

Viroids & the RNA World: from genomic scale (RNA) to atomic scale (ribozyme)

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Viroids & the RNA World

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C-U-U-C-U-U-G-U-U

U-C-C-U-C

A G U U U A

Viroids & the RNA World

249-NT

from genomic scale (RNA) to atomic scale (ribozyme)

Viroid (ASBVd)

HHRz

79-NT

C-U-U-C-U-U-G-U-U

Introduction

- evolution (RNA world)& genomics
- RNA biology & RNomics (molecular and cellular functions)
- structural biology & structural bioinformatics (structural basis for functions)

 enzymology & computational enzymology (catalysis)

Prebiotic & RNA Worlds







Viroids: Families



Viroids: Plant Parasites



Ding & Itaya, Mol Plant Microbe Interact, 2007.

Viroids: Replication



Rz: hammerhead ribozyme

Viroids: 2D Structures Cleavage site Pospiviroids (+) PSTVd (G95-96) 7000 HPII' GC box Loop E GC box Transcription HPII initiation (C1 or U359) Variable Pathogenicity TR TL С **Cleavage site** (A48-G49) (+) PLMVd Cleavage site (C289-U290)

Transcription

initiation (A286)

in the (-) strand

Avsunviroids

¹⁰ Ding & Itaya, Mol Plant Microbe Interact, 2007.

Kissing-loop

interactions

Viroids: Pospiviroids



Hammann & Steger, RNA Biol., 2012.

Viroids: Avsunviroids





ASBVd: 2D Structures



Ding & Itaya, Mol Plant Microbe Interact, 2007.

ASBVd(-): 2D Structures



Leclerc et al., Sci. Rep., 2016.





Flores et al., Adv, Virus Res., 2000.

HHR motifs in life forms



Interdiscip. Sci., 2016.

A prototype for RNA Catalysis

"Minimum" Hammerhead Ribozyme



Scott, Q. Rev. Biophys., 1999

Self-Cleaving / Self-Splicing



Catalytic Metal Ions: One/

Iwo

B (–

Ni

-H



3'

 N_{i+1}

41-NT

X-ray (active)

experimental: Pontius et al., 1997; Lott et al., 1998 theoretical: Boero et al., JCTC, 2005 19

theoretical: Leclerc & Karplus, JPC, 2006

Contribution of Metals to Catalysis



HHR: reaction mechanism



Folding Metal Ions Models



 20Å 41-NT

X-ray (active)

Metal Binding Sites in the Hammerhead Ribozyme ?



Chartrand et al., RNA, 1997

Hansen et al., RNA, 2008

Minimum/Full-Length HHR



Wang *et al.*, Biochem., 1999

Khvorova et al., Nat. Struct. Biol., 2003

de la Peña et al., EMBO J., 2003

Canny et al., JACS, 2004

Variations in HHR motifs



Perreault et al., PLoS Comput. Biol., 2011

Loop-Loop interactions in HHR folding



Penedo *et al.*, RNA, 2004.

Loop-Loop interactions in HHR catalysis



Minimum HHR, Tertiary Contact and Catalysis



HHR morphing



A Nucleobase Catalyst



X-ray (active)

Metal Catalysts in the 2'OH activation ?



Chval *et al.*, JPC, 2011

Metal Catalysts in the Hammerhead Ribozymes ?







Osborne et al., Biochem., 2009

32

Cooperative Models in Self-Cleaving ?



Cooperative Models in Self-Cleaving?

34





Metal Ions back in the Hammerhead Catalysis





Ward & DeRose, RNA, 2011

 $K_{1/2}(S) < K_{1/2}(O)$

K_{1/2}(S) ~ K_{1/2} (O)
HHR: Active Conformation and Metal Ions



Mir et al., Biochem., 2015

HHR: Metal Ions and Catalysis



Leclerc, Molecules, 2010

Mir & Golden, Biochem., 2015





HHR(-): 2D structures



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3D Modeling of HHR(-)





loops HI-HII









HHR folding



HHR morphing

Highly active form Hoogsteen pair O'Rourke et al., JMB, 2015 ASBVd: $R_g(I)/(F) \sim 1.2$ $R_{g}(I)/(F) \sim 1.1$ 43

Modeling/SANS

$$R_{g}^{exp} = 31 \text{\AA}$$

 $R_{g}^{*calc} = 31 (26) \text{\AA}$



 $d^{exp} = 96.0\text{\AA}$ $d^{calc} = 96.7\text{\AA}$

HHR (-): dimerization









79b





79b





HHR(-) dimer









HHR(-): monomer seeds



HHR(-) monomers



HHR: Monomer & Dimer



Mir et al., Biochem., 2015



MD setup for HHR dimer

- •~ 300 000 atoms
- K+ & Cl- (0.15M)
- T = (283K, 313K)
- NAMD



Dynamics of HHR(-) dimer



HHR dimer: MD trajectory



ASBVd(-): self-association



ASBVd(-): self-association



monomer 2

ASBVd(-): self-association

What did we learn?

- for RNA and ribozymes: « too short » may be bad
- don't forget about dynamics
- SANS & modeling approaches to infer selfassociation modes
- theoretical approaches to explore reaction mechanisms and pathways

Viroids: Plant Parasites

Genus *Pospiviroids:* PSTVd (potato spindle tuber)

Genus *Hostuviroids*: HSVd (hop stunt)

Genus Cocadviroids: CCCVd (coconut cadang-cadang)

Genus *Apscaviroids:* ASSVd (apple scar skin)





Genus *Coleviroids*: CbVd 1 (coleus blumei 1)





Genus *Pelamoviroids*: PLMVd (peach latent mosaic)









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Viroid & HDV: Hepatitis D



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Origins of Life: Transition from Geochemistry to Biogeochemistry

NITA SAHAI and HUSSEIN KADDOUR, Guest Editors

ransition from Geochemistry to Biogeochemistry Staging Life: Early Ocean **Incubating Life: Prebiotic Sources** Foundation Stones to Life **Metal Catalysts** Protometabolism and Early Protocells

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Assembling the RNA World

а

Prebiotic chemical synthesis

- How can nucleotides be synthesized in appreciable quantities?
- How can nucleotides be polymerized into strands long enough to be functional?

b

Finding functional ribozymes

- How small is the fraction of random sequences that can act as functional ribozymes, and how long do functional sequences have to be?
- Are there ribozymes that can make accurate copies of themselves by any mechanism?

С

Evolutionary theory and modelling

- Is it easier to begin life with an autocatalytic set or a single polymerase?
- What is the error threshold for cooperative trans-acting replicators in a spatially structured model?

d

Molecular cooperation

- Can larger cooperative sets be assembled?
- Can an autocatalytic set be designed that uses single nucleotides as input?

.

RNA replication inside cells

- Did surface-based replication precede protocells?
- How were growth and division of protocells controlled by the genetic material inside?

f

Early Earth environment

- What were the temperature, pressure, salinity and other physical conditions in which replication got going?
- What other molecules were relevant to replication (for example, lipids, mineral catalysts and peptides)?

е

Energy and metabolism

- What was the source of energy and raw materials for RNA-based organisms?
- Can we find a set of ribozymes that will catalyze all the metabolic reactions involved in their own synthesis?

Higgs & Lehman, Nat. Rev. Genet., 2011

Viroids: Phylogeny

REPLICATION	FAMILY	SUBFAMILY	GENUS	SPECIES
<section-header></section-header>	Pospiviroidae	Pospiviroinae	Pospiviroids	Potato spindle tuber (PSTVd) Mexican papita (MPVd) Tomato planta macho (TPMVd) Chrysanth emum stunt (CSVd) Citrus exocortis (CEVd) Tomato apical stunt (TASVd) Iresine 1 (IrVd 1) Column ea latent (CLVd)
			Hostuviroids	Hop stunt (HSVd)
			Cocadviroids	Coconut cadang-cadang (CCCVd) Coconut tin angaja (CTiVd) Hop latent (HLVd) Citrus IV (CVd-IV)
		Apscaviroinae	Apscaviroids	Apple scar skin (ASSVd) Citrus III (CVd-III) Apple dimple fruid (ADFVd) Grapevine yellow speckle 1 (GYSVd 1) Grapevine yellow speckle 2 (GYSVd 2) Citrus bent leaf (CBLVd) Pear blister canker (PBCVd) Australian grapevine (AGVd)
		Coleviroinae	Coleviroids	Coleus blumei 1 (CbVd 1) Coleus blumei 2 (CbVd 2) Coleus blumei 3 (CbVd 3)
SYMMETRIC PATHWAY	Avsunviroidae		Avsunviroids	Avocado sunblotch (ASBVd)
			Pelamoviroids	Peach latent mosaic (PLMVd) Chrysanthemum chlorotic mottle (CChMVd)
		66		

Modeling RNA-RNA Interactions



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HHR motifs



HHR (-): symmetric dimerization



ASBVd(-): symmetric self-association



ASBVd(-): symmetric self-association



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HHR design & engineering



Glms ribozyme



Viroid Pathogenicity & Localization



Owens & Hammond, Viruses, 2009.

Viroid& RNA silencing



Gomez et al., Trends Plant. Sci., 2009.

Viroid disease symptoms



Potato spindle tuber viroid



Apple viroid disease





chrysanthemum stunt viroid



Avocado Sunblotch Viroid



Coconut cadang-cadang viroid



