Sensing and sensibility: the role of non-coding RNAs in autoinflammation and viral infection

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General introduction

RNA are multifaceted molecules with many functions

The central dogma of molecular biology is used to illustrate the main flow of information in biological systems: genetic information encoded within DNA is transcribed to messenger (m)RNA, which can subsequently be translated into proteins[1]. In this traditional view on biology, RNA was perceived as an intermediate molecule, which has put the study of proteins and their function within the cell at the forefront of research. However, RNA has emerged as more than just a relay molecule between DNA and proteins. RNA molecules exhibit characteristics of both: they hold genetic information as copies of DNA, but RNA molecules can also fold into complex secondary and tertiary structures, allowing them to catalyze chemical reactions in a manner similar to proteins[2]. This dual functionality highlights the fact that RNA molecules have a more complex function than was initially believed.

The majority of the human genome is actively transcribed, while only 2% of human DNA codes for proteins[3]. The other 98%, classically referred to as 'junk DNA', gives rise to various classes of non-coding (nc)RNA. Advancements in molecular biology and RNA sequencing have uncovered a vast and diverse world of ncRNAs. These RNAs do not give rise to proteins but can interact with proteins, DNA, and other RNA molecules, thereby performing crucial functions in the cell[3]. Small ncRNAs, like microRNAs (miRNA) and small nucleolar (sno)RNAs are strongly conserved between species and are involved in processes like transcription and gene expression regulation[4,5], while long ncRNAs (lncRNAs), which are classified as longer than 200 nucleotides (nt), are less well-conserved[6,7]. They are similarly involved in processes like gene expression regulation, cell cycle progression, and protein synthesis, although many lncRNAs are still poorly characterized[8].

The wide variety of ncRNAs comes with a broad range of functions, many of which are still poorly understood. Many ncRNAs act by interacting with RNA-binding proteins (RBPs), forming complexes that are called ribonucleoprotein (RNP) complexes. The identity, posttranscriptional modifications, and secondary and tertiary structures of ncRNAs incorporated in an RNP guide the function of the complex[5]. Many RBPs have been characterized and bind to RNA via their RNA-binding domain. Additionally, some proteins bind to RNA but lack a known RNA-binding domain, many of which were initially studied for unrelated functions[9]. In some instances, however, ncRNAs function on their own[2].

Amongst their many functions, ncRNAs can have catalytic activity. For example, the active site of the ribosome is entirely composed of ribosomal (r)RNA. The ribosomal proteins that bind rRNA maintain the structure and orientation of the active site, while rRNAs catalyze protein synthesis reactions[10]. In other instances, ncRNAs regulate gene expression. For instance, miRNAs associate with the RNA-induced silencing complex (RISC), guide it to complementary mRNA molecules and induce degradation of the target mRNA[11]. This process is called RNA interference, and it plays a crucial role in regulating cellular processes. Besides these major classes of ncRNAs, many other species exist, like small nucleolar snoRNAs, long intergenic (linc)RNAs, Y RNAs, 7SL RNA, and vault (vt)RNAs. These ncRNAs interact with a multitude of RBPs and modulate their function. In doing so, ncRNAs can serve as molecular scaffolds for building large RNP complexes, assist in RNA splicing, serve as RNA decoys, direct proteins to certain subcellular localizations, and affect their capacity to multimerize[2,5,8,12–14]. In conclusion, ncRNAs play diverse and crucial roles in cells. As our knowledge of long and small ncRNAs is still rapidly expanding, it is highly likely that new ncRNAs and their functions will continue to be discovered.

RNA viruses and their detection by RNA receptors of the innate immune system

Viruses are obligatory intracellular parasites that depend entirely on host cells for replication of their genomes and generation of progeny. A large group of viruses uses RNA to store its genomic information, which has advantages over DNA genomes. One of the benefits of using RNA as a genomic carrier is the high mutation rate associated with RNA replication[15,16]. Viral RNA is replicated in the cytoplasm by a viral RNA-dependent RNA polymerase (RdRp) that does not possess proofreading capacity. The lack of proofreading introduces a relatively high frequency of mutations during genome replication, leading to diversification of the viral genome and ultimately to evolutionary selection based on the fitness of newly introduced mutations[16]. The high evolution rate of RNA viruses also enables immune evasion, a key advantage in the tug of war between highly dynamic viruses and complex eukaryotic host cells[17,18]. Besides the benefits of high mutation rates, viral RNA provides advantages in terms of viral gene expression. Viruses need to compete with host mRNAs for the proteins that orchestrate translation. The propensity of viral RNA to form secondary and tertiary structures allows for interactions with proteins involved in the translational machinery, thus favoring their own translation and enabling viruses to regulate their own gene expression[19]. For example, members of the *Picornaviridae* family use RNA elements folded in a three-dimensional structure called internal ribosomal entry sites to recruit the 40S subunit of ribosomes to the viral genome and to initiate cap-independent translation[20]. An additional property of RNA viruses is that their genomes can be translated almost directly upon entering a host cell, especially in the case of positive single-stranded RNA viruses[19]. This enables the rapid initiation of the viral replication cycle, giving viruses a head start in getting control over the host cell.

Host cells must be able to rapidly detect viral replication to mount a proper antiviral response to clear the infection, as unchecked viral reproduction is detrimental to the infected cell and the surrounding tissue. Viral nucleic acids represent the main pattern-associated molecular pattern (PAMP) during infection. Since the scope of this thesis is about RNA viruses and RNA sensing, I will focus on the sensing of viral RNA in this introduction. A wide repertoire of pattern recognition receptors (PRRs) of the innate immune system can sense viral RNA. The extracellular and endosomal compartments are scanned for viral nucleic acids by Toll-like receptors (TLR)3, 7, 8, and 9. The cytoplasm is surveyed for viral RNA by retinoic acid-inducible gene I (RIG-I), melanoma differentiation-associated protein 5 (MDA5), and laboratory of genetics and physics 2 (LGP2), collectively named the RIG-I-like receptors (RLRs)[21]. Upon activation of these receptors, a signaling pathway is initiated that leads to the production and secretion of type I interferons (IFNs), such as IFN-α and IFN-β. Type I IFNs are potent cytokines that can activate a secondary antiviral signaling pathway in the infected cell itself or neighboring cells by binding to the type I IFN receptor (IFNAR1/2)[22]. This culminates in the expression of hundreds of interferon-stimulated genes (ISGs), that directly or indirectly limit viral replication and aid the activation of adaptive immune responses[23,24].

The RIG-I-like receptors are ISGs as well, which serves as a positive feedback loop during an ongoing type I IFN response[23]. Other RNA receptors are also interferon-inducible, such as protein kinase R (PKR), 2′-5′-oligoadenylate synthetase 1 (OAS1), and Z-DNA-binding protein 1 (ZBP1). Instead of inducing the type I IFN response, these receptors mostly induce translational arrest and cell death after sensing viral RNA, as an additional route to contain and halt viral infection[25,26]. The presence of these different PRRs and their ability to initiate a strong antiviral response equips the cell with powerful tools to detect and fight viruses that enter the cell.

Self/non-self-discrimination in RNA sensing

Given that the core chemical structure of RNA is shared between viruses and eukaryotic cells, PRRs must be able to discriminate between own (self) and viral (non-self) nucleic acids based on features that are unique to the latter[21]. Most of these receptors sense double-stranded (ds) RNAs, which are a hallmark of RNA virus replication in the cytoplasm. RIG-I, a key cytosolic RNA receptor, senses viral RNA through a triphosphate or diphosphate moiety at the 5′ end of short, blunt-ended dsRNA[27–30]. After activation, RIG-I forms short oligomers that activate the type I IFN response. MDA5, on the other hand, recognizes long dsRNAs (> 500 base pairs), irrespective of 5′ end modifications[31]. Once a ligand is sensed, MDA5 forms long filaments along dsRNA, which induces subsequent type I IFN signaling. The ligand for LGP2 is less well-defined, but LGP2 has a similar affinity for long dsRNA as MDA5[32–34]. LGP2 is signaling-deficient, but nucleates MDA5 filaments, making them shorter, more stable, and more potent in inducing the type I interferon response[33–37]. As triphosphorylated or long double-stranded RNA structures are usually absent from self RNA, their presence represents a strong hint of viral infection.

Interestingly, eukaryotic cells also produce endogenous dsRNAs that have the potential to activate various PRRs[38]. It is therefore crucial that safeguarding systems are in place to avoid recognition of self RNAs by these receptors. The cell prevents self RNAs from unwanted activation of PRRs using three properties: 1) the availability of immunostimulatory RNAs in cells, 2) their subcellular localization, and 3) their post-transcriptional modifications[39]. The availability of immunostimulatory dsRNA is determined by gene expression and RNA decay mechanisms. Genomic regions that encode transcripts that form dsRNAs may be epigenetically silenced to prevent their transcription, while cytoplasmic RNases limit their intracellular concentration[40,41]. Certain RNAs, like rRNAs, may also be bound ('scavenged') by RBPs to avoid recognition by RLRs[42]. The subcellular localization of RNAs also determines their capacity to activate RLRs. For example, mitochondrial (mt)RNA, which is bidirectionally transcribed from the mitochondrial genome, has a strong tendency to form long RNA duplexes and is therefore particularly immunostimulatory. To prevent these dsRNAs from entering the cytoplasm, mitochondrial enzymes such as SUV3 and PNPase degrade mt-dsRNA within the mitochondria to keep it out of reach of RLRs[43]. Lastly, co- or posttranscriptional modifications of RNA molecules may lower the affinity of endogenous RNA for RNA sensors. For example, all nascent RNA molecules carry a 5′-triphosphate group, which might activate RIG-I. To circumvent this, the 5′ ends of RNA polymerase II transcripts are capped with a 7-methylguanosine modification and 2′-O-methylation during transcription, while RNA polymerase III transcripts are dephosphorylated by nuclear RNA-specific phosphatases such as DUSP11[44,45]. Additionally, modified nucleotides in self RNA such as *N*-6-methyladenosine may protect against unwanted activation of RIG-I[46,47]. Endogenous dsRNAs that may form a ligand for MDA5 are modified by ADAR1[48,49] – an enzyme that will be central in **Chapters 3** and **4** of this thesis. ADAR1 modifies adenosine into inosine residues in stretches of dsRNA[50–52]. Inosine residues are highly similar to guanosines, which disturbs base-pairing within dsRNA, thereby reducing its perfect complementarity and availability to MDA5 and LGP2[53,54]. Together, these mechanisms form the basis of safeguarding self RNA and are crucial for self/non-self-discrimination.

When protective measures that govern self/non-self-discrimination fail, RNA receptors may mistakenly recognize self RNA as foreign and trigger an unwanted type I IFN response, leading to sterile inflammation and autoinflammatory diseases[55,56]. This is illustrated by type I interferonopathies, a group of rare monogenic diseases in which pathology is caused by

constant type I IFN production in the absence of a viral pathogen. Type I interferonopathies such as Aicardi-Goutières Syndrome (AGS) are severe autoinflammatory diseases, which share symptoms of intracranial calcification and developmental delays[57]. Patients with these diseases suffer developmental deficiencies and usually die before reaching adulthood. The genetic alterations that cause AGS are mostly linked to loss-of-function mutations in enzymes responsible for RNA metabolism and gain-of-function mutations in enzymes involved in RNA sensing or regulation of IFNAR signaling[56]. For example, mutations in *ADAR* (coding for ADAR1) lead to the accumulation of unedited dsRNA that can be collectively sensed by MDA5 and LGP2[48,49,54,58]. Mutations in *PNPT1*, which codes for mitochondrial PNPase, cause a build-up of mt-dsRNA which leaks into the cytoplasm and activates MDA5[43]. Alternatively, gain-of-function mutations in MDA5 and RIG-I can deregulate their affinity for RNA, causing aberrant activation of the receptors[52]. Interestingly, the ligands that are thought to cause AGS are noncoding RNAs, derived from retroelements[52,59]. Retroelements make up a large portion of the genome and share similar structural features with viral dsRNAs. Once mechanisms that control expression, localization, or degradation of retroelements become mutated - such as the AGS-related genes *ADAR*, *TREX1*, or *SAMHD1* - uncontrolled production of type I IFNs is induced[52]. The identification of an increasing number of syndromes and pathologies that are classified as type I interferonopathies underscore that RNA sensing and the type I IFN response require tight regulation, and that mutations in proteins governing the activation of these pathways have detrimental consequences.

RNA molecules at the host-virus interaction interface

The interplay between viruses and their host cells is complex. Viruses need the host cellular machinery for their replication, while the host cell employs a wide range of PRRs to sense viral nucleic acids to ultimately eliminate the infection. The close evolution between viruses and eukaryotic cells has resulted in many intricate mechanisms by which viruses evade immune detection and hijack the cell.

Upon entering the cell, viruses must take control of the host translation machinery, tipping the balance in favor of viral over host protein translation[19]. Additionally, viruses recruit RBPs to bind the viral genomes and RNAs. This results in higher viral RNA stability, improved RNA processing, and shielding from innate immune receptors[60,61]. Besides these two strategies of host take-over, multiple other hijacking mechanisms exist. Viruses may manipulate host metabolism to favor their own replication, use the membranes of organelles to generate a replication organelle to physically separate their viral genome from PRRs, and/or rewire the secretory pathway to enhance the release of their progeny from the cell[62–64]. Notably, viruses also hijack ncRNAs to favor their replication and survival. For example, several host miRNAs have been identified that target host genes involved in the type I IFN response, thereby suppressing the antiviral response and helping viral replication. For example, the miRNA miR-132-3p is upregulated during influenza A virus (IAV) infection. It targets the transcription factor IFN regulatory factor 1 (IRF1) mRNA for degradation, thereby suppressing type I IFN production and preventing an efficient antiviral response[65]. Other host ncRNAs also contribute to viral replication[66]. The lncRNAs PAAN and IPAN are also upregulated during IAV infection and increase the stability of the viral RdRp complex[67,68]. Of note, host cells also produce many ncRNAs that have an antiviral function[66]. For example, the RNA polymerase III transcript *RN5SP141*, an rRNA pseudo-transcript that is normally bound by host proteins, is released in the cytoplasm during herpes simplex virus 1 (HSV-1) infection. Because of its

5' triphosphate group, it activates cytoplasmic RIG-I and initiates a type I IFN response[42]. The increasing body of literature that highlights the function of ncRNAs during viral infection sheds light on another level of virus-host interactions, while also presenting new targets for antiviral therapies.

Outline of the chapters in this thesis

Cells possess many ways to prevent the activation of PRRs by self RNAs. However, self RNAs do interact with PRRs, thereby modulating their activity depending on the context. In **Chapter 2**, we review known host ncRNAs that activate or inhibit RIG-I-like receptors in viral infections, autoinflammatory diseases, or cancer, and discuss the mechanisms by which they do so.

In **Chapter 3** and **Chapter 4**, we study the key players that sense self RNA in a model of a type of AGS that is caused by ADAR1 deficiency. MDA5 has long been the sole sensor of unedited self RNA in ADAR1 deficiency, but the role of the least well-studied RLR, LGP2, was unknown. In **Chapter 3**, we show that LGP2 is essential to mount an IFN response in cells lacking ADAR1 expression. The RNA sensing capacity of LGP2 is required, showing that LGP2 serves as an RNA receptor together with MDA5. In **Chapter 4**, we zoom in on the ligand that activates LGP2 in ADAR1 deficiency. Using iCLIP, we aim to identify the self RNA that binds to LGP2 in ADAR1-deficient cells.

In **Chapter 5**, we shift the focus to host ncRNAs that are hijacked by viruses. Vault (vt)RNAs are a group of small ncRNAs that are strikingly upregulated during various distinct viral infections. We find that genetic loss of vtRNA expression impairs viral replication, implying that they are hijacked by the virus. Using a mass spectrometry-based interactome study, we identify two RBPs as novel interaction partners of vtRNAs in homeostatic conditions and during viral infection. We then show that vtRNA expression facilitates the nuclear export of these proteins, which is required to promote viral replication.

Finally, in **Chapter 6**, the key findings of this thesis are discussed and placed in the context of existing literature. Based on our observations, I also discuss opportunities for future research and potential clinical implications.

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