解析人类感染DNA病毒核酸结合蛋白的序列识别密码

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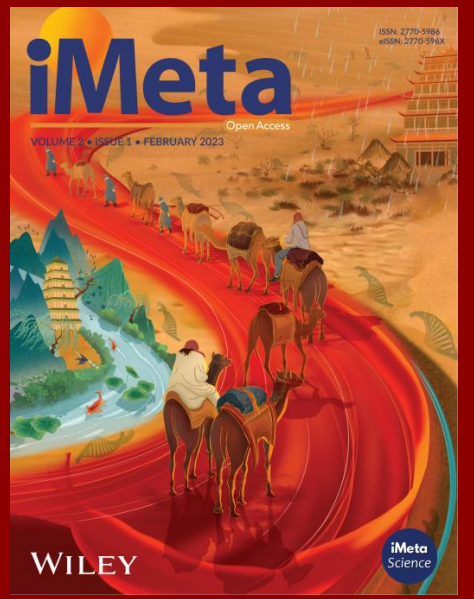
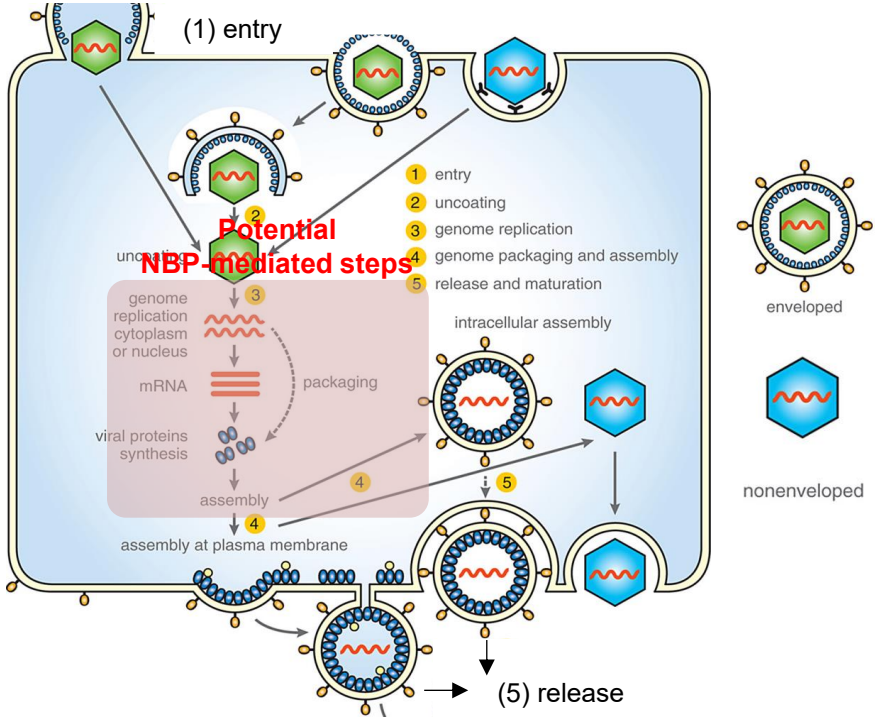


Meifang Tang, Shifei Yang, Haiqian Ma, Ruoying Guo, Jie Chen, Hui Zhang, Jinghan Zhang, et al. Decoding sequence recognition code of nucleic acid-binding proteins of human-infecting DNA viruses. ***iMeta*** 5: e70170.
https://doi.org/10.1002/imt2.70170

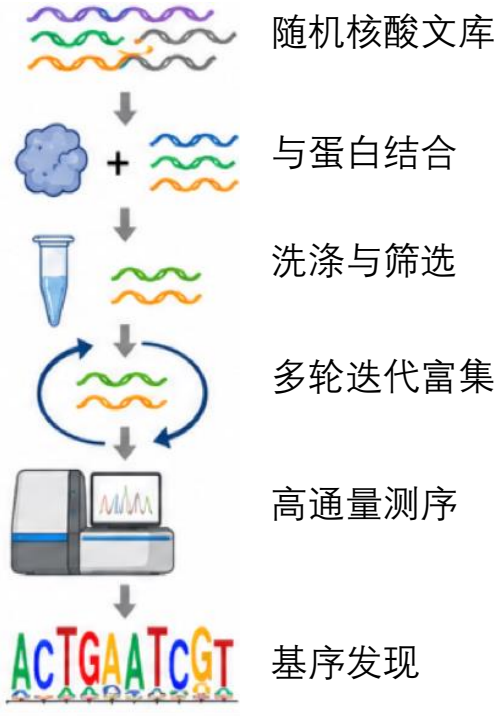
背景

1 病毒基因组识别与包装是病毒生命周期的关键步骤



Rumlová, M., et al. ***Biotechnology Advances***, 2018.

2 SELEX可系统鉴定结合基序



Jolma, A. et al. ***Cell***. 2013.

3 现有局限

- 目前仅少数DNA病毒蛋白的DNA结合特异性得到解析。
- 人感染DNA病毒NBP–DNA识别仍缺乏系统性研究。

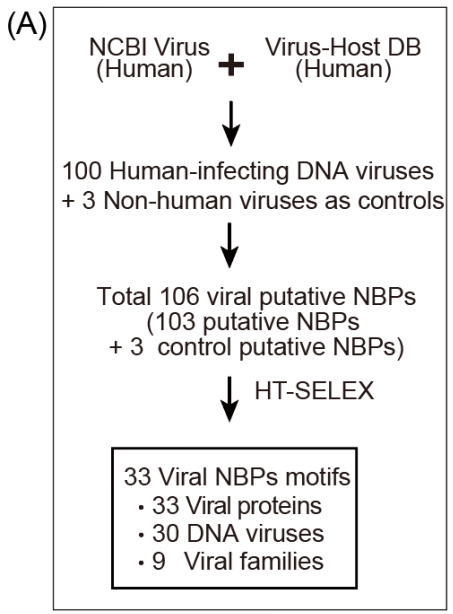
NBPs：核酸结合蛋白

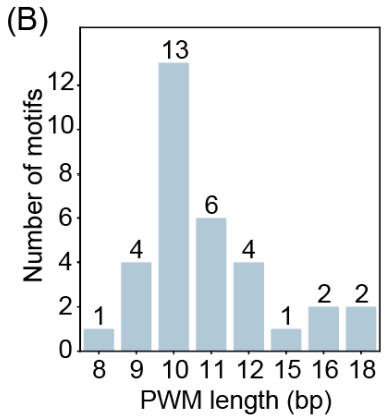
科学问题

不同人感染DNA病毒NBPs是否具有DNA识别特异性？

HT-SELEX系统性解析人感染DNA病毒NBPs的DNA识别特异性

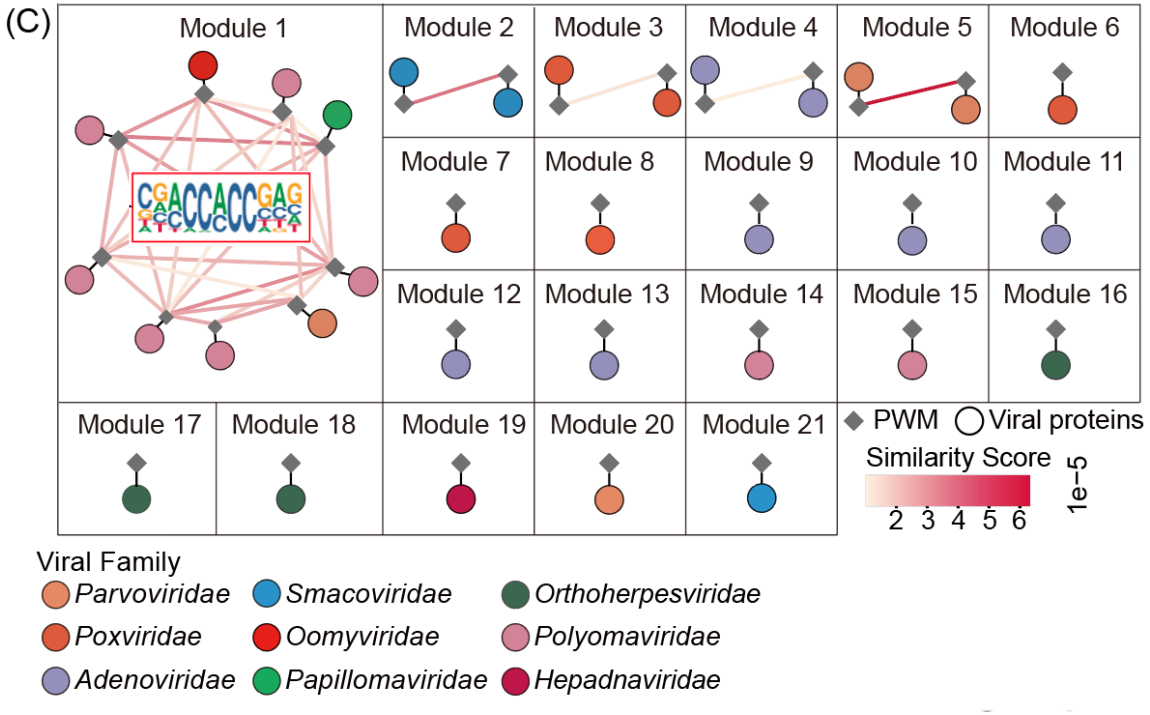
1 HT-SELEX系统性筛选与基序鉴定





HT-SELEX：高通量指数富集的配体系统进化技术

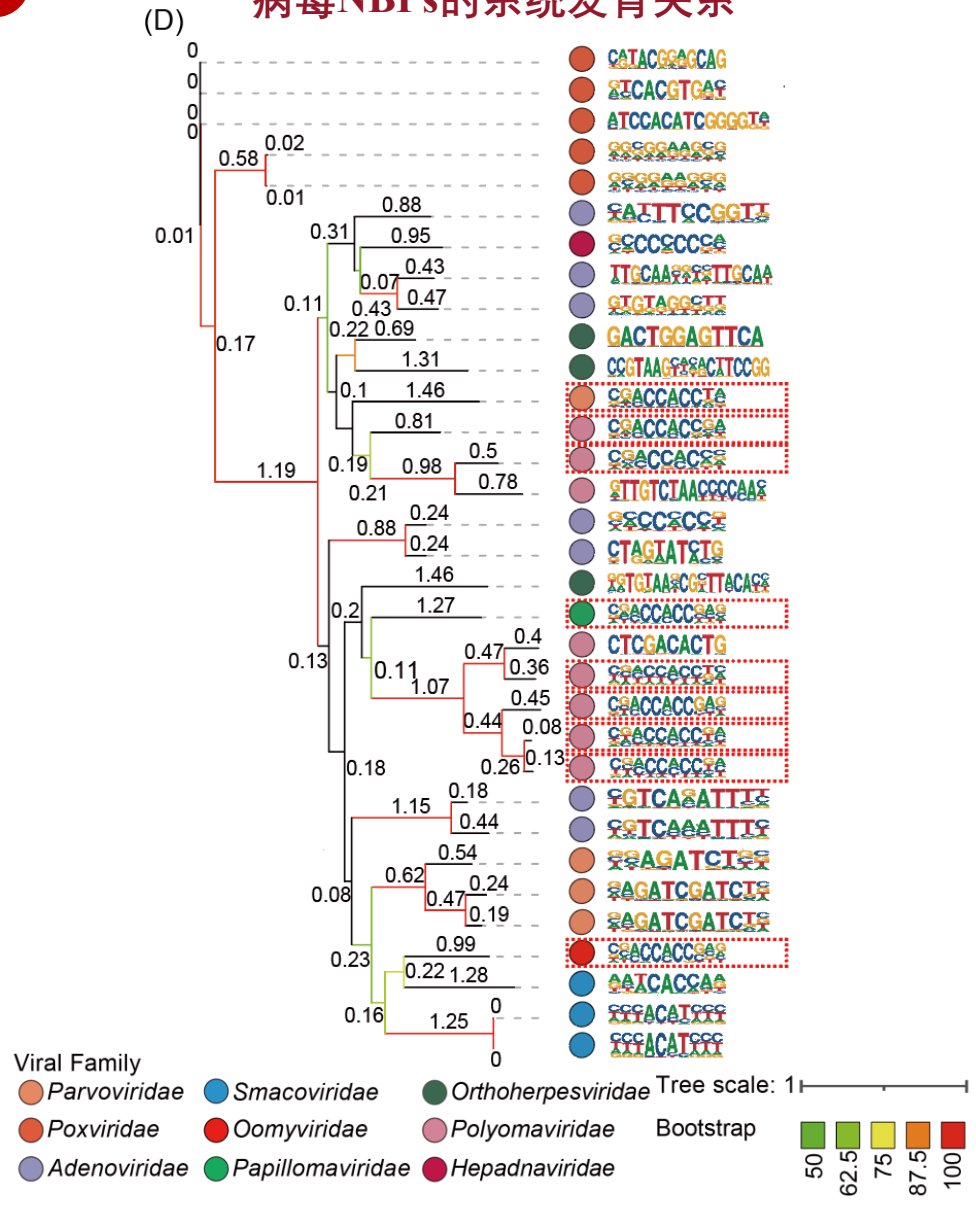
2 基序相似性网络分析



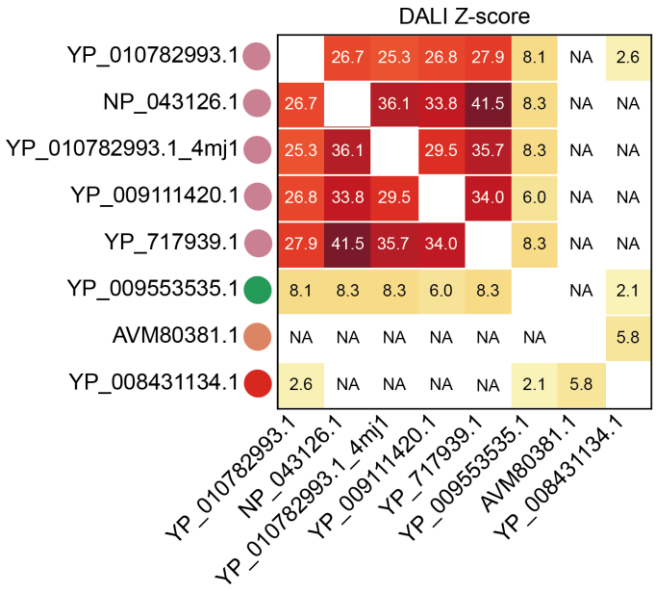
模块1包含来自多个病毒科的9个NBPs，共享保守CCACC核心基序。

病毒 NBPs 的趋异与趋同DNA识别模式

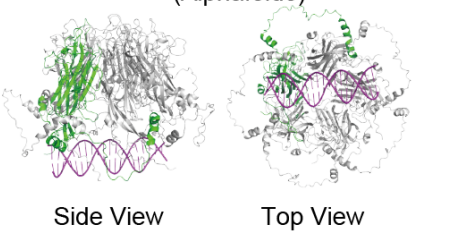
1 病毒NBPs的系统发育关系



2 模块1 NBPs的预测结构比较



(E)



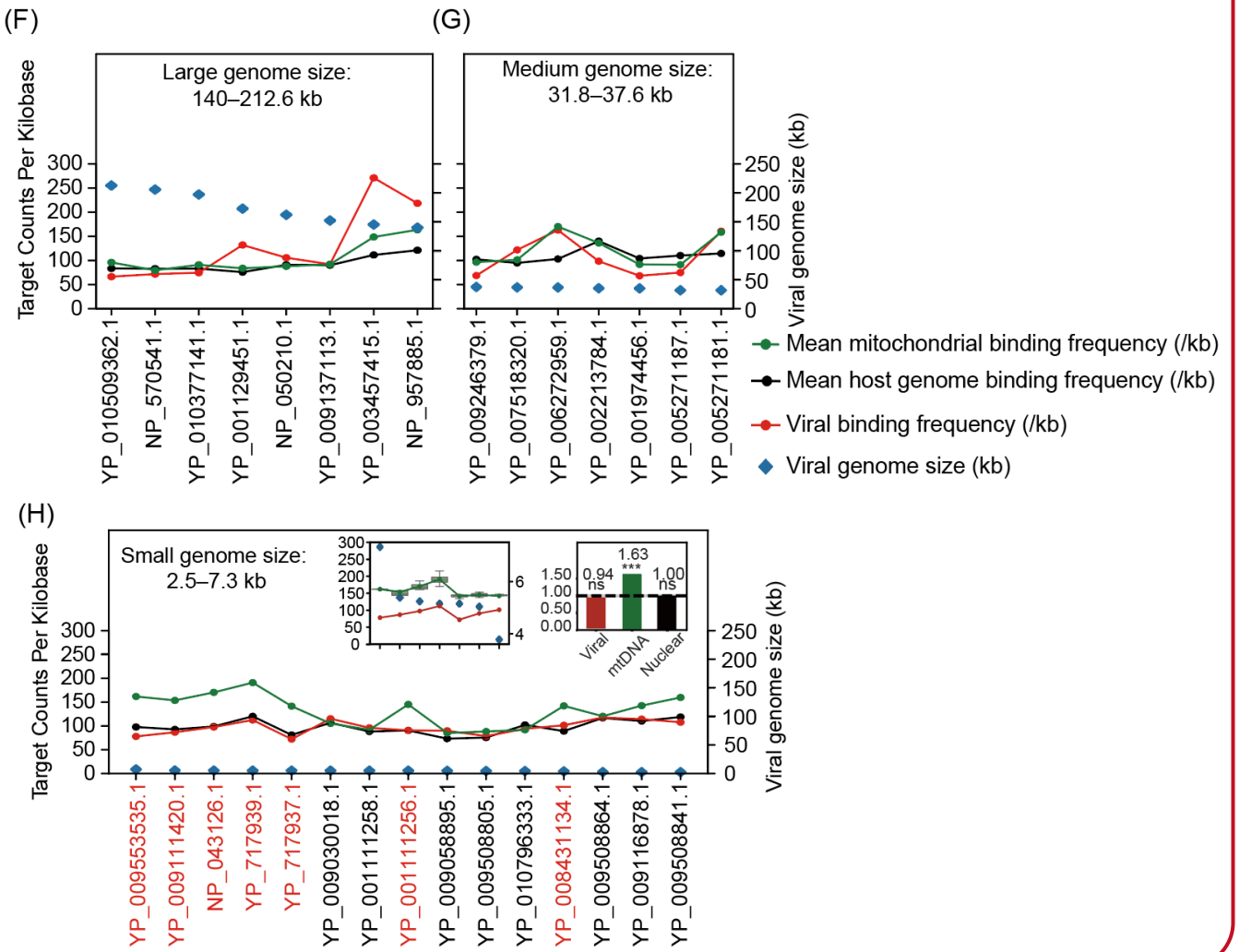
Probe AATTGCTCCCACCACATATC
TTAACGAGGGTGGTGTATAG

Pentameric structure of viral NBP YP_717939.1 (PDB: 4MJ1) ;
See Figure S7 for details.

病毒NBPs呈现科内保守与跨科CCACC基序趋同的DNA识别模式。

预测结合位点分布与病毒基因组大小相关

基因组大小相关的预测结合模式



按病毒基因组相对线粒体基因组大小分组（mtDNA约16.6 kb）：

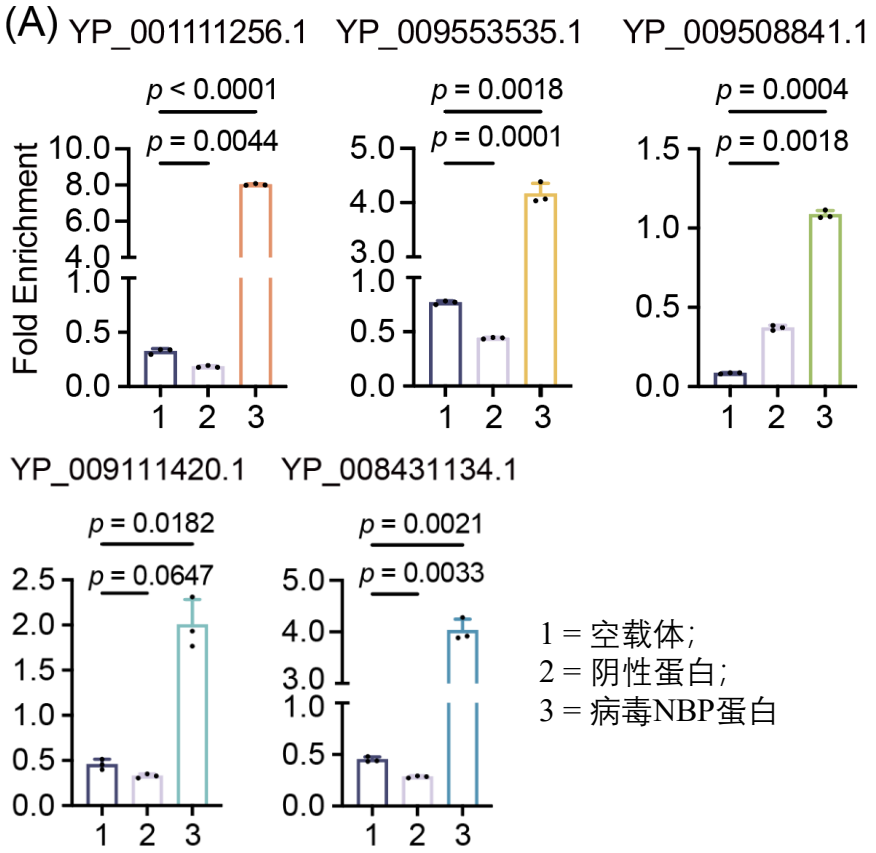
- 大基因组（140–212.6 kb；＞8x）：预测结合位点主要富集于对应病毒基因组；
- 中等基因组（31.8–37.6 kb；约1.9–2.3x）：未呈现明确富集偏好；
- 小基因组（2.5–7.3 kb；＜0.5x）：富集于宿主线粒体，尤其是模块1中识别 CCACC基序NBPs。

不同基因组大小的病毒NBPs表现出不同的预测结合位点分布模式。

部分小基因组病毒NBPs的mtDNA关联与线粒体膜电位改变

1

MitoChIP-qPCR

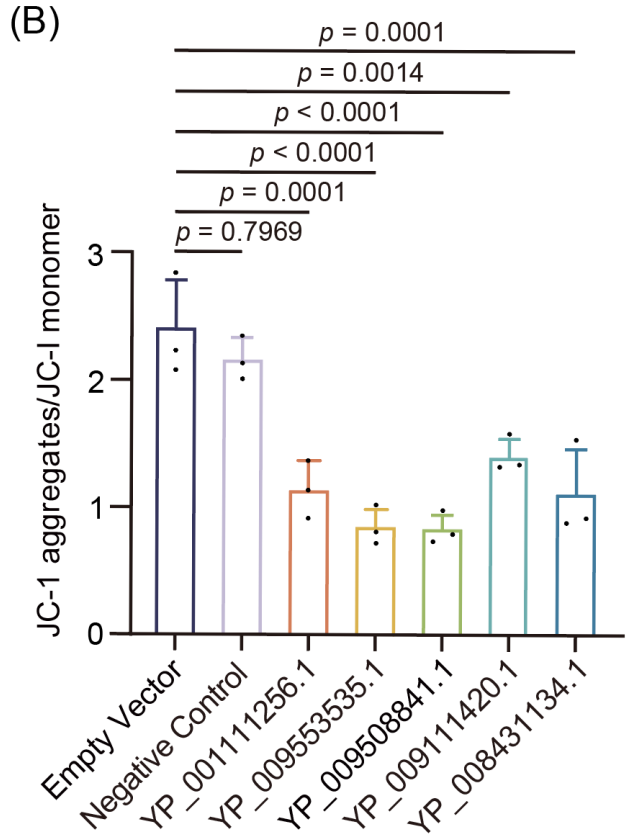


1 = 空载体;
2 = 阴性蛋白;
3 = 病毒NBP蛋白

这些NBPs在预测mtDNA位点的富集水平均高于对照。

2

JC-1线粒体膜电位检测



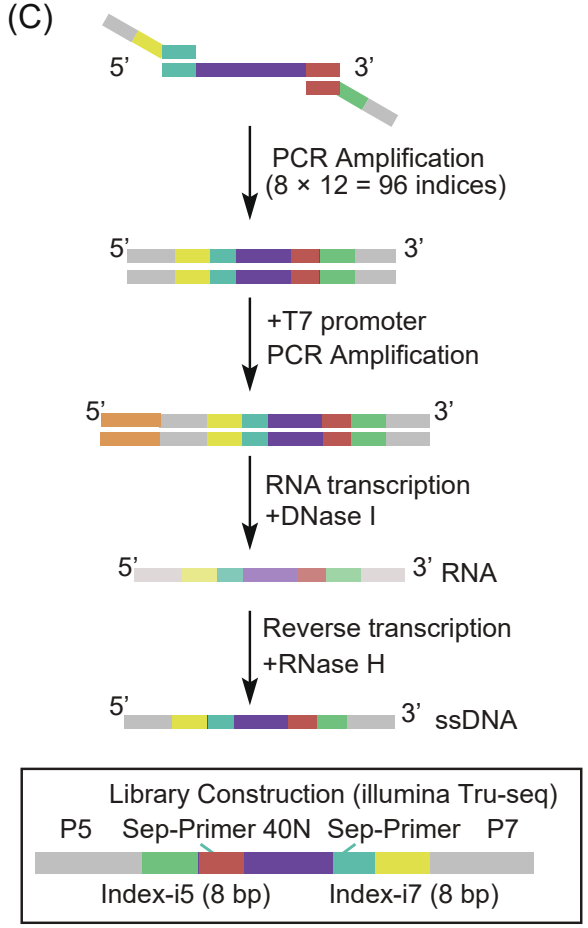
JC-1聚合体/单体比值降低提示线粒体去极化。

结果支持所选病毒NBPs与mtDNA的关联及其与线粒体膜电位改变之间的相关性，但尚不能建立直接因果关系。

ssDNA-SELEX拓展了病毒NBP的单链DNA识别图谱

1 ssDNA-SELEX 流程

(C)

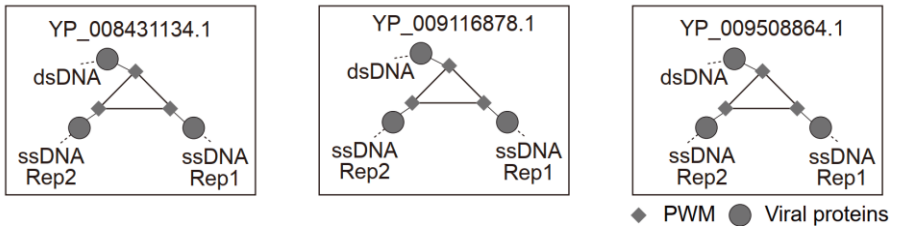


2 HT-SELEX与ssDNA-SELEX识别基序比较

(D)

Protein ID	HT-SELEX	ssDNA -SELEX Rep1	ssDNA -SELEX Rep2
YP_008431134.1			
YP_009116878.1			
YP_009508864.1			
YP_009508841.1		N/A	N/A
YP_009508805.1		N/A	N/A
YP_010796333.1		N/A	N/A
YP_009058895.1		N/A	N/A
AVM80381.1		N/A	N/A

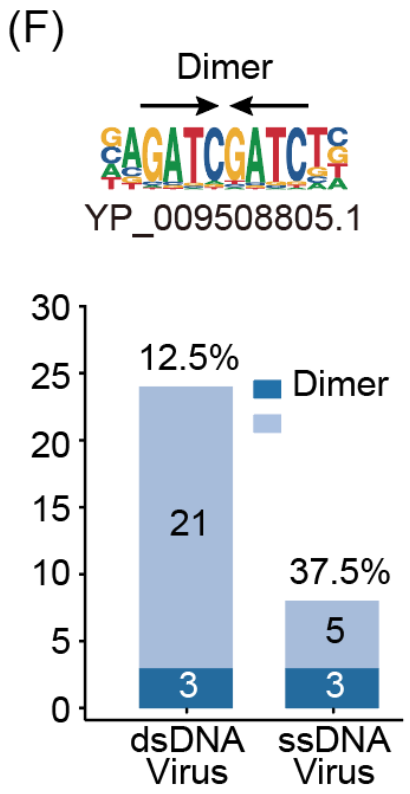
(E)

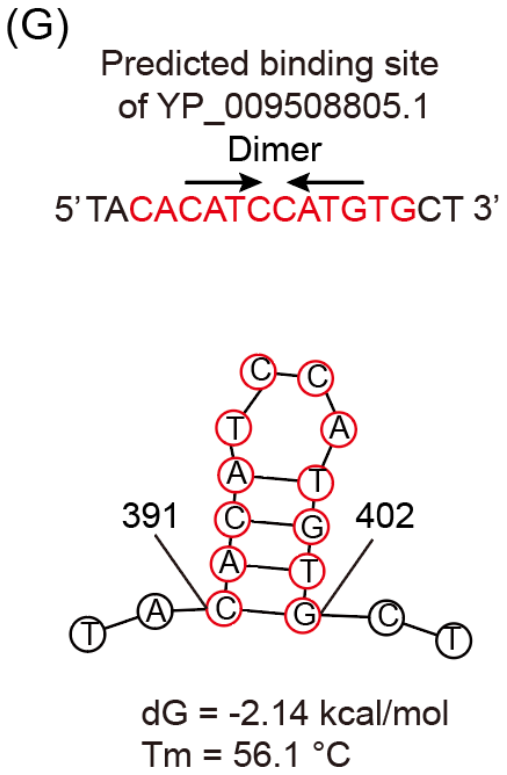


3个ssDNA病毒来源的NBPs在两种SELEX方法中呈现相似核心基序，揭示其核心识别在很大程度上不受DNA单双链状态影响。

ssDNA病毒NBPs呈现二聚体样结合模式

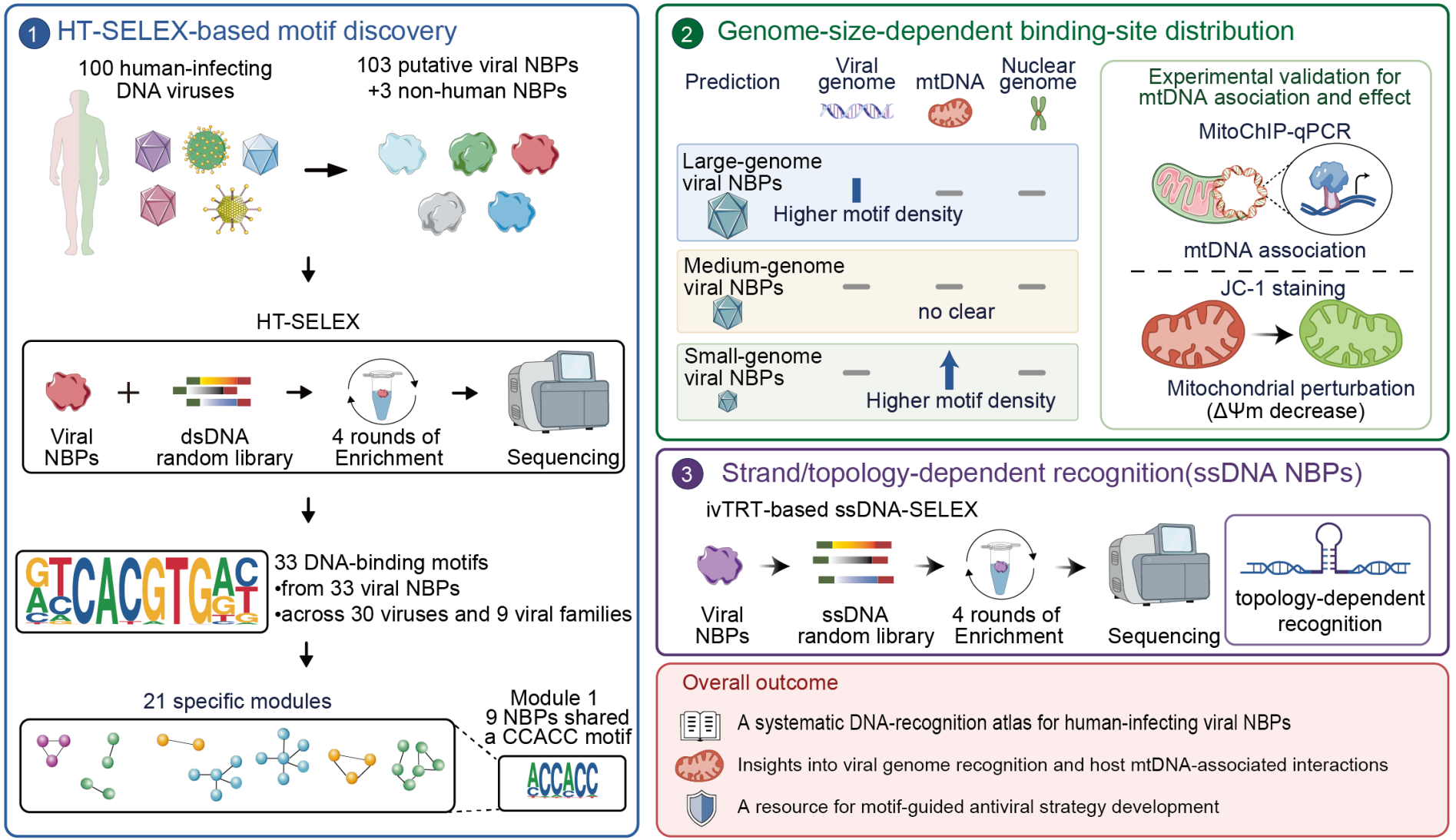
单体与二聚体结合模式





二聚体样基序在ssDNA病毒NBPs中更常见，并揭示其可能识别具有反向重复特征、可形成茎环结构的核酸序列。

总结



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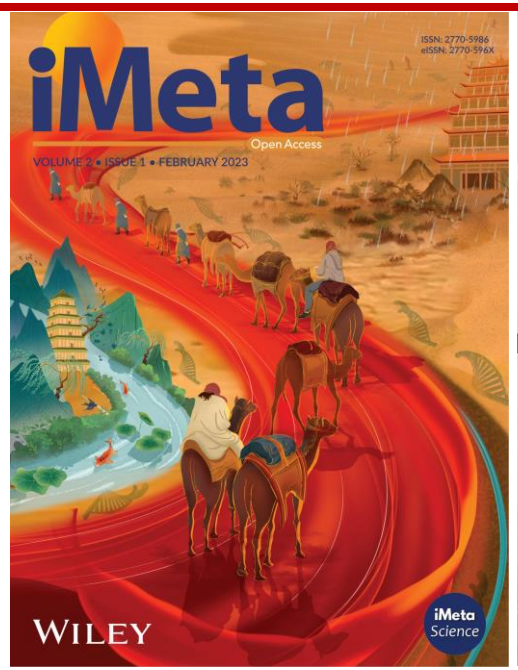

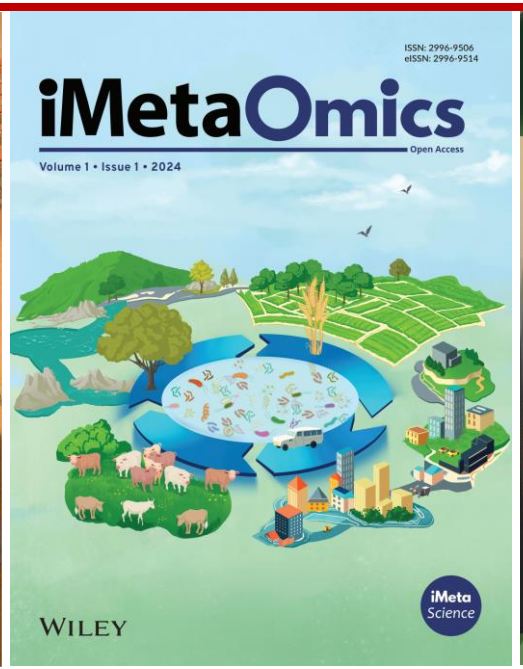

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