Preview of up-coming attractions: HSQC of ubiquitin

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What are those?
HIV-1 life cycle

HIV-1 Genome

What does Gag do?
Structural components of Gag
Immature Virion:
MA domain

Myristoyl chain = green; basic residues = blue; PI(4,5)
P2=yellow

Immature Virion: Capsid proteins (CA) and SP1

Immature Virion: Nucleocapsid proteins
Mature Virion: Capsid proteins

Mature Virion: Mature Capsid
Most recent EM model of mature capsid

Byeon et al., Cell, 139, 780, (2009)
Most recent EM model of mature capsid

Byeon et al., Cell, 139, 780, (2009)
NMR solution structure model of the building block of the mature capsid

Byeon et al., Cell, 139, 780, (2009)
Previous data: hexameric arrays of CA at 9Å resolution

Ganser-Pornillos et al., Cell, 131, 70, (2007)
Previous X-ray and NMR models could not fit well into the 9Å EM density map.

Ganser-Pornillos et al., Cell, 131, 70, (2007)
Current model (left) fits well into the 9Å EM reconstruction data (right, magenta)
Current model (left) fits well in the 9Å EM reconstruction data (right)

Byeon et al., Cell, 139, 780, (2009)
Ganser-Pornillos et al., Cell, 131, 70, (2007)
Comparison between current NMR data (pink) and previous data

Byeon et al., Cell, 139, 780, (2009)
How do you go from a “flat” organization to a spherical assembly?

Why does the virus take the trouble of building the core particle?

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TRIM-Cyp is a close homologue of TRIM5α

Cyp is a peptidyl prolyl isomerase

cyclophilin binding loop
Novel HIV-1 inhibitors

- viral protease (PR) inhibitors stop Gag processing by PR

- methylphenylurea compounds (CAP-1) bind to processed CA and inhibit capsid assembly

Kelly et al., JMB, 373, 355, (2007)
How was CACTD dimer structure determined by NMR?

…to be continued in Lecture 3