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# Condensates, the place to hide self-immunostimulatory RNA

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**Distinguishing the self from the non-self by the immune system is essential to avoid inflammatory and autoimmune diseases. Maharana et al. (2022) reveal a mechanism for hiding self-immunostimulatory RNA involving a three-variable equation: SAMHD1 and its exonuclease activity, single-stranded RNA, and RNA-protein condensate.**

The innate immune system acts as the first line of defense, sensing the virus through pattern-recognition receptors (PRRs). Vertebrate cells express many different PRRs that can detect pathogen-associated molecular patterns (PAMPs) of viruses and other microbes and trigger a signaling pathway leading to transcriptional upregulation of antiviral interferon (IFN) and proinflammatory genes. Via autocrine and paracrine signaling pathways, the IFN response is amplified and transmitted to neighboring cells to establish an antiviral state mediated by IFN response genes (ISGs) that exhibit strong antiviral activities ranging from viral nucleic acid degradation to inhibition of viral gene expression. ISGs also ensure the activation of inflammatory pathways that promote viral clearance. In the case of viral infection, viral nucleic acids are the major PAMP detected by the host innate immune receptors, which include retinoic acid-inducible gene (RIG)-like receptors in the cytosol and a subfamily of toll-like receptors that localize to the endosomal membrane. Importantly, host cells possess mechanisms that prevent self-immunostimulatory nucleic acids, such as mRNA, tRNA, mtDNA and genomic DNA that are released during the stress response or cell death, from engaging with PRRs to induce IFNs and the inflammatory response. Indeed, the subcellular localization of PRRs, the modifications of nucleic acids, and the degradation of unnecessary nucleic acids ensure the non-engagement of self-immunostimulatory nucleic acids with the PRRs (Schlee and Hartmann, 2016; Bartok and Hartmann, 2020). Inappropriate or prolonged detection of endogenous nucleic acids underlies many autoimmune diseases (Crow and Stetson, 2022).

In a recent issue of *Molecular Cell*, Maharana and colleagues report that compartmentalization of self RNA in condensates prevents their detection by RNA sensors and the triggering of an innate immune response. They found that enhanced levels of single-stranded RNA (ssRNA) results in dissolution of condensates and release of self-immunostimulatory double-stranded RNA (dsRNA), which accumulates in the cytoplasm and engages with the RNA sensor, RIG-I, leading to activation of type-1 IFN. Remarkably, they revealed a function for the Aicardi–Goutières Syndrome (AGS) (Crow and Stetson, 2022) and HIV restriction factor (Laguette et al., 2011; Hrecka et al., 2011), SAMHD1, in regulating the formation of RNA-protein condensates by modulating the level of cell-associated ssRNA. While highly purified recombinant wild type SAMHD1 possesses 3′ exonuclease activity toward ssRNA *in vitro*, SAMHD1 with an invalidating mutation found in AGS patients does not. Loss of SAMHD1 ssRNA 3′ exonuclease activity results in increased amounts of cell-associated ssRNA, dissolution of condensates, and liberation of dsRNA, which activates the RNA sensor RIG-I and, consequently, the IFN response. Interestingly, among all the nucleases tested in this study, modulation of ssRNA levels and condensate dissolution was restricted to SAMHD1. The use of AGS cells with a SAMHD1-invalidating mutation suggests that the described function plays a role in the associated interferonopathy. This discovery is important at many levels. First, it reveals an additional and important function for RNA-protein condensates in negatively regulating the innate immune response against self-immunostimulatory RNA. Indeed, RNA-protein condensates have been reported to play a positive role in triggering innate immune signaling leading to the activation of IFN genes (Harapas et al., 2022; Xiao et al., 2022). Such a mechanism can be used by RNA viruses to escape innate immunity by restricting the site of replication to condensates (Nevers et al., 2020). Second, it highlights a function for ssRNA in modulating RNA-protein condensate formation and in preventing self-immunostimulatory RNA recognition and the autoinflammatory response. Third, it reinforces the cross-regulation between intrinsic immunity mediated by restriction factors such as SAMHD1 and the innate immune response mediated by PRRs. Finally, the discovery that RNA condensates function as a hiding place for self-immunostimulatory RNA may allow deeper understanding of the etiology of the diseases associated with RNA condensate dissolution, particularly those with increased inflammation such as amyotrophic lateral sclerosis, frontotemporal dementia, and AGS (Hallegger et al., 2021; Alberti and Hyman, 2021; Crow and Stetson, 2022).

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## DECLARATION OF INTEREST

The author declares no competing interests.

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# Right on target: Chromatin jets arise from targeted cohesin loading in wild-type cells

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**Uncovering an informative feature of 3D genome structure, Guo et al. (2022) describe chromatin jets in quiescent murine thymocytes: 1–2 Mb structures formed by targeted cohesin loading at narrow accessible chromatin regions and visible as prominent off-diagonal stripes on contact maps.**

Eukaryotic genomes are organized into complex 3D structures across a range of length scales. Understanding the formation and regulation of these structures is crucial, as they regulate diverse processes including gene expression, DNA repair, recombination, and replication. Chromatin conformation capture methods, such as Hi-C, have been instrumental in uncovering patterns of 3D genome organization, including A/B compartments, topologically associating domains (TADs), and loops. A/B compartments arise from active and inactive chromatin regions associating primarily with other regions of the same type both intra- and inter-chromosomally and are visible on contact maps as a checkerboard pattern (Figure 1). TADs are local chromatin domains characterized by increased contact within the region compared with outside the region; they are visible on contact maps as squares (Figure 1) (Fudenberg et al., 2017). TADs often exhibit strong stripes/flames and corner peaks on contact maps, which are indicative of cohesin-mediated loop extrusion, wherein the SMC (Structural Maintenance of Chromosomes) complex cohesin loads onto DNA and extrudes bidirectionally until encountering a block or being unloaded (Davidson et al., 2019; Kim et al., 2019; Fudenberg et al., 2017; Gabriele et al., 2022). However, many aspects of the loop extrusion process remain poorly understood, including the factors that regulate cohesin loading