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Antiviral resistance of stem cells

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Abstract

Stem cells are important for growth and regeneration given their ability to self-renew and differentiate into mature cells. Resistance to certain viral infections has been established as a phenotype of stem cells, a protection in line with their important physiological function. Antiviral resistance is critical to all cells, but it is differentially regulated between stem cells and differentiated cells. Stem cells utilize antiviral RNA interference, interferon-independent repression of endogenous retroviruses and intrinsic expression of antiviral interferon-stimulated genes. Differentiated cells often rely on the interferon-associated protein-based response to induce a local antiviral state. This review outlines the antiviral resistance mechanisms of stem cells and discusses some ideas as to why stem cells and differentiated cells may have evolved to utilize distinct mechanisms.

Introduction

Through self-renewal and differentiation, stem cells are critical for maintaining proper tissue structure and function. These effectors of growth and regeneration must not only be protected from damage and loss, but also be exposed to their environment to receive physiological cues for cell replacement and repair. To achieve this balance between protection and exposure, stem cells are maintained in specialized microenvironments [1,2]. These dynamic niches often facilitate the interactions of stem cells with humoral and cellular factors through their close association with the vascular system [3,4]. Some stem cells even circulate directly in peripheral blood [5,6]. Despite enabling stem cells to receive environmental signals, these same blood vessel networks place stem cells at risk of viral infection. In humans, retroviruses and herpesviruses can target hematopoietic stem cells in the bone marrow [7–9]. However, it has been known for decades that embryonic stem cells (ESCs) and other primitive cells resist viral infection. More recent studies have established that diverse viruses, including West Nile virus, cytomegalovirus and myxoma virus, are also

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unable to infect adult stem cells efficiently [10–16]. Thus, resistance to certain viral infections appears to be a general property of stem cells.

In this review, we briefly introduce the interferon-associated protein-based response and outline the various antiviral mechanisms proposed to operate in stem cells. After highlighting the distinct mechanisms utilized by stem cells and differentiated cells, we end with a discussion of the potential reasons why two distinct sets of antiviral responses may have evolved.

Interferon-associated protein-based response

Differentiated eukaryotic cells protect themselves against viral infection using the interferon-associated response, which was first described in the 1950s [17–19]. The present discussion will be centered on the cellular response to double-stranded RNA (dsRNA), a common intermediate in the replication of RNA viruses with the exception of retroviruses. Upon the detection of dsRNA by sensors like TLR3, RIG-I and MDA5, cells activate the transcription factors IRF3, IRF7 and NF- κ B to produce interferons (Table 1) [20,21]. Secreted interferons bind to cell surface receptors and transduce a signal through the JAK/STAT pathway that induces the expression of hundreds of interferon-stimulated genes (ISGs) [22]. ISGs form the basis of the antiviral properties of interferons and can interfere with the virus lifecycle at virtually any step. For example, the interferon-induced transmembrane (IFITM) protein family interferes with viral entry whereas bone marrow stromal antigen 2 (BST2) prevents virion release [23,24]. Acting as both autocrine and paracrine signaling molecules, interferons rapidly attempt to establish an antiviral state in both the infected cell and neighboring cells [25]. Although interferon signaling also induces the expression of non-coding RNAs including microRNAs, circular RNAs and long non-coding RNAs [26], this review will focus on the interferon-associated protein-based response.

Two decades later, it was observed that stem cells do not adhere to this paradigm. Burke et al. showed that pluripotent cells do not produce type I interferons in response to viral infection or treatment with poly I:C, a dsRNA mimic, and that they exhibit a severely attenuated response to interferon treatment [27]. At the molecular level, one study suggested that undifferentiated cells are deficient in various signaling components needed to mount an effective interferon-associated response since ESCs express lower levels of dsRNA sensor genes like *OAS1*, *PKR*, *MDA5* and *TLR3* compared to immortalized HeLa cells [28]. However, transcriptome analyses of ESCs and their differentiated products, a markedly different system from HeLa cells, reveals that these differences are not so clear [29**]. While certain sensors like *OAS1* and *MDA5* increase with differentiation into hepatocyte-like cells and neuron-like cells, *TLR3* and *PKR* decrease. Therefore, further work is needed to establish a clear explanation for the molecular basis of the attenuated interferon response in ESCs. As for the poor response of stem cells to interferon treatment, Hong et al. showed that ESCs express higher levels of SOCS1, a negative regulator of JAK/STAT signaling, than differentiated cells [30]. Since pluripotent stem cells show attenuated interferon production and ISG induction, these cells are unlikely to rely on the canonical interferon-associated response when exposed to viruses.

Antiviral RNA interference response in mouse ESCs

RNA interference (RNAi) is a mechanism largely conserved across eukaryotes that allows for specific gene silencing via sequence-dependent targeting by small RNAs of 20–30 nucleotides in length. A cytoplasmic RNase Dicer detects and cleaves dsRNA substrates to produce small interfering RNAs (siRNAs). These siRNAs are loaded onto Argonaute (Ago) effector proteins in complex with other proteins to form the RNA-induced silencing complex (RISC). The mature RISC then cleaves target RNA on the basis of perfect siRNA sequence complementarity [31]. RNAi can act on viral dsRNA replication intermediates to suppress viral accumulation in plants and forms the basis of a systemic immune response in flies and nematodes [32*, 33, 34].

Various groups have asked whether RNAi plays an equally active role in mammalian systems [35**,36**]. While gene knockdowns are achieved in somatic cells after transfection of mature siRNAs to induce RNAi, these same cells are unable to process long dsRNA substrates effectively into siRNAs [37]. After viral infection, the pool of small RNAs in somatic cells reveals negligible amounts of siRNAs derived from viral genomes [38]. In contrast, recent evidence suggests that mammalian germ cells and ESCs may retain the ability to process long dsRNAs [39–41]. The small RNA pool in ESCs contains siRNAs, which are absent in somatic cells, derived from the dsRNAs produced by endogenous retrotransposons. Given their ability to produce siRNAs, pluripotent stem cells may rely on RNAi to fight viral infection. Maillard et al. observed that mouse ESCs infected with encephalomyocarditis virus (EMCV) formed EMCV-derived siRNAs with the characteristic siRNA size and 3' overhangs [36**]. Similarly, infection of mouse ESCs with a mutant Nodamura virus (NoV) lacking the ability to antagonize the RNAi pathway produced higher levels of NoV-derived siRNAs than wild-type NoV infection. Indirectly demonstrating RISC-mediated silencing, mutant NoV replication was significantly impaired, but could be rescued in part by knockout of Ago proteins [36**]. Hence, pluripotent stem cells can produce functional siRNAs in response to viral infection.

Thus, it appears that stem cells can utilize RNAi while differentiated cells can mount an interferon response. Notably, each cell type seems to rely predominantly on one antiviral effector mechanism; stem cells exhibit an attenuated interferon response and differentiated cells do not produce siRNAs. As ESCs were differentiated, progressively fewer virus-derived siRNAs were found after EMCV infection [36**]. The simultaneous loss of RNAi and gain of a functional IFN response indicates that the two mechanisms may serve overlapping roles in antiviral immunity. This line of thinking is supported by a recent study that deleted mitochondrial antiviral-signaling component (MAVS), which is required to link dsRNA sensing to interferon production, in mouse embryonic fibroblasts (MEFs) [42**]. Prior transfection of *Mavs*^{-/-} MEFs with long dsRNA protected cells from subsequent infection by viruses whose genomes contained homologous sequences. This RNAi-mediated virus suppression was absent in wild-type MEFs and interferon-responsive cells. Therefore, the IFN response and RNAi may act as redundant antiviral effectors, where RNAi appears to be masked by IFN responsiveness in differentiated cells [43]. More recently, Li et al. reported that interferon-competent mammalian somatic cells infected with influenza A virus produced virus-derived siRNAs that co-immunoprecipitated with Ago, which contradicts the

masking suggested by Maillard et al [36**,44**]. This study is only one example of the controversy over RNAi in differentiated cells. As a detailed discussion lies beyond the scope of this review, we direct readers to a recent commentary by tenOever [45] and review by Ding et al [46].

Interferon-independent epigenetic repression of endogenous retroviruses in ESCs

Beyond exogenous viral infections, the mammalian genome also contains many endogenous retroviruses (ERVs) now fixed in the genome from ancient retroviral infections. ERV copies and related sequences account for approximately 8% of the human genome and 10% of the mouse genome [47,48]. The long terminal repeats (LTRs) in the ERVs themselves and solitary LTRs found next to cellular genes can drive undesirable high-level gene expression. Repression of ERVs and their LTRs is thus important to maintain genomic integrity by preventing ERV activation and regulating gene expression by avoiding aberrant transcription. As a tightly regulated gene expression profile controls development, stem cells depend on epigenetic mechanisms to repress ERVs. One example is histone methylation via the H3K9me3 mark mediated by Zfp809, Trim28 and Eset, which targets the conserved retroviral primer binding site (PBS) [16,49–52]. Recently, a genome-wide siRNA screen identified more than 300 genes involved in silencing the Moloney murine leukemia virus (MMLV) provirus in mouse ESCs including histone chaperones, sumoylation factors and chromatin modifiers [53]. Sumo2 and chaperone Chaf1a both localize to ERVs; sumoylation of Trim28 by Sumo2 leads to the binding of Trim28 to the ERV LTR whereas Chaf1a interacts with Eset. As there are likely multiple mechanisms that maintain ERV repression, one group asked whether the HUSH (human silencing hub) complex composed of TASOR, MPP8 and PPHLN1, which silences transcriptional reporters placed into heterochromatin by recruiting methyltransferase SETDB1 [54**] was involved. Using mouse ESCs, however, the results suggest that although TASOR strongly binds ERVs, it is redundant in transcriptional repression given binding of Trim28 [55]. Thus, the tight regulation of ERVs in mouse ESCs is the cumulative outcome of many distinct epigenetic and genetic mechanisms.

Differentiated cells also actively repress ERVs, but this repression does not rely on the same regulatory machinery as stem cells [16,53]. The expression of factors implicated in ERV repression in mouse ESCs either decreases significantly or remains similar during progression from ESC to terminal differentiation (unpublished data). Moreover, shRNA knockdown of these same factors, including Sumo2 and Chaf1a, showed no effect on MMLV proviral reporter expression in MEFs, in stark contrast to experiments in mouse ESCs [53]. In differentiated CD4⁺ T cells, the HUSH complex was shown to be a novel host restriction factor that must be inhibited by HIV-2 and SIV for successful infection [56]. Beyond retroviral infection, however, it remains unknown whether the HUSH complex plays an important or redundant role in ERV repression in differentiated cells. Overall, these studies suggest that pluripotent and differentiated cells likely rely on different mechanisms for ERV repression, similar to the differential dependence on RNAi.

Intrinsic expression of ISGs in mammalian stem cells

Mouse ESCs, human ESCs and human induced pluripotent stem cells (iPSCs) are all refractory to interferon stimulation [27,30]. Despite this well-characterized phenotype, ISGs from the interferon-associated protein-based response remain important in mediating antiviral immunity [29**,57**]. Rather than the widespread ISG induction that follows interferon treatment in differentiated cells, recent studies have shown that a subset of ISGs is intrinsically expressed in human stem cells [29**,57**]. This intrinsic ISG expression is present in pluripotent stem cells like ESCs and iPSCs, as well as adult tissue stem cells. Interestingly, the subset of highly expressed ISGs varies by stem cell type, but consistently decrease with progression to terminal differentiation. While intrinsic ISG expression is lost after reaching this latter stage, these cells have become interferon responsive. Additionally, intrinsic ISG expression was also present in mouse and chimpanzee pluripotent stem cells, suggesting that intrinsic ISG expression is conserved across mammals. Interestingly, all stem cells analyzed expressed high levels of the potent antiviral IFITM family members. Triple knockout of intrinsically expressed IFITM1, IFITM2 and IFITM3 in ESCs greatly increased viral susceptibility. Moreover, several well-characterized ISGs targeting retroviruses, such as *BST2*, *MOV10* and *IDO1*, were intrinsically expressed in both human and mouse pluripotent stem cells. Constitutive expression of this group of ISGs could further enhance the repression of ERVs beyond the aforementioned antiviral proteins, as previously shown for *MOV10* [58,59]. Intrinsic ISG expression may even work in conjunction with other antiviral mechanisms to mediate the stem cell phenotype of viral resistance. As RNAi was observed following removal of interferon responsiveness in MEFs, it would be interesting to see whether RNAi is enhanced after ablation of intrinsic ISG expression.

Given their lack of interferon responsiveness, stem cells are unlikely to rely on JAK/STAT signaling for intrinsic ISG expression, indicating the possible existence of a distinct transcriptional regulatory mechanism. At an epigenetic level, histone modifications are heavily involved (for example, see Figure 1). H3K4me3 and H3K27ac modifications, which commonly mark active promoters, are enriched in the promoters of highly expressed ISGs relative to silent ISGs. Throughout differentiation, a marked transition from active to silent histone marks correlated with the decreasing expression pattern of ISGs. At the transcriptional level, analyses of highly expressed transcripts in human ESCs and interferon-treated ESC-derived hepatocytes indicate that only a small fraction of ISGs utilize alternative transcription start sites. Thus, stem cells likely rely on the same transcriptional binding sites or transcription factors as differentiated cells for ISG expression. Further analyses of transcription factor binding revealed that the difference in the subset of ISGs expressed between cell types was due to cell type-specific transcription factor expression. Interestingly, some transcription factors associated with intrinsic ISG expression have previously been tied to cell fate determination [60*,61]. Further elucidation of this potential overlap in the transcriptional regulation of ISGs and stem cell identity could deepen our understanding of the evolution of pathogen defenses during differentiation.

These findings demonstrate the existence of two antiviral ISG programs during stem cell differentiation. Stem cells, both ESCs and tissue stem cells, show an attenuated response to interferon, but maintain constitutively elevated levels of selected ISGs that serve as

prophylactic mediators against viral infection. By contrast, differentiated cells lack intrinsic ISG expression, but respond to interferon signaling with general ISG induction mediating broad viral resistance. By focusing on ISG expression, our recent study [29**] did not consider the expression of other proteins that could have antiviral functions in pluripotent or differentiated cells. For instance, a subset of CD141⁺ dendritic cells constitutively resists viral infection due to expression of RAB15, a vesicle-trafficking protein that colocalizes with HIV-1 to prevent fusion [62]. As discussed above, similar non-ISG restriction factors have also been reported in mouse ESCs. Nonetheless, this study adds a new layer to the distinct antiviral mechanisms that function in stem cells and differentiated cells.

The advantage of being different

Altogether, recent findings in conjunction with earlier studies suggest that different antiviral programs are used by stem cells and differentiated cells (Figure 2). This intriguing dichotomy leads one to ask: why might interferon-independent programs have been selected over the interferon response in undifferentiated cells? It is first important to recognize that the endogenous small RNA processing machinery serves roles beyond antiviral immunity [40,41]. Knockout of Dicer in mammalian embryos is lethal and the stem cell compartment is abrogated completely [63]. This finding is consistent with defects seen in the proliferation and differentiation of *Dicer*^{-/-} mouse ESCs [64,65], which could suggest that Dicer-processed siRNAs and microRNAs play important roles in stem cells [66]. One potential explanation can be found in the differential presence of dsRNAs derived from inverted repeat structures, bidirectional transcription products and antisense transcripts between pluripotent and differentiated cells. dsRNAs are rarely found in the cytoplasm of differentiated cells due to effective nuclear retention mechanisms. However, such mechanism is not robust in pluripotent cells, suggesting a greater need for RNAi in stem cells [67]. In line with this idea, siRNAs complementary to endogenous dsRNAs were found in mouse ESCs and oocytes, but not differentiated cells [39–41]. Although mouse oocytes actively produce siRNAs complementary to the transposable element (TE) long interspersed element-1 (LINE-1), these siRNAs have not been observed to target LINE-1, but rather cellular genes whose 3' UTRs contain TE repeats [40,41]. Such results suggest that RNAi may serve to regulate the expression of particular classes of genes in the female germline. Noting that this purpose is distinct from antiviral RNAi, future studies could also investigate the effectiveness of RNAi as a defense mechanism against TEs in pluripotent cells. Thus, there may be a need for the RNAi machinery in stem cells that is lost following differentiation.

In addition to the benefits of RNAi in stem cells, relying on a dsRNA-induced interferon response may have adverse effects on stem cell function. Interferons mediate well-characterized anti-proliferative activity through a subset of ISGs including *IFIT1* and *CH25H* [68]. This feature may be incompatible with the self-renewal of stem cells required for tissue regeneration and repair [69]. Moreover, several studies show that interferons can also stimulate differentiation [70]. As such, undifferentiated stem cells may need to dampen both interferon production and signaling to maintain their pluripotent state. Another potential complication stems from how interferons can induce pro-apoptotic ISGs like *TRAIL* and *ISG12* that sensitize cells to undergo apoptosis following viral infection [71].

This would be bad for stem cells given their rarity and importance. By contrast, these consequences of interferon signaling do not fundamentally oppose the function of differentiated cells. Overall, stem cells may not rely on the conventional interferon response if interferon signaling induces genes that are incompatible with their role in self-renewal and differentiation. However, they may still benefit from subset of potent antiviral effector functions normally induced by interferon. As recently shown, mammalian stem cells constitutively express a selection of antiviral ISGs including members of the IFITM family [29**,57**]. Notably, this intrinsic ISG profile does not include ISGs with known anti-proliferative or pro-apoptotic activity. In contrast, a macrophage subset constitutively expresses *Usp18*, an ISG that inhibits type I IFN responsiveness [72]. *Usp18* expression, which is absent in other macrophages, allows viral replication in these particular differentiated cells and is thus critical for mounting an effective immune response [73]. While these macrophages and stem cells both show decreased IFN responsiveness, the former supports viral replication whereas the latter inhibits it through expression of antiviral ISGs. Therefore, the attenuated IFN response exhibited by both cell types has likely evolved to serve distinct physiological purposes.

At an epigenetic level, previous study has shown that ESC chromatin exists mostly in an open state [74]. Many genes are thus accessible to the transcriptional machinery and expressed at low basal levels including factors involved in self-renewal and differentiation. This baseline transcriptional activity may keep stem cells primed to respond to physiological cues. Beyond this subset of lowly expressed transcripts, the intrinsic antiviral ISGs are expressed at high levels in ESCs. The allocation of cellular resources to maintaining this elevated level of expression suggests that the prophylactic antiviral state is critical to stem cell identity and function. An interesting parallel for this idea can be found by looking at transcript expression in differentiated cells. These cells have defined identities as part of terminal lineages, so they maintain a low level of expression of far fewer genes than pluripotent cells. Moreover, they allocate their cellular machinery towards producing transcripts and proteins relevant to cellular structure and function consistent with their identity. For example, hemoglobin and anion exchanger family genes account for a significant portion of the total transcripts expressed by erythrocytes, transcripts encoding albumin and apolipoproteins represent a significant fraction of the mRNAs expressed by hepatocytes, and similarly, transcripts encoding smooth muscle actin and myosin are the predominant mRNAs expressed by myofibroblasts. To avoid incurring an additional “fitness cost” in Darwinian terms, differentiated cells may have evolved to maintain their functions and turn off constitutive ISG expression in favor of an interferon-inducible system. Just as albumin production is a critical hepatocyte function, we suggest here that intrinsic antiviral ISG expression is a core part of the stem cell identity either at the level of genomic integrity or to maintain pluripotency.

Concluding remarks

Stem cells do not rely on the interferon-associated protein-based response that induces a local antiviral state after infection of differentiated cells. Rather, three major mechanisms have been reported to operate in stem cells: antiviral RNAi, epigenetic repression of ERV, and intrinsic expression of antiviral ISGs (Figure 2). These mechanisms not only serve

functions in stem cells beyond antiviral resistance, but may also enable stem cells to avoid responding to interferons, which could induce responses incompatible with self-renewal and differentiation.

Despite recent progress in the field, important questions remain unsolved regarding the intrinsic ISG profiles that mediate stem cell antiviral resistance. Single-cell RNA sequencing has revealed considerable transcriptional heterogeneity in mouse ESCs upon chemical perturbation [75]. As such, it would be worthwhile examining whether differences in the constitutive ISG profiles arise at single-cell level. From a mechanistic perspective, further work is necessary to elucidate how ISGs are regulated in stem cells. While preliminary data implicate histone modifications, additional epigenetic changes are likely involved as well. At the transcriptional level, it is particularly interesting that common transcription factors may mediate stem cell identity and intrinsic ISG expression. Exploring this functional overlap and the changes that accompany differentiation may provide insights into the development of pathogen responses. When considering the potential therapeutic implications of stem cell antiviral resistance, it will be interesting to ask whether cancer stem cells also intrinsically express ISGs as such findings could significantly impact the effectiveness of oncolytic virotherapy.

From an evolutionary perspective, it will be particularly interesting to understand how stem cells have come to express these intrinsic ISG profiles. Each stem cell investigated expressed not only a common set of ISGs, but also a unique subset based on its identity as, for example, an intestinal or neuronal stem cell. Given the elevated baseline transcriptional activity of stem cells, it is possible that viral receptors are expressed at low levels, which could dictate a need for intrinsic ISG expression. From another angle, ERVs have been shown to shape IFN-associated regulatory networks by dispersing IFN-inducible enhancers upstream immune genes [76**]. This shaping likely developed independently between species, as *AIM2* expression is IFN-inducible in humans, but constitutive in mice. It would be interesting to see whether the independent dispersion of ERV enhancers is responsible for species differences in stem cell intrinsic ISG profiles [29**]. Another interesting line of inquiry might look at memory B and T cells, which are stem cell-like [77]. Earlier work with influenza virus showed that infection induced a population of lung tissue-resident memory CD8⁺ T cells that maintained IFITM3 expression [78**]. Given that viral infection appears capable of selecting for cell populations with particular antiviral profiles, a broad question is how these stem cell-specific intrinsic ISG programs were shaped over the course of evolution. Finally, one can wonder how aspects of viral infection might alter or “train” the antiviral ISG profile of these immune cells. This shaping could take place through direct selection of cell populations that resist viral infection, through the induction of transcriptional changes within infected cells, or through the secretion of factors by infected cells to promote transcriptional changes in neighboring cells. Thus, further research into mechanisms of stem cell antiviral resistance and their broader implications will enhance our understanding of the evolution of stem cells and pathogen resistance.

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Papers of particular interest, published within the period of review, have been highlighted as

* of special interest

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Highlights

- Stem cells are resistant to infection by diverse viruses
- Stem cells and differentiated cells use distinct antiviral resistance mechanisms
- Interferon responsiveness may be incompatible with stem cell function
- Intrinsic interferon-stimulated gene expression may be vital to stem cell identity

Figure 1. The epigenetic landscape showing dynamic histone modifications along cardiomyocyte differentiation of human stem cells.

The dynamic levels of H3K4me3, H3K27ac and H3K2me3 for unexpressed and highly expressed ISGs along cardiomyocyte differentiation. Mx1 represents an example of unexpressed ISGs; IFITM3 represents an example of highly expressed ISGs in hESCs. ChIP-Seq (H3K4me3, H3K27ac and H3K2me3, y axis represents reads over million unique mapped reads) are shown and derived from ENCODE. The scale for each modification is constant throughout the time course of differentiation. This figure is modified from reference 29 with permission.

Figure 2. Overview of antiviral resistance strategies employed by stem cells and differentiated cells.

The **top panel** depicts how RNAi is functional in stem cells as long viral dsRNA is processed by Dicer into small siRNAs for incorporation into RISC, but in differentiated cells potentially masked by dsRNA sensors that trigger interferon production. The **middle panel** highlights the epigenetic repression of endogenous retroviruses in both stem cells and differentiated cells, but shows that these cells rely on distinct regulatory machinery to mediate this repression. The **bottom panel** illustrates how stem cells are unresponsive to interferon and intrinsically express a subset of ISGs to mediate antiviral resistance, whereas differentiated cells show general ISG induction in response to interferon.

Table 1.

Glossary of proteins discussed in the text and their main functions.

Protein	Class	Function
TLR3	RNA sensors	A toll-like receptor family member that recognizes viral dsRNA
RIG-I and MDA5		Innate immune receptors that detect viral dsRNA in the cytoplasm
OAS1		A member of the 2–5A synthetase family involved in the innate immune response to viral infection
PKR		An interferon-induced dsRNA-dependent serine/threonine-protein kinase with a key role in responding to viral infection that is also involved in regulating apoptosis and cell proliferation
NF- κ B	Signaling transducers	A family of transcription factors that play critical roles in inflammation and immunity
IRF3 and IRF7		Primary transcription factors downstream of MAVS signaling that regulate the type I IFN response after RNA virus infection
JAK/STAT		A conserved signaling pathway involved in processes such as immunity, cell division, cell death and tumor formation
SOCS1	Interferon-stimulated genes	A member of the STAT-induced STAT inhibitor (SSI) family that acts as inducible negative regulator of cytokine signaling
MAVS		An adaptor protein that coordinates signaling leading to the activation of NF- κ B, IRF3 and IRF7 for antiviral cytokine production
MOV10		RNA helicase that potently inhibits retrotransposition in cells
IDO1		An indoleamine 2,3-dioxygenase enzyme that catalyzes the first rate-limiting step in tryptophan catabolism to -formyl-kynurenine
IFIT1		An interferon-induced protein with tetratricopeptide repeats 1 that inhibits viral replication and translational initiation
CH25H		A protein involved in cholesterol and lipid metabolism that catalyzes the production of 25-hydroxycholesterol
TRAIL		A cytokine secreted by cells in most tissues that causes apoptosis primarily in tumor cells by binding to death receptors
ISG12		An interferon-induced protein that promotes cell death by rapidly releasing cytochrome C from the mitochondria and caspase activation
Dicer	Small RNA processing machinery	A cytoplasmic endoribonuclease that cleaves dsRNA and pre-microRNA into short small interfering RNAs and microRNAs
Ago		An essential component of the RNA-induced silencing complex (RISC) that mediates gene silencing targeted by small RNAs
TASOR	Human silencing hub (HUSH) complex	This complex is recruited to genomic loci rich in H3K9me3 and maintains transcriptional silencing by promoting recruitment of SETDB1
MPP8		
PPHLN1		
Zfp809	Endogenous retroviral silencers	A member of the Krüppel-associated box-zinc finger protein family that initiates the silencing of endogenous retroviruses by recruiting heterochromatin-inducing complexes
Trim28		A transcriptional co-repressor for the Krüppel-associated box-zinc finger family of transcription factors
Eset		A histone methyltransferase that specifically trimethylates Lys-9 of histone H3, which is central to silencing euchromatin genes
Chaf1a		A core component of the chromatin assembly factor 1 complex that mediates chromatin assembly in DNA replication and DNA repair by binding histones H3 and H4
Sumo2		A member of the small ubiquitin-like modifier protein family that covalently attaches to proteins as a monomer or lysine-linked polymer