Virology 479-480 (2015) 457–474

Contents lists available at ScienceDirect

Virology

journal homepage: www.elsevier.com/locate/yviro

Review

Nuclear proteins hijacked by mammalian cytoplasmic plus strand RNA viruses

Richard E. Lloyd *

Department of Molecular Virology and Microbiology, Baylor College of Medicine, Houston, TX 77030, United States

ARTICLE INFO

Article history:
Received 8 December 2014
Returned to author for revisions
12 January 2015
Accepted 3 March 2015
Available online 26 March 2015

Keywords:
RNA virus
Enterovirus
Poliovirus
Flavivirus
Norovirus
Hepatitis C virus
Coronavirus
PTB
PCBP2
La protein
UNR
SRp20
hnRNP C
hnRNP A1
hnRNP K
hnRNP M
RNA helicase A
NSAP
Tia1/TIAR
G3BP1

ABSTRACT

Plus strand RNA viruses that replicate in the cytoplasm face challenges in supporting the numerous biosynthetic functions required for replication and propagation. Most of these viruses are genetically simple and rely heavily on co-opting cellular proteins, particularly cellular RNA-binding proteins, into new roles for support of virus infection at the level of virus-specific translation, and building RNA replication complexes. In the course of infectious cycles many nuclear-cytoplasmic shuttling proteins of mostly nuclear distribution are detained in the cytoplasm by viruses and re-purposed for their own gain. Many mammalian viruses hijack a common group of the same factors. This review summarizes recent gains in our knowledge of how cytoplasmic RNA viruses use these co-opted host nuclear factors in new functional roles supporting virus translation and virus RNA replication and common themes employed between different virus groups.

Contents

* Tel.: +1 713 798 8993.
E-mail address: rlloyd@bcm.edu

http://dx.doi.org/10.1016/j.virol.2015.03.001
0042-6822/

Introduction

Viral spread and ultimately pathogenesis require efficient replication in key host cells that aid spread of the virus within hosts and throughout host populations. RNA viruses are typically small, encoding as little at three genes, and thus must rely on many host factors interacting with viral RNAs to assist with essential replication functions, and control many interaction points within host cells to promote replication. This often results in redirecting host metabolism on several levels to support the infection and at the same time suppress innate host defense systems that are triggered. Comparing plus and minus stranded RNA viruses, there are stark differences at the time of uncoating of genomic viral RNA in the cytoplasm. The plus strand RNA virus genome that is released is naked, however the minus strand RNA virus genome is completely enclosed in a functional nucleocapsid with RNA replicase poised ready to produce transcript mRNAs. Thus, the plus strand virus RNA can, and does, interact with many host RNA binding proteins (RBPs), whereas there is a little opportunity for minus strand virus genomic RNA to interact directly with host RBPs. Most RNA-binding proteins are nuclear shuttling proteins and many more nuclear RBPs have been reported to play roles in replication of plus strand RNA viruses than minus strand RNA viruses. Accordingly, this review focuses heavily on plus stranded RNA viruses, particularly mammalian viruses.

RNA viruses interact with a multitude of host factors during the course of infection. Several screening approaches have been employed to identify which of the 15–20,000 proteins that may be expressed in a given cell are host factors required for RNA virus replication. These include genetic screens in yeast that implicated 130 proteins that could affect plant virus replication (tomato bushy stunt virus) (Jiang et al., 2006) and about 100 genes that affect brome mosaic virus (Kushner et al., 2003; Panavas et al., 2005). RNAi knockdown studies in mammalian cells with Hepatitis C virus (HCV), Dengue virus (DENV) and West Nile virus (WNV) have identified several hundred other genes that affect virus replication. However, many or most of these may function quite indirectly, affecting pathways that produce metabolites or products the virus needs, movement or trafficking of constituents that are directly required, factors that control divalent cation fluxes and ATPase pumps, the stress or innate immune activation levels that counteract general cellular biosynthetic potential, or include general off-target effects from the silencing step. It is likely that the spectrum of factors that directly interact in meaningful ways with virus RNA and proteins will be larger than that known today, but also smaller than the first lists that have emerged from such screenings (Box 1). Recently the novel approach of thiouracil cross-linking mass spectroscopy (TUX-MS) was used to more precisely identify host proteins bound to poliovirus RNA during replication. This procedure identified all proteins known to interact with enterovirus RNA, plus 66 additional factors previously unidentified (Lenarcic et al., 2013). Eight of the new proteins were chosen and validated as playing roles in replication, indicating this new method is powerful and should be applied to other virus systems. However, standard molecular biology and biochemical approaches will still be required to tease out the functions and impact of each of these factors on virus replication. Proteins that interact with viral RNA do not present interesting targets for antiviral development unless it is determined that they play critical roles in virus replication.

Plus strand RNA viruses must translate incoming viral genomic RNA as the first biosynthetic step in replication cycles, thus, control of translation becomes the first battleground with the host that involves co-opted nuclear factors. It makes sense for the virus to utilize the host factors it commonly encounters at sites of replication. Thus, translation regulation involves virus co-opting of cellular translation factors. These are mostly cytoplasmic resident proteins since translation is a cytoplasmic process. However, translation does not occur on transcripts that are naked and devoid of RNA-binding proteins, rather, cellular transcripts are continually bound to a host of RNA binding proteins from the instant they emerge from RNA polymerase during their synthesis. In mammalian cells, RNA binding proteins control most aspects of RNA biology and the RNA cycle; from splicing, transport out of the nucleus, cellular function, transcript-specific translation control, and cytoplasmic localization and mRNA half-life. Mammalian cells encode hundreds of RBPs (~860), most with several splice variants (Castelló et al., 2012). The cytoplasmic milieu encountered by plus strand RNA virus genomes as they are released from capsids is poised to greet the interloper as any other mRNA, with a ready store of RNA binding proteins ready to interact and impart functions. No wonder viruses have evolved to interact with RBP in