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REVIEW

Drawing on disorder: How viruses use histone mimicry to their advantage

Alexander Tarakhovsky[1] and Rab K. Prinjha[2]

Humans carry trillions of viruses that thrive because of their ability to exploit the host. In this exploitation, viruses promote their own replication by suppressing the host antiviral response and by inducing changes in host biosynthetic processes, often with extremely small genomes of their own. In the review, we discuss the phenomenon of histone mimicry by viral proteins and how this mimicry allows the virus to dial in to the cell's transcriptional processes and establish a cell state that promotes infection. We suggest that histone mimicry is part of a broader viral strategy to use intrinsic protein disorder as a means to overcome the size limitations of its own genome and to maximize its impact on host protein networks. In particular, we discuss how intrinsic protein disorder may enable viral proteins to interfere with phase-separated host protein condensates, including those that contribute to chromatin-mediated control of gene expression.

There are an estimated 37.2 trillion cells in the human body (Bianconi et al., 2013), organized into anatomically and functionally defined tissues that maintain their phenotypic stability in the face of environmental pressure, stochastic changes in gene and protein expression, and even structural genetic alterations (Barabási and Oltvai, 2004; Stelling et al., 2004). Yet, cells can be challenged with extreme perturbations caused by invasion of foreign life forms (pathogens) that aim to exploit the cell's resources to ensure their own replication. Viruses, both DNA and RNA forms, represent the most impactful types of pathogens with respect to the interference with intracellular environment. Although bacterial species and protozoans mostly use extracellular resources to support their replication, viral replication requires cooperation from the host cell's biosynthetic processes and concomitant suppression of the host antiviral response (Virgin, 2014; Pfeiffer and Virgin, 2016). To understand the degree to which viruses impact on human life, one needs to consider the actual number of viruses that exist in the biosphere. Although many of the calculations can be seen as arbitrary, it is estimated that there are ∼100 million different viruses populating 1,740,330 species of vertebrates, invertebrates, plants, lichens, mushrooms, and brown algae (Woolhouse et al., 2012). All adult humans are chronically infected with RNA and DNA viruses—most originating in animals—that could be either pathogenic or innocuous (Virgin et al., 2009; Cadwell, 2015). Each human harbors an estimated 8–12 chronic infections (Virgin et al., 2009). The size of the mammalian virome is not known, but the fact that there are 10^8–10^9 viruses, which represent multiple viral species, per gram of human feces offers a glimpse into the complexity and abundance of viruses in the human body (Mokili et al., 2012; Reyes et al., 2012). This number significantly underestimates viruses residing outside of the gastrointestinal tract; with these considered, the total number of viruses within the human body is probably closer to ∼10^{15} (Mokili et al., 2012; Nikolich-Zugich et al., 2017).

Beneficial virome–host interactions

In their enormous diversity, human viruses can be pathogenic and disease-causing or opportunistic and relatively harmless. The pathogenic and highly destructive viruses such as influenza, dengue fever, yellow fever, HIV, and hepatitis C viruses (HCVs) affect the health of hundreds of millions people worldwide every year. By contrast, opportunistic viruses can benefit the host, and this virus mutualism is evolutionarily old. An impressive example of this mutualism is the rosy apple aphid, *Dysaphis plantaginea*—a major pest of apple trees—which is infected by a densovirus that induces wing development in the aphid. This morphotype is important in enabling aphids to move to new plants (Ryabov et al., 2009; Roossinck and Bazán, 2017).

Virus-induced changes to the mammalian immune system that benefit the host are also common. The mouse norovirus can replace the function of commensal gut bacteria in the establishment of intestinal architecture and subsequent establishment of the innate immune system (Kernbauer et al., 2014). Mouse

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γ-herpesvirus protects mice from the bacterial pathogens that cause bubonic plague (*Yersinia pestis*) and the foodborne disease listeriosis (*Listeria monocytogenes*) via prolonged production of IFN-γ and macrophage activation (Barton et al., 2007). Human cytomegalovirus, a nearly ubiquitous latent herpesvirus, provides enhanced immune response to influenza, especially in young adults, with evidence for heightened immune activation (Furman et al., 2015). This appears not to be an isolated case because other herpesviruses may also increase the immune response to other pathogens (Sandalova et al., 2010). In humans, the *Flavivirus* GB virus C, also known as hepatitis G virus, is asymptomatic and could thus be considered a commensal virus, but under some conditions it behaves as a mutualist. For example, HIV-positive patients who are infected with GBV0C show slower disease progression, a process that involves down-regulation of cell receptors for HIV entry, normalization of IFN and other cytokine levels, and decreased HIV replication (Bhattarai and Stapleton, 2012). The beneficial effect of viruses on the host are indicative of the existence of virus-encoded molecules that can drive the establishment of complex nondevelopmentally predetermined phenotypes in animal or human cells.

Viral tactics for maximal replication and immune evasion

At the core of the viral strategy is the ability of viruses to attenuate innate and adaptive immune responses, while coopting the transcriptional and translational machineries of infected cells to generate new viral particles (García-Sastre and Biron, 2006). This strategy generates a phenotypically new infected cell state that combines the features of the normal host cell with the features that support viral replication and spreading (Nagy and Pogany, 2011). The strategic aims of the rely on different tactics that reflect differences between viral genomes as well as the nature of the affected cells (García-Sastre, 2017). In turn, the differences in virus tactics yields phenotypic diversity among infected cells as defined by patterns of gene and protein expression and metabolic states.

In case of pathogenic viruses such as influenza, suppression of type I IFN expression and numerous IFN-stimulated genes (ISGs) dominates the infected cell phenotype (García-Sastre, 2017). With type I IFN and ISGs suppressed, the influenza virus can survive and use cell biosynthetic machinery to generate new viral particles. In the case of pathogenic flaviviruses such as dengue, yellow fever, or HCV, infection not only suppresses IFN/ISG but also results in accumulation of a new ER-associated lipid compartment that supports viral infection. To achieve this aim, the flaviviruses alter expression of genes that control lipid accumulation by fatty acid oxidation (Bozzao et al., 1989). These gene expression changes alter lipid metabolism in a way that facilitates the build-up of a membranous web—a de novo-generated intracellular compartment that supports virus RNA replication and assembly of the viral particles (Martín-Acebes et al., 2016). HVB, a double-stranded DNA virus of the Hepadnaviridae family, encodes a regulatory X protein, HBx, that triggers lipogenesis and ensuing generation of the lipid vesicles that support virus replication (Na et al., 2009; You et al., 2013). Human cytomegalovirus infection also induces major metabolic reprogramming, thus stimulating broad-spectrum RNA and DNA synthesis associated with an increase in cellular ribosome numbers (Tanaka et al., 1975), as well as increased glucose uptake and glycolysis in infected fibroblasts (Landini, 1984).

Nonpathogenic viruses affect transcription in a yet more stealthy fashion. Studies that have directly assessed the effects of chronic herpesvirus or polyomavirus infection on expression of host genes in different tissues have revealed substantial virus- and organ-specific effects (White et al., 2012; Canny et al., 2014). The numerous examples of virus-mediated manipulation of host gene expression have been thoroughly discussed in many outstanding reviews (García-Sastre and Biron, 2006; García-Sastre, 2017). The diversity of virus-induced phenotypes is contrasted by the common outcome of successful infection, in which the final phenotype is the production of new viruses. The ability of an infected cell to reach an end point in which it acquires an infection-supporting phenotype (or viral infection state) can be seen as a state of virus-induced quasidifferentiation.

Establishment of the infected cell state

To generate the viral infection state, viruses must overcome the robustness of the infected cell phenotype. In development, robustness is described as canalization, whereby developing cells are directed toward a specific outcome from uncertain starting conditions and despite various cellular and environmental perturbations (Waddington, 1942). In Waddington's "epigenetic landscape," environmental influences lead to the establishment of "valleys" that guide the direction of genetic processes and define a generation of cell types with a discrete nature (Waddington, 1942). Accordingly, distinct cell phenotypes are represented by the placement of a cell state within a particular valley (Fig. 1 A). The Waddington landscape is not just a metaphor but rather an accurate reflection of the state of gene regulatory networks that operate within cells (Huang et al., 2005). The gene expression levels in the cells can be viewed within the high-dimensional state space, where each point in the state space represents one gene expression pattern within the gene regulatory network (Fig. 1 B). The convergence of individual dimensions, i.e., gene expression trajectories, from the high energy, unstable state to the low energy, stable state generates the so-called attractor state, toward which specific cells are pulled over time (Macarthur et al., 2009; Fig. 1 C). The stable attractor state occupies the basin of the state space and is surrounded by unstable states. Such topography provides an explanation for the self-stabilizing nature of gene networks where the hills that separate attractors represent unstable network states. It has been proposed that attractor states define the stable phenotypes of specific cell types (Sooranna and Saggerson, 1979; Huang et al., 2009). The self-organizing and self-stabilizing property of the cell state, which defines gene expression profiles, is a natural feature conferred by attractors. The attractor state can be reached via an almost infinite number of paths, all of which lead to cell type–specific gene expression patterns that are highly resistant to noise and can reestablish themselves after small perturbations (Huang et al., 2009). However, in the presence of sufficiently high levels of fluctuations or in response to a deterministic signal, cells can switch between attractors and generate new and potentially heritable phenotypes (Kalmar et al., 2009; Muñoz-Descalzo et al., 2012; Li et al., 2016).

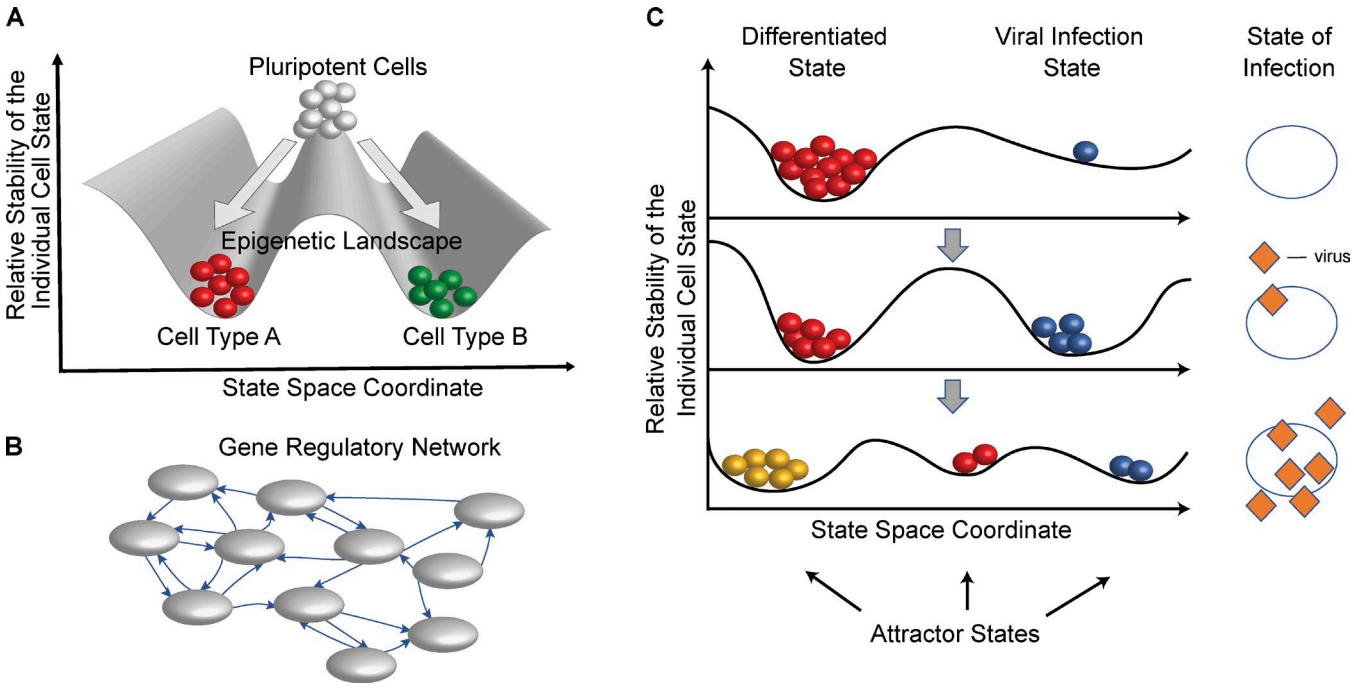

Figure 1. **Viral infection leads to generation of novel cell states. (A)** Simplified scheme of the epigenetic landscape. The gene regulatory network that operates in pluripotent cells (open circle) yields the stable and distinct (attractor) states of network that define the specific cell types. The attractor occupies the low-energy stable basin, and providing robustness against perturbations. The y axis represents the relative stability of individual cell states where higher positions indicate less stability. The valleys represent stable attractor states. **(B and C)** Gene regulatory networks (B) generate stable differentiated cell phenotypes (red) as well as innate antiviral states (blue) of differentiated cells (C). The latter is defined by expression levels of various antiviral proteins in the absence of detectable viral infection. Progression of viral infection is associated with virus-mediated suppression of the antiviral state, characterized by expression of type I IFN and ISGs, and establishment of the proviral state (yellow) that supports viral replication. Generation and stability of antiviral or proviral attractors may determine the outcome of the viral infection.

The ability of viruses to install the viral infection state implies the existence of mechanisms that allow the virus to override the robustness of the differentiated cell state imposed by the gene regulatory network (Macarthur et al., 2009; Huang, 2010). Viral infection may cause a destabilization of the high-dimensional gene regulatory network, thereby facilitating exit of the cell from the differentiated attractor and entry into a potentially new metastable attractor state that benefits infection (Fig. 1 C). To achieve this aim, viruses need to interfere with the gene regulatory networks at points that operate as network hubs, or at multiple points, thus generating multiple perturbations to the system. The attractor view of the virus-induced cell phenotype can help to explain how multiple and diverse virus-driven events can lead to a common outcome, characterized by reduced antiviral responses and a rewiring of biosynthetic pathways to favor viral replication. In support of this model, screens for genes that control influenza infection performed by different laboratories have suggested highly variable cellular approaches toward antiviral resistance, with an abundance of host factors shown to contribute to the outcome of influenza infection. Remarkably, out of 1,539 total hits obtained in five genetic screens, 1,417 were unique to individual screens, and no genes were common to all five (Mehle and Doudna, 2010). Moreover, only four genes were common in genome-wide screens in human cells (Brass et al., 2009; Karlas et al., 2010; König et al., 2010). The same degree of inconsistency has been observed in multiple screens for the HIV host factors, for which several explanations have been proposed, mostly based on technical nuances of the screens (Goff, 2008; Bushman et al., 2009; Mehle and Doudna, 2010). In our view, it is conceivable that these variations reflect the fact that establishment of the viral infection state can follow different paths that involve different genes. One can speculate that individual effects of the virus on the host do not need to be particularly specific or severe, but that the multiplicity of effects contributes to the establishment of the infected cell state. Such a scenario is similar to the use of different genetic networks for the generation of macrophages from undifferentiated tumor HL60 cells in response to chemically distinct triggers, all of which drive cells to the same attractor state (Huang et al., 2005). How can viruses, frequently carrying just a bundle of genes, establish the infected cell state?

Intrinsically disordered proteins (IDPs) in virus–host interactions

It appears that viruses are well equipped to implement a multitarget strategy toward interference with multiple cell functions. At the foundation of this viral feature is the abundance of potentially polyreactive IDPs or intrinsically disordered regions (IDRs) in the viral proteome (Dunker et al., 2000, 2001, 2005; Tompa, 2002; Uversky, 2002; Ward et al., 2004; Uversky and Dunker, 2010). IDPs/IDRs, which are also common in the mammalian proteome, are characterized by high proportions of charged and hydrophilic amino acids combined with a low abundance of bulky hydrophobic amino acids. The IDP are unable to fold spontaneously into stable three-dimensional globular structures and

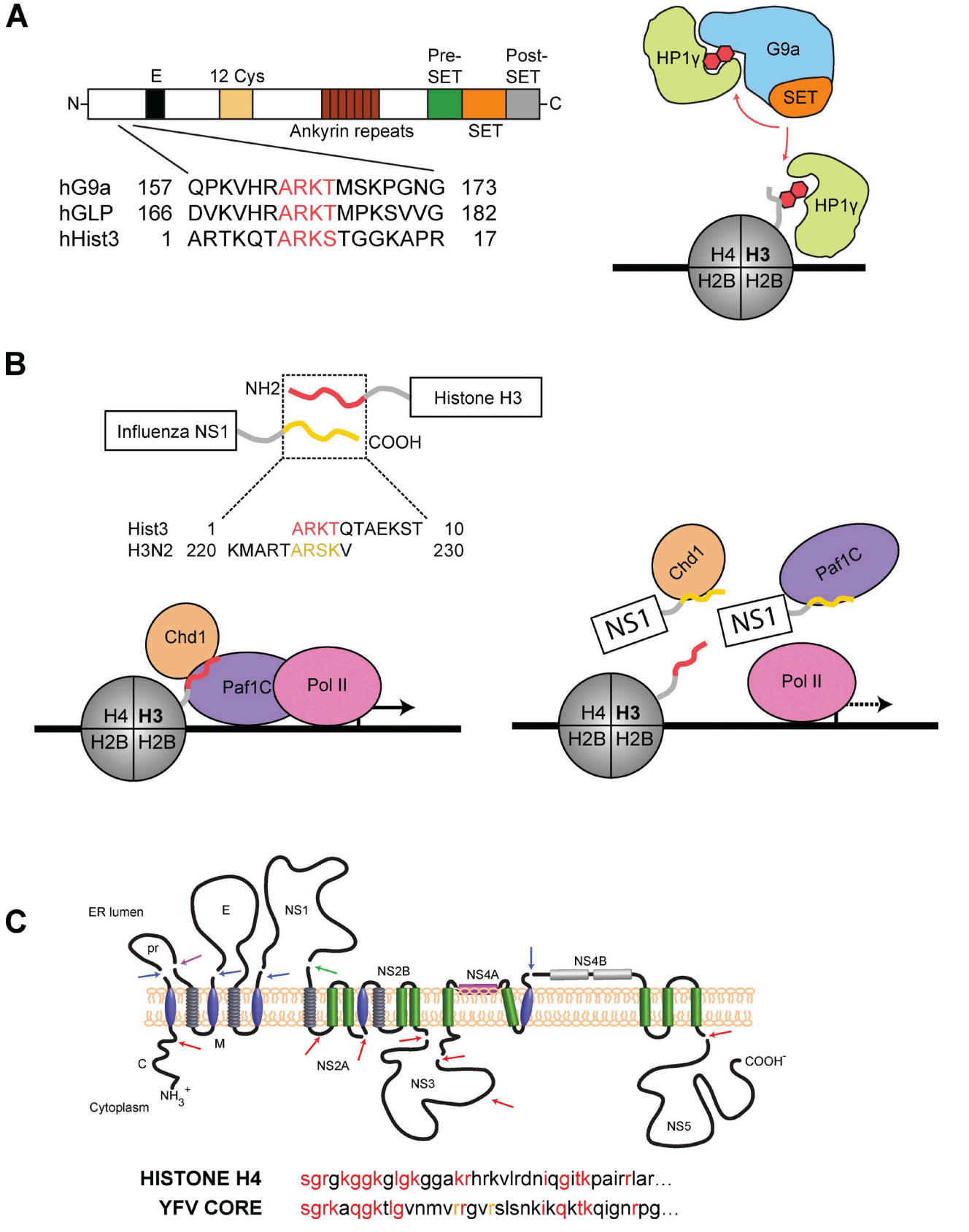

Figure 2. **The structure and function of histone mimics. (A)** The methyltransferases G9a and GLP possess a functional histone-like sequence (red letters), localized within the N-terminal domain of the proteins. The G9a histone mimic methylation (red hexagon) is mediated in cis by the catalytic SET domain that is flanked by pre- and post-SET domains. The ankyrin repeat domain is involved in G9a interaction with methylated histones, and the methylated histone mimic

fluctuate through a range of conformations (Dyson and Wright, 2005). This feature allows IDPs to form dynamically heterogeneous complexes with multiple binding partners (Ferreon et al., 2009; Ishiyama et al., 2010). The dynamic nature of most IDPs also allows for increased availability of binding sites, with binding diversity greatly augmented by the propensity of IDPs to be posttranslationally modified (Gibson, 2009). These features contribute to the governing role of IDPs in signaling networks (Dunker et al., 2005; Dyson and Wright, 2005; Ishiyama et al., 2010). IDRs participate in the assembly of numerous signaling complexes through reversible protein–protein interactions that promote formation of either fully reversible cellular assemblies or stable amyloid scaffolds (Li et al., 2012).

The recent studies of 2,278 viral genomes comprising 41 viral families (Selenko et al., 2008) show striking variation in the amount of protein disorder both within and between viral families (from 2.9 to 23.1% of residues). Remarkably, the degree of disorder correlates negatively with the genome sizes within each of the five main viral types (single-stranded [ss]DNA, double-stranded [ds]DNA, ssRNA$^+$, dsRNA, retroviruses), with the exception of negative single-stranded RNA viruses, in which disorder increases with the size of the genome. More than 20 small viruses that encode five or fewer proteins have 50% or more disordered residues in their proteomes (Xue et al., 2014a). As the proteome size increases among different viruses, the fractions of disordered residues converges to 20–40%. Protein disorder is highly abundant in human viruses such as HCV, HIV-1 (Xue et al., 2012), and human papillomaviruses (Uversky et al., 2006; Fan et al., 2014; Xue et al., 2014b), and the varying magnitude of disorder may enable viruses to impact numerous host factors. Additionally, the lack of inherent structure reduces the constraints of protein function and allows for creation of novel protein motifs that could be used by the virus to subvert host functions (Selenko et al., 2008; Sanjuán and Domingo-Calap, 2016). It has been also suggested that flexible structures may help viral proteins to evade the host immune system (Goh et al., 2008, 2009, 2012, 2013). In particular, protein disorder may help viruses tolerate a high mutation rate and hence adapt to the host defenses. Additionally, a lack of structural constraints is supposed to promote a multiplicity of viral protein interactions with the host proteins and target multiple elements of the host cell defense system (Xue et al., 2014a).

Short linear motifs and histone mimicry by viruses.

The peptide motifs most found in IDPs fall into two groups: disordered sequences that adopt structure upon binding to other proteins, or short linear motifs (commonly referred to as SLiMs; Tompa et al., 2014). SLiMs, also called eukaryotic linear motifs, contribute to localized interactions of the IDPs with their partners (Neduva and Russell, 2005; Tompa et al., 2005, 2014; Van Roey et al., 2014). The interactions are transient and have low micromolar affinities (Dyson and Wright, 2002; Van Roey et al., 2014), and multiple SLiMs can act synergistically to increase the binding affinity of an IDP to a target (Dyson and Wright, 2002). The human proteome is estimated to contain more than 100,000 short linear binding motifs located within IDRs. Because most of the binding specificity and affinity of a SLiM is embedded within a 2–5-residue-long core of amino acids, it is predictable that potential host SLiMs could be easily mimicked by viruses. Indeed, viruses carry numerous motifs that resemble host protein SLiMs (Ferreon et al., 2010; Sakon and Weninger, 2010; Gebhardt et al., 2013).

One of the most remarkable constellations of SLiMs is found in histone proteins. The N-terminal histone tail could be viewed as a collection of multiple overlapping SLiMs, with each motif (whether unmodified or posttranslationally modified) functioning as a discrete unit that is recognized by a particular histone-binding protein (or reader; Fischle et al., 2003; Ruthenburg et al., 2007; Taverna et al., 2007). This feature of the histone tail may contribute to its unique capability to facilitate binding of numerous nonhistone proteins and the formation of highly diverse protein complexes involved in various aspects of chromatin function.

The existence of histone-like SLiMs (histone mimics) in nonhistone proteins was first demonstrated in our studies that revealed the presence of a histone H3–like sequence within the histone methyltransferase G9a, which catalyzes dimethylation at lysine 9 of histone H3 (Sampath et al., 2007; Fig. 2 A). G9a carries a 163-ARKT-166 motif that resembles the 7-ARKS-10 motif of its histone H3 target. Consistent with the presence of the histone mimic, G9a can automethylate itself on lysine 165 (Sampath et al., 2007), and this methylation facilitates the formation of a repressor complex between G9a and chromodomain-containing protein HP1γ (Sampath et al., 2007; Fig. 2 A). The H3-like sequence in G9a is also conserved in its homologue and heterodimerization partner GLP (Sampath et al., 2007), although the two proteins share relatively poor primary sequence conservation in their N-terminal domains. The initial discovery of histone mimics in G9a/GLP led to the identification of numerous histone mimics in other nuclear and nonnuclear proteins, where they contribute to protein–protein interactions or protein stability (Dzimiri and Odenthal, 1990; Lee et al., 2010; Shi et al., 2014).

Histone mimicry by influenza viruses

The first example of viral histone mimicry was the identification of a histone H3–like sequence within the C-terminal portion of

in G9a (red hexagon) binds to the chromodomain-containing protein HP1γ, which can also interact with methylated histone H3 (red hexagon). **(B)** The NS1 proteins of the influenza A H3N2 virus possess a functional histone H3K4-like sequence (yellow letters), localized within the nonstructured C terminus of the protein, whereas the homologous H3 sequence (red letters) is localized within its N terminus. The NS1 histone mimic (yellow tail) is present in the nucleus, where it interacts with Paf1 complex and Chd1 proteins. Interaction with Chd1 depends on NS1 lysine methylation, whereas Paf1 can bind to the unmethylated or methylated NS1 histone mimic. The pattern of Paf1 and Chd1 binding to NS1 is similar to the interactions between these proteins and histone H3. The schematic model describes a putative mechanism of NS1 interference with Paf1-mediated transcription of virus-induced genes. **(C)** Histone mimicry by the core protein of the YFV. The N-terminal portion (40 aa) of the H4 histone and the YFV core protein display a high degree of homology, and share the presence of the lysine residues in YFVC that become acetylated in the infected cells (not depicted).

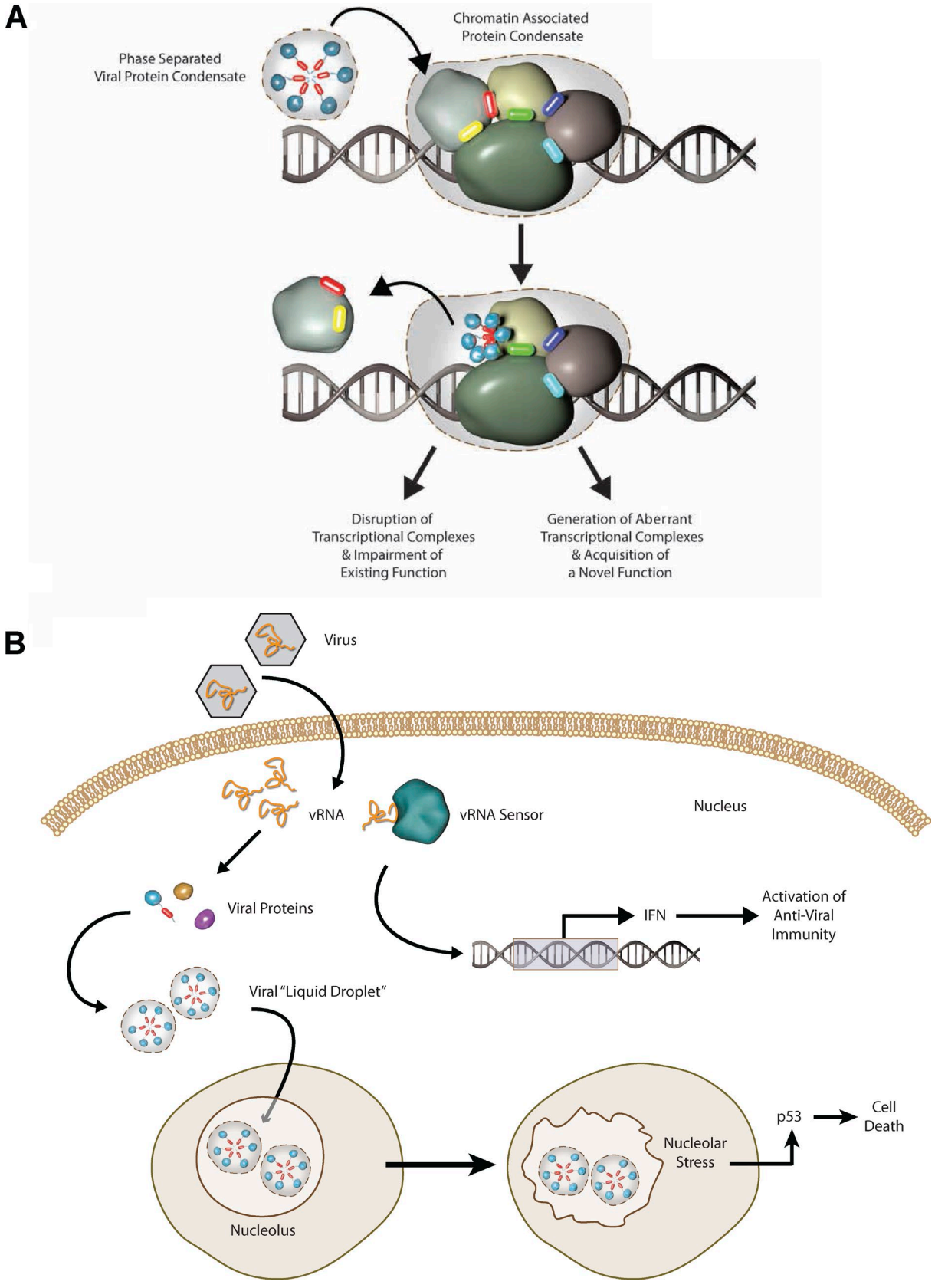

Figure 3. **The model for viral protein interference with gene regulatory network. (A)** The intrinsic disorder of viral proteins that carry histone mimics (red) may facilitate multiple interprotein interactions followed by formation of phase-separated viral protein condensates (liquid droplets). The ability to form liquid droplets may maximize the impact of viral proteins, including those that carry histone mimics, on chromatin followed by alteration of host chromatin–associated

the nonstructural protein 1 (NS1) of the H3N2 subtype of influenza A virus (Marazzi et al., 2012; Fig. 2 B). The NS1 protein suppresses the type I IFN response during influenza infection (García-Sastre et al., 1998; Wang et al., 2000) and is essential for virus infection. The sequence 226-ARSK-229 of NS1 resembles the first four amino acids (1-ARTK-4) of the histone H3 protein. The H3N2 subtype of influenza is the predominant carrier of the histone H3K4-like sequence, whereas tails of NS1 proteins from other influenza subtypes (Bao et al., 2008) either display no recognizable motifs or possess highly specific motifs, such as PDZ ligand (PL) motifs (Obenauer et al., 2006; Jackson et al., 2008; Thomas et al., 2011) or SUMOylation sequences, as found within the NS1 tail of the H1N1 (1918) strain (Santos et al., 2013). This NS1 tail diversity may contribute to unique features of the individual virus subtypes. The PL motifs ESEV and EPEV within the NS1 tails of avian-derived influenza strains have been associated with highly pathogenic human isolates such as H5N1 (Obenauer et al., 2006; Jackson et al., 2008; Thomas et al., 2011). These PL motifs enable viruses to attenuate apoptotic death of the infected cells, thus increasing the viral load (Golebiewski et al., 2011).

In the H3N2 strain, the presence of the histone mimic may contribute to the unique ability of the virus to compete with the cognate histone sequences for their common binding partners, including those that drive antiviral gene expression. In support of this model, we found that both the histone H3 tail and the H3N2 NS1 tail bind in a sequence-dependent fashion to the polymerase-associated factor 1 (Paf1) component of the Paf1 complex that contributes to RNA elongation as well as other cotranscriptional processes (Marazzi et al., 2012). As expected, the NS1 tails from influenza H5N1 (Marazzi et al., 2012) and H1N1 (Schaefer et al., 2013) that lack the histone mimic did not bind to Paf1.

Overall, the NS1 tail could be viewed as a highly interactive, internally disorganized motif where amino acid variations contribute to target specificity and hence to the unique features of individual virus subtypes. This feature of NS1, which was recently underscored by a study showing that the NS1 domain interacts with the chromatin remodeling protein CHD1 (Qin et al., 2014), might be critical in the ability of different influenza subtypes to choose their optimal strategy for the host–pathogen interaction, based on the genetic and epigenetic state of the infected host during the emergence of infection. In turn, the counterselection against certain viral subtypes, including some of the NS1 tail-less viruses, could be explained by the inability of NS1 to match host factors, including those localized in the cell nucleus.

Other examples of viral histone mimicry

In addition to the histone mimicry by NS1, a few other examples of viral histone mimicry have been described (King et al., 2016). The insect polydnavirus *Cotesia plutellae* bracovirus (CpBV) encodes an orthologue of the insect histone H4 (CpBV-H4; Hepat et al., 2013) that enables the wasp to parasitize its host, the diamondback moth, *Plutella xylostella*. The life cycle of *C. plutellae* requires colonization of young larvae of *P. xylostella*, which display growth retardation and immunosuppression once parasitized. These phenotypic changes are mediated by CpBV-H4, which is highly homologous to the host histone H4 and is additionally equipped with an extended lysine-rich 38-residue-long N-terminal tail. CpBV-H4 suppresses host immunity by inhibiting expression of genes encoding phenoloxidase and other antimicrobial peptides (Hepat and Kim, 2011), and causes developmental retardation by inhibiting expression of insulin-like peptide in host larvae. CpBV-H4 affects host chromatin by joining eukaryotic nucleosomes (Hepat and Kim, 2013), the epigenetic impact of which is gene expression changes affecting nearly 20% of the moth genome (Kumar et al., 2017). Notably, the gene expression and phenotypic alterations mediated by CpBV-H4 depend completely on its lysine-rich N-terminal tail (Kim and Kim, 2010).

Viral histone mimicry with relatively broad effects has also been reported for human adenoviruses. The human adenovirus–encoded protein VII shares limited sequence similarity with histone H3 and carries a conserved AKKRS histone mimic motif in the N terminus of the protein (Lee et al., 2003; Avgousti et al., 2016). Binding of protein VII to chromatin appears to sustain binding of the immune modulatory protein HMGb1 to chromatin in the infected cells, which reduces HGMn1-mediated activation of innate immune response (Avgousti et al., 2016).

Overall, in silico analyses show the presence of the histone-like sequences in numerous DNA and RNA viruses. For example, the core protein of the yellow fever virus (YFV), which contributes to virus assembly but also accumulates in the nucleus of the infected cells (not depicted), possesses impressive homology to the histone H4 as well as other histone proteins (Fig. 2 C). The YFV core is intrinsically disordered and features lysine residues that are spaced in a fashion similar to histone H4. Moreover, our unpublished studies show that the YFV core is acetylated in infected cells and binds to nuclear proteins in a fashion similar to acetylated histone H4.

Histone mimicry and phase separation

The other fascinating aspect of the histone mimicry—in the context of the overall disordered nature of NS1 and flavivirus core proteins—is the ability of IDP/IDR to facilitate formation of nonmembranous structures that are based on phase separation (Banani et al., 2017). The multivalent protein–protein interactions often mediated by IDR can promote liquid–liquid separation to form membraneless cytoplasmic and nuclear compartments (Pontius, 1993; Oldfield et al., 2005; Weber and Brangwynne, 2012). It has been speculated that assembly of numerous transcriptional regulators of the enhancer arrays (coined super-enhancers [SE]) leads to formation of these gel-like structures

complexes. The high concentration of the histone mimic within the phase-separated condensate may allow viral proteins to compete with cognate host chromatin proteins. The outcome of the competition may differ from loss of the host function, i.e., antiviral gene expression, or generation of aberrant virus–host hybrid protein complexes and acquisition of a new cell phenotype that can benefit viral replication. **(B)** Upon infection, viral RNA (vRNA) recognition by sensor proteins (e.g., RIG-I, MDA5) leads to activation of IFN and IFN-driven antiviral immunity. As infections progress, vRNA transcription and translation yield viral proteins, including those that carry histone mimics. The accumulation of viral histone mimics in the nucleolus of the infected cells might be sensed by dedicated (as yet unknown) sensors followed by nucleolar stress and death of the infected cell, thereby limiting the spread of viral infection.

(Hnisz et al., 2017). In their model, Hnisz et al. (2017) postulate that multiple components of SEs, including bromodomain-containing transcriptional regulator BRD4, RNA Pol II, and RNA, can form cross-links, defined as "any reversible feature, including reversible chemical modification, or any other feature involved in dynamic binding and unbinding interactions" (Hnisz et al., 2017). Given the documented or computationally predicted abundance of IDRs in many of the transcriptional regulators, the cross-link is likely to reflect the multivalency of the IDP or IDR. The liquid phase separation at the SEs is likely to increase the fragility of these transcriptional hubs to perturbations based on the interaction between virus-derived and host-derived gel-like compartments rather than on specific protein–protein interactions. In this scenario, the viral IDP will interact with chromatin not as an individual protein but rather as a virus-derived protein-based membranous organelle (Fig. 3 A). Such interaction is likely to have a dramatic impact on chromatin function, as it will drastically increase the concentration of histone-like sequences in the vicinity of gene regulatory regions, followed by negative or positive changes in gene expression, including genes that are critical for the antiviral response as well as genes that support virus replication.

Phase separation contributes to the formation of numerous intracellular membraneless organelles, including PML bodies and the nucleolus (Banani et al., 2017; Woodruff et al., 2018). One of the potentially relevant aspects of viral histone mimicry relates to the compartmentalization of viral proteins to the nucleolus. The presence of viral proteins, including core proteins of different flaviviruses, leads to nucleolar stress followed by up-regulation of p53 and cell death (Rawlinson and Moseley, 2015; Slomnicki et al., 2017; Yan et al., 2017). Virus-induced nucleolar stress and cell death cannot be beneficial for the virus, and is thus likely to represent a rather dramatic effort by the cell to limit spread of infection and effectively counteract viral histone mimicry. Moreover, phagocytosis of cells killed by viruses will amplify the systemic immune response against infection. It is tempting to speculate that nucleolar stress represents an innate defense pathway that involves host-mediated uptake of viral proteins to the nucleolus followed by their recognition by hypothetical host-encoded sensors and subsequent nucleolar stress. As such, it is possible that nucleolar proteins, such as TCOF1 or other proteins involved in prevention of the nucleolar stress (Calo et al., 2018), bind to nonmodified or posttranslationally modified viral histone mimics, followed by alteration of nucleolar function and death of infected cells (Fig. 3 B).

In conclusion, the histone mimicry by pathogens should be seen in a big picture context, whereby utilization of intrinsic disorder by viruses enables flexible, yet impactful, interaction with the host. The presence of histone mimics in structurally distinct viral proteins underscores the ability of viruses to use highly evolvable host protein sequences to develop optimal strategies for pathogen–host interaction. By imitating histones, viruses can challenge the adaptive capacity of the host cell, which cannot modify the primary sequence of histones without endangering the very foundation of its own cellular organization. In this scenario, the pressure imposed by viral proteins may have driven cells to devise a strategy whereby compartmentalization of viral proteins to the nucleolus leads to nucleolar stress and cell death. This could be seen as an example of a cell defense mechanism that minimizes the impact of viral disordered proteins on the host while preventing further viral spread. Finally, it is tempting to speculate that pharmacological imitation of the viral strategy to target multiple cellular components or single components that target multiple genes/proteins might yield therapeutic outcomes by altering attractors associated with pathological cell states including cancer or chronic inflammation.

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