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Pathogen-associated regulatory non-coding RNAs and oncogenesis

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1. ABSTRACT

Among all new cancer cases in 2012, on average, 15.4% were caused by *Helicobacter pylori* or oncoviruses, including Epstein-Barr virus, human papillomavirus, *hepatitis B virus*, *hepatitis C viruses*, Kaposi sarcoma-associated herpesvirus and human T-lymphotropic virus. These pathogens encode a variety of non-coding RNAs, which are important cofactors for oncogenesis. In this review, we focus on recent developments in the study of long and small non-protein-coding RNAs, including microRNAs, of oncogenic pathogens, and discuss their mechanisms of action in the multiple steps of oncogenesis.

2. INTRODUCTION

In 2001, the human genome sequencing consortium released its final draft of the human genome (1). Although only 2.94% of the genome was revealed to encode protein coding genes, subsequent large-scale transcriptomic analyses, such as deep sequencing and/or whole genome high-density tiling array analyses combined with bioinformatics, revealed that the majority of the genome (74.7%) was indeed transcribed but was not translated into proteins (2, 3). These unexpected findings, that a much larger part of the human genome than was previously assumed is pervasively transcribed into ncRNA (non-protein-coding RNA), revolutionized our view of genome organization and content. These findings have challenged the traditional central dogma of molecular biology, which states that genic DNA codes for RNA and RNA codes for protein (4). These results also changed the definition of a gene; a gene encodes information not only for protein-coding RNAs but also for ncRNAs. Recent advances in gene studies revealed that ncRNAs play important functional roles in gene expression and the term 'RNA gene' has been proposed (5).

The transcripts from such RNA genes can be further categorized according to the length of transcripts, and ncRNAs exceeding 200 nucleotides in length are typically classified as lncRNAs (long non-coding RNAs) (6). LncRNAs are functionally very diverse (7, 8). In addition to architectural ncRNAs, such as rRNAs, tRNAs and paraspeckle assembly transcripts, a large fraction of ncRNAs is involved in the regulation of gene expression (7, 9, 10); i.e. they can positively or negatively affect gene expression in an epigenetic (11) or a post-transcriptional manner (12, 13).

Many reports have documented dysregulated transcription of ncRNAs in diverse cancers, with

Table 1. Pathogens and cancers

Pathogens[1]	Cancers elicited	Reference
Hepatitis B virus (HBV)	Hepatocellular carcinomas (HCCs)	(122, 123)
Hepatitis C virus (HCV)	Hepatocellular carcinomas (HCCs)	(124)
Human herpesvirus 4 (Epstein-Barr virus; EBV)	Burkitt lymphoma (BL), Hodgkin's lymphoma (HL), Nasopharyngeal carcinoma (NPC), Gastric carcinoma (GC), and Opportunistic lymphoma	(125)
Human herpesvirus 8 (Kaposi sarcoma-associated herpesvirus; KSHV)	Kaposi's sarcoma	(126)
Human papillomavirus (HPV)	Cervical cancer	(127, 128)
Human T-lymphotropic virus 1 (HTLV-1)	Adult T-cell leukemia (ATL)	(129)
Helicobacter pylori	Gastric carcinoma	(130)

[1]Virus nomenclatures are based on International Committee on Taxonomy of Viruses (ICTV) 2014 Master Species List. Only formal taxonomic names are written in italics.

ncRNAs being overexpressed or suppressed (14-23), leading to the downregulation of tumor suppressor genes, such as p53 (24). Such dysregulation of ncRNA expression and hence, disruption of their regulatory roles is increasingly recognized to be of great importance in oncogenesis (25, 26).

Several viral and also *Helicobacter pylori* infections are strongly related to human oncogenesis (Table 1). In 2012, an average of 15.4% of all new cases resulted from such infections, varying from less than 5% in the USA, Canada, Australia, New Zealand, and several countries in western and northern Europe to more than 50% in several countries in sub-Saharan Africa (27, 28).

Six oncoviruses are known to be causative agents for human cancers. Human oncoviruses do not sit in a single viral class but fall into a wide range of taxonomic classifications. They include complex exogenous retroviruses (such as HTLV-1 or human T-lymphotropic virus 1), positive-stranded RNA viruses (such as HCV or *hepatitis C virus*), DNA-RNA viruses (DNA viruses that use reverse transcription as a part of their replication process, such as HBV or *hepatitis B virus*), and both large double-stranded DNA viruses (such as HHV4 or *human herpesvirus 4* also known as Epstein-Barr virus or EBV and HHV8 or *human herpesvirus 8*, also known as Kaposi sarcoma-associated herpesvirus or KSHV), and small double-stranded DNA viruses (such as HPV or human papillomavirus) (27, 28).

Among these pathogens, gastric *H. pylori* is the strongest risk factor, playing virtually indispensable roles in the development of both intestinal and diffuse gastric non-cardia adenocarcinomas (29).

Like their host cells, many, but not all, viruses synthesize their own ncRNAs. Similar to their host counterparts, viral ncRNAs associate with proteins that are essential for their stability or function, or both. Diverse biological roles, including the regulation of viral replication, viral persistence, host immune evasion, and cellular transformation, have been ascribed to viral ncRNAs (30).

In this review, we focus on the interplay between virus-encoded ncRNAs and their targets with respect to pathogen-associated oncogenesis and the cancer hallmarks proposed by Hanahan and Weinberg (31, 32) (see Table 2).

3. ONCOVIRAL microRNAs AND ONCOGENESIS

miRNAs (microRNAs) are incorporated into RISCs (RNA-induced silencing complexes) by binding to host AGO (argonaute) family proteins and downregulate protein production of target mRNAs. The use of viral miRNAs instead of viral proteins to manipulate gene expression has several advantages; although miRNAs are short, they are capable of regulating the expression of a large number of mRNAs, which share a common MRE (miRNA response element). Moreover, oncoviral miRNAs are less likely than proteins to be recognized by the host immune system (30). Such miRNAs may help oncoviruses maintain the latent infection state in host cells by escaping from host immunosurveillance.

Oncoviruses inhibit both transition to the lytic cycle (33) and the induction of apoptosis (34-37), leading to latent infection. Oncovirus infection then upregulates the production of inflammatory cytokines (38-40), which induces a local inflammatory response at the site of infection. Latent infections within the host induce chronic inflammation (41), which favors oncogenesis by stimulating angiogenesis, damaging DNA, maintaining stem cells in a cancer microenvironment and chronically stimulating cell proliferation (42, 43).

Table 2. Viral ncRNAs and oncogenesis

Virus	ncRNA	Target	Cancer hallmarks[1]	Reference
EBV	miR-BHRF1-3	CXCL-11/I-TAC	Avoiding immune destruction	(47)
EBV	miR-BART5	PUMA	Resisting cell death and maintaining latency	(34)
EBV	miR-BART4/15	Bim	Resisting cell death	(35, 36)
EBV	miR-BART16	TOMM22	Resisting cell death	(37)
EBV	miR-BART6-3p	PTEN	Resisting cell death	(49)
EBV	miRNAs from BHRF1 locus		Resisting cell death and favoring cell cycle progression and proliferation	(50)
EBV	miR-BART2	BALF5	Maintaining latency	(33)
EBV	miR-BART6-5p	EBNA2, Dicer	Maintaining latency	(51)
EBV	miR-BART3	DICE1/INTS6	Promoting cell growth	(54)
EBV	miR-BART9	CDH1	Activating invasion and metastasis	(61)
EBV	BART miRNA cluster 2	NDRG1	Activating invasion and metastasis	(62)
EBV	EBER1 and EBER2	IL-6 and IL-10	Tumor-promoting inflammation	(52, 53)
	EBER1	IL-10	Resisting cell death	(91)
	EBER1 and EBER2	IL-6	Evading growth suppressors	(53)
	EBER1 and EBER2	FAK, PAK, RhoGD1 and KAI-1	Activating invasion and metastasis	(53)
	EBER1	PKR	Avoiding immune destruction	(86, 90)
	EBER1 and EBER2	RIG-I	Immune destruction	(52)
	EBER1	TLR3	Immune destruction	(89)
	EBER1	miR-200	Activating invasion and metastasis	(53)
KSHV	miR-K12-9	IRAK1	Avoiding immune destruction	(67)
KSHV	miR-K12-5	MYD88	Avoiding immune destruction	(67)
KSHV	miR-K12-11	IKBKE/IKKepsilon	Avoiding immune destruction	(68)
KSHV	miR-K12-5, -9, -3 and -10b	BCLAF1	Resisting cell death	(69)
KSHV	miR-K12-10a	TWEAKR	Resisting cell death	(70)
KSHV	miR-K12-1, -3 and -4-3p	caspase 3	Resisting cell death	(71)
KSHV	miR-K12-11	LDOC1	Resisting cell death	(72)
KSHV	miR-K12-1	IkappaBalpha	Maintaining latency	(73)
KSHV	miR-K12-4	Rbl2	Maintaining latency	(74)
KSHV	miR-K12-7 and -9	RTA	Maintaining latency	(75)
KSHV	miR-K12-3-5p and -7	LIP	Tumor-promoting inflammation	(76)
KSHV	miR-K12-1	p21	Evading growth suppressors	(77)
KSHV	miR-K12-1, -3-3p, -6-3p, -11	THBS1	Inducing angiogenesis and anchorage independent proliferation	(78)
KSHV	miR-K12-3-5p	GRK2	Activating invasion and metastasis	(79)
KSHV	PAN	IRF4	Avoiding immune destruction	(101)
	PAN	Target: unknown	Cell growth	(102)
HCV	vmr11	HNF4alpha	Activating invasion and metastasis	(116)
	vmr11	TNPO2	Genome instability and mutation	(119)

[1]The hallmarks of cancer proposed by Hanahan and Weinberg (31, 32) constitute an organizing principle for rationalizing the complexities of neoplastic disease, which include; (1) sustaining proliferative signaling; (2) evading growth suppressors; (3) enabling replicative immortality; (4) activating invasion and metastasis; (5) inducing angiogenesis; (6) resisting cell death; (7) deregulating cellular energetics; (8) avoiding immune destruction; (9) genome instability and mutation and (10) tumor-promoting inflammation.

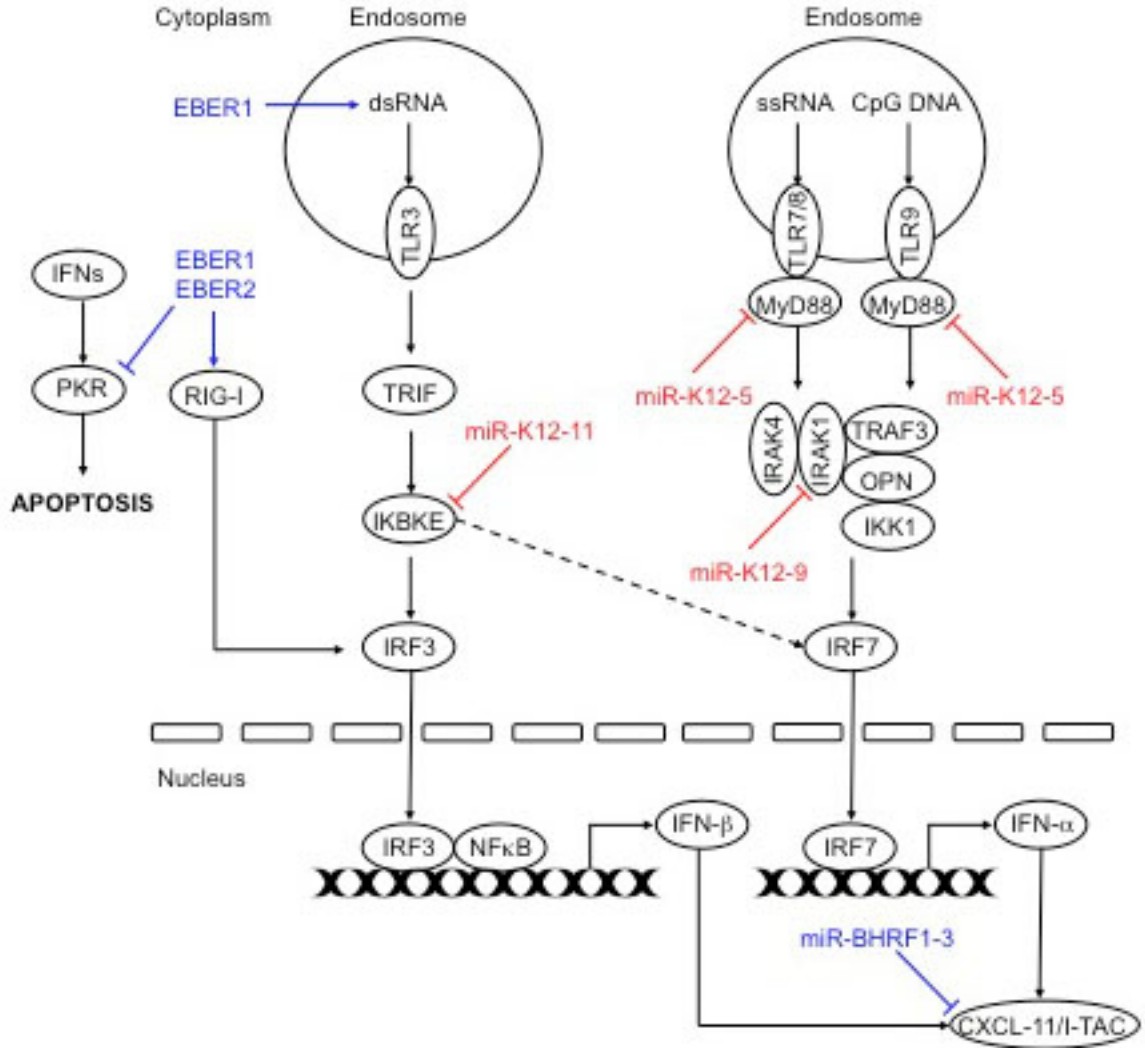

Figure 1. Immune evasion by pathogen-associated ncRNAs. EBV BHRF1-3 miRNAs target chemokine CXCL-11/I-TAC mRNA for suppression, which encodes the IFN-inducible T-cell-attracting chemokine. EBER1 and EBER2 are recognized by the cytosolic double-strand RNA sensor, RIG-I, and the plasma membrane receptor for double-strand RNA, TLR3, recognizes EBER1, leading to induction of the type I IFN response. EBERs, however, inactivate PKR, the major IFN response gene product and antiviral effector, resulting in inhibition of apoptosis. KSHV miR-K12-9 and -K12-5 evade host immunosurveillance by suppressing the expression of IRAK1 and MYD88 mRNAs. KSHV miR-K12-11 downregulates IKBKE mRNA expression, causing the deactivation of IRF3/7 in infected cells. The dashed line indicates a possible commitment. EBV miRNAs and EBERs are in blue font and KSHV miRNAs are in red font.

3.1. EBV miRNAs and oncogenesis

The EBV genome encodes up to 25 miRNA precursors from BART and BHRF loci (44-46). The miRNAs derived from these loci are involved in escape from immune surveillance, apoptosis inhibition, and maintaining the latent stage of infection, as discussed above. For example, recent studies show that EBV BHRF1-3 miRNAs target and suppress chemokine CXCL-11/I-TAC mRNA, which encodes the IFN (interferon)-inducible T-cell attracting chemokine (Figure 1) (47). These miRNAs may play a role in the immune evasion strategy with which EBV downregulates the CTL (cytotoxic T lymphocyte) cytokine networks (48).

EBV miR-BART5 inhibits the expression of the cellular protein, PUMA (p53 upregulated modulator of apoptosis), to promote host cell survival and hence the establishment of latent EBV infection (34). Additionally, miR-BART4/15, miR-BART16 and miR-BART6-3p target the mRNAs encoding Bim (Bcl-2 interacting mediator of cell death), TOMM22 (translocase of outer mitochondrial membrane 22) and PTEN (phosphatase and tensin homologue deleted on chromosome 10), respectively, leading to inhibition of apoptosis (Figure 2) (35-37, 49). Furthermore, another group of EBV-encoded miRNAs from the BHRF1 locus also inhibits apoptosis and favors cell cycle progression and proliferation of infected B cells early after infection (Figure 2) (50).

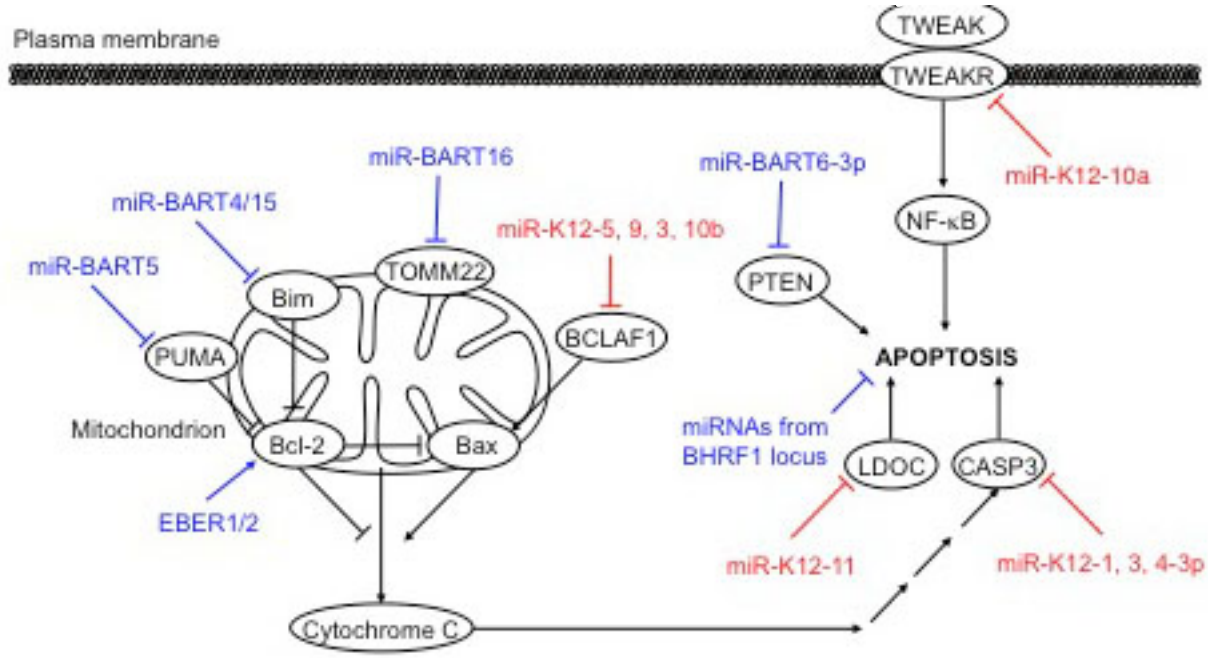

Figure 2. Inhibition of apoptosis by pathogen-associated ncRNAs. EBV miR-BART5 reduces the levels of PUMA mRNA, which encodes a modulator of apoptosis for promoting host cell survival. EBV miR-BART4/15, miR-BART16 and miR-BART6-3p target mRNAs of Bim, TOMM22 and PTEN, respectively, leading to the inhibition of apoptosis. EBV EBER1 and EBER2 upregulate the apoptosis inhibitor, Bcl-2. EBV-encoded miRNAs from the BHRF1 locus also manage to inhibit apoptosis and favor cell cycle progression. BCLAF1 mRNA, encoding a pro-apoptotic protein, is the target of KSHV miR-K12-5, -9, -3 and -10b. KSHV miR-K12-10a targets TWEAKR mRNA, thereby protecting KS cells from TWEAK-induced apoptosis. KSHV miR-K12-1, 3 and 4-3p target caspase 3 mRNA, resulting in resistance to apoptosis. miR-K12-11 targets LDOC mRNA, which encodes a factor responsible for apoptosis regulation. Bcl-2 is an integral outer mitochondrial membrane protein and is inhibited by PUMA and Bim. Bcl-2 inhibits pro-apoptotic protein, Bax, which is activated by BCLAF1. Bcl-2 and Bax are considered to contribute to the release of cytochrome C, which activates caspases, leading to apoptosis. EBV miRNAs and EBERs are in blue font and KSHV miRNAs are in red font.

EBV miR-BART2 downregulates the viral DNA polymerase, BALF5, and inhibits transition from latent to lytic viral replication (33), thereby maintaining the latent stage (Figure 3). In a more direct manner, miR-BART6-5p suppresses EBNA2 (EBV nuclear antigen 2) expression, which is required for transition from immunologically less responsive type I and II latency to the more immunoreactive type III latency. miR-BART6-5p also suppresses expression of the EBV immediate-early gene product, ZTA, and RTA (replication and transcription activator) proteins for lytic replication through silencing of dicer mRNA (Figure 3) (51).

In the latent stage of infection, EBV expresses the LMP1 (latent membrane protein-1) which upregulates expression of a number of factors, including tumor-promoting inflammatory cytokines and chemokines, such as IL-6 (Interleukine-6), IL-1beta, IL-1alpha, CXCR4 (C-X-C chemokine receptor type 4), RANTES (Regulated on Activation, Normal T Cell Expressed and Secreted), MCP1 (Monocyte Chemotactic Protein-1), IL-8 and IL-10 (38). Upregulation of some of these factors by LMP1 is mediated through its ability to activate NF-kappaB signaling (38). NF-kappaB has a dual role in oncogenesis; its expression in potentially malignant cells can prevent cell death by targeting a number of inhibitors of apoptosis, including Bcl-XL (B-cell lymphoma XL), cIAPs (cellular inhibitors of apoptosis proteins), GADD45beta (growth arrest and DNA-damage-inducible 45beta), BCL2A1 (B-cell-lymphoma-2-related protein A1) and SOD2 (superoxide dismutase 2) (40). NF-kappaB also acts as a prominent mediator of inflammation, by regulating the expression of pro-inflammatory cytokines, such as IL-1, IL-6, IL-8 and TNF-alpha (tumor necrosis factor-alpha) (Figure 4) (39, 40). Furthermore, EBV encodes small ncRNAs, EBER1 (EBV-encoded small RNA 1) and EBER2 that upregulate the expression of tumor-promoting inflammatory cytokines such as IL-6 and IL-10 (Figure 4) (52, 53) (see also chapter *4.1.*).

The chronic state of inflammation induced by these cytokines, and by the chemokines discussed above, can act to promote tumorigenesis. Chronic inflammation induces cell proliferation, recruits inflammatory cells, increases production of reactive oxygen species leading to oxidative DNA damage, and reduces DNA repair. Subversion of cell death and/or repair programs occurs in chronically inflamed tissues, resulting in DNA replication and proliferation of cells that have lost normal growth control (41). As such, inflammation can be considered to enable the acquisition of core cancer capabilities (Table 2, 10 of cancer hallmarks). More specifically, the virally encoded miR-BART3 plays a role in EBV-dependent oncogenesis by suppressing DICE1/

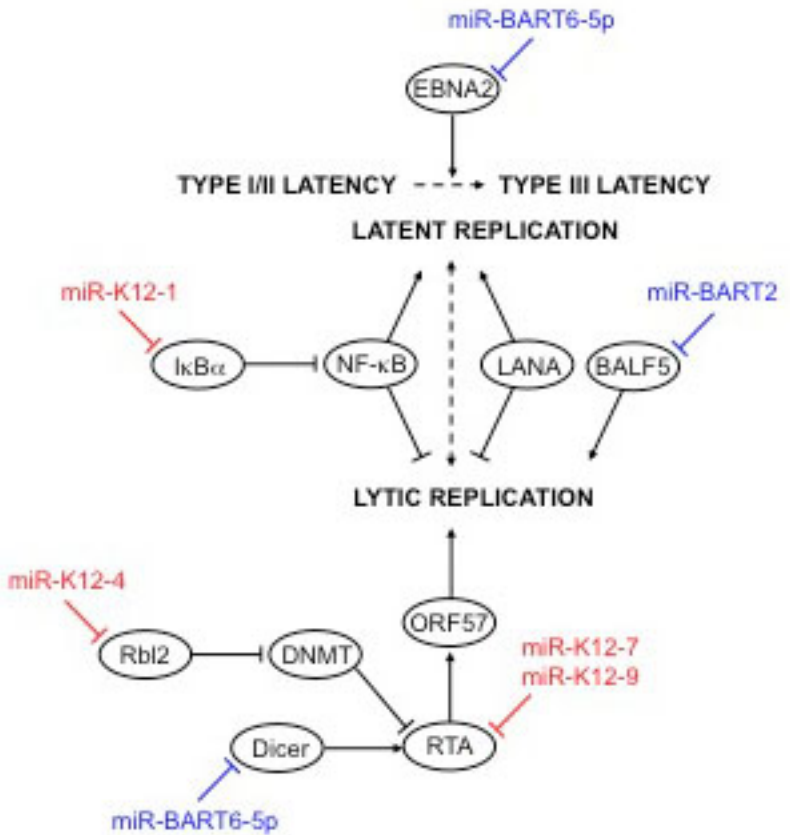

Figure 3. Maintenance of latency by pathogen-associated ncRNAs. EBV miR-BART2 downregulates the expression of viral DNA polymerase BALF5, resulting in inhibition of transition from the latent stage to the lytic stage of infection. EBV miR-BART6-5p suppresses EBNA2 viral oncogene expression, which is required for transition to immunoreactive type III latency. miR-BART6-5p also silences dicer mRNA, leading to suppression of RTA expression, which acts on viral lytic replication. KSHV miR-K12-1 reduces IkappaBalpha mRNA expression, resulting in the suppression of lytic gene transcription. KSHV miR-K12-4 inhibits the expression of Rbl2 mRNA, which encodes a repressor of DNMT function. KSHV miR-K12-7 and -K12-9 reduce expression of RTA mRNA. The dashed line indicates transition between the latent and lytic stages. EBV miRNAs are in blue font and KSHV miRNAs are in red font.

INTS6 (Deleted in cancer cells 1/Integrator complex subunit 6) expression (54). Indeed, consistent with low expression levels of DICE1 in EBV-positive NPC (nasopharyngeal carcinoma), tumor cell proliferation was observed (Figure 5A) (54).

Tumor-promoting inflammation recruits inflammatory cells, including TAMs (tumor-associated macrophages), which constitute a large portion of the tumor mass (55). While TAMs in the mass cause cancer initiation and promotion by secreting cytokines for chronic inflammation, these macrophages may also be obligatory for invasion, metastasis and angiogenesis (56). In the progressive stage of oncogenesis, TAMs are localized to points of basement-membrane breakdown during the transition to malignancy and to the invasive front of more advanced tumors. This suggests that tumors exploit the normal matrix remodeling capacities of macrophages, enabling them to egress into and migrate through the surrounding stroma (56, 57). Thus, TAMs are endowed with exaggerated extracellular-matrix remodeling activity and invasive properties (58). Tumor-derived signals for TAM-recruitment include hypoxia caused by the tumor outgrowing the vascular supply (59). Hypoxia induces the HIF transcription factors in these cells, whose targets include genes for many angiogenic factors, such as VEGF (vascular endothelial growth factor), which enhance angiogenesis in these avascular areas (60).

EBV encodes miR-BART9 to promote the migration of NPC (nasopharyngeal carcinoma) cells by specifically inhibiting E-cadherin to induce a mesenchymal-like phenotype (61). The virus also encodes BART miRNA cluster 2 to promote tumor invasion and metastasis by targeting NDRG1(N-myc downstream regulated gene 1) mRNA, which encodes a suppressor of metastasis (Figure 6) (62). NDRG1 protein inhibits the TGF-beta-induced EMT (epithelial-mesenchymal transition) by maintaining E-cadherin at the plasma membrane (63). NDRG1 also inhibits the nuclear translocation of beta-catenin, leading to the expression of metastasis-associated genes such as cyclin D1 (Figure 6) (64). These results strongly suggest that EBV encodes miRNAs that are, at least in part, responsible for the aggressive phenotype of

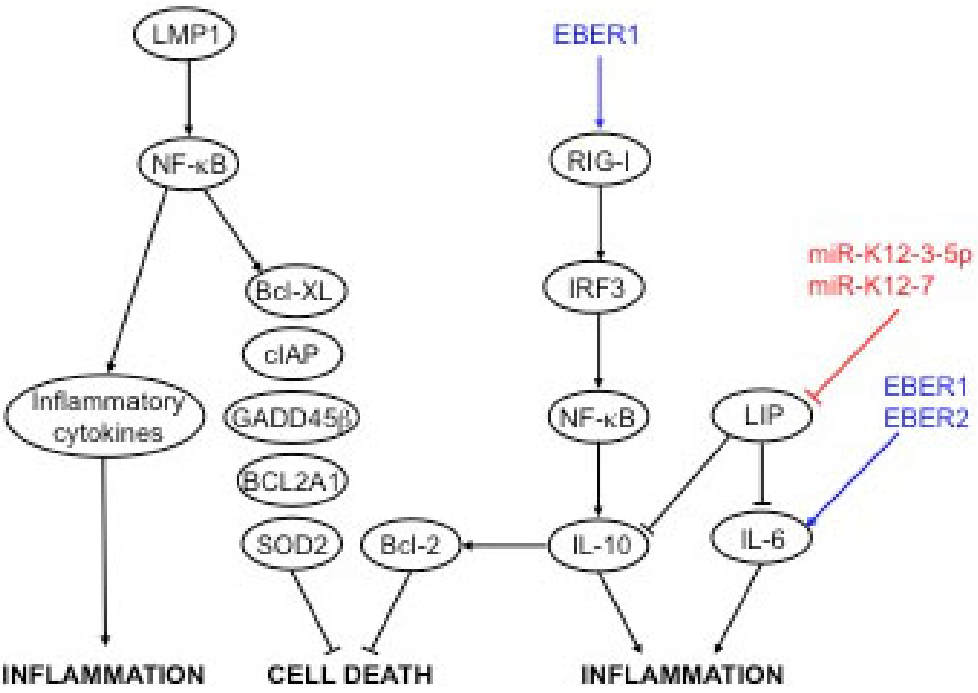

Figure 4. Tumor-promoting inflammation by pathogen-associated ncRNAs. EBV EBER1 induces IL-10 expression through RIG-I-mediated IRF3 signaling. IL-10 upregulates the apoptosis inhibitor, Bcl-2, resulting in cell proliferation. KSHV miR-K12-3-5p and miR-K12-7 target LIP mRNA, resulting in upregulation of IL-6 and IL-10 expression in infected human myelomonocytic cells. EBV LMP1 and EBER1 are in blue font and KSHV miRNAs are in red font.

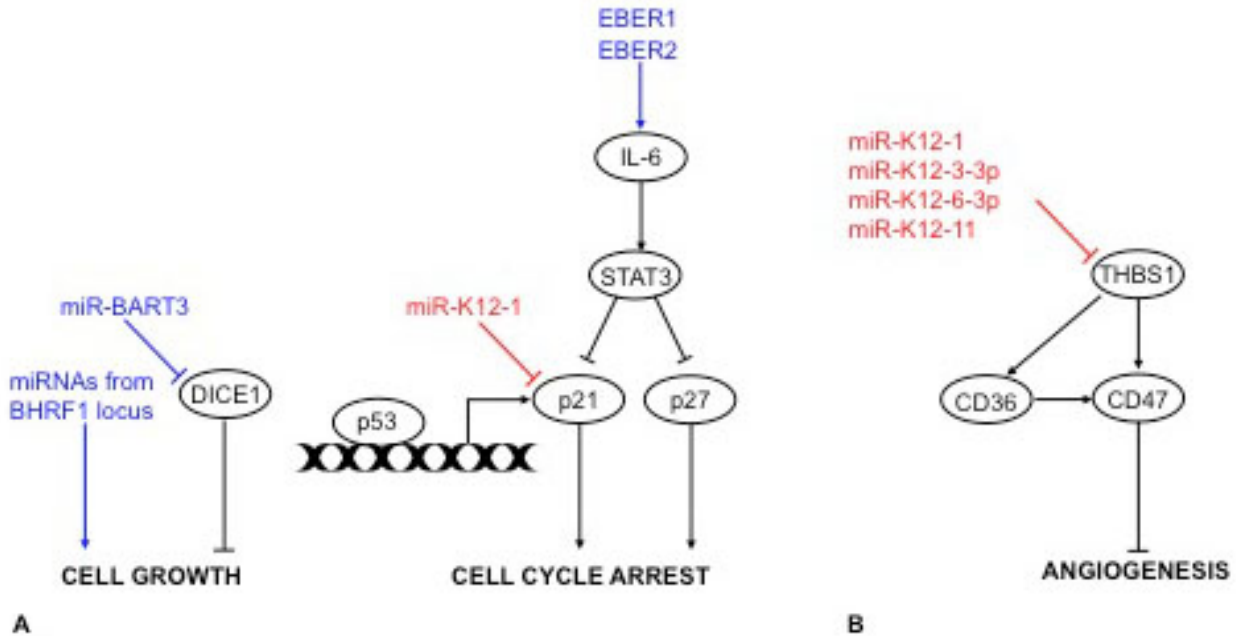

Figure 5. A) Cell proliferation and release from cell cycle arrest by pathogen-associated ncRNAs. EBV miR-BART3 suppresses DICE1 mRNA expression, leading to the promotion of cell proliferation and transformation. EBV miRNAs from the BHRF1 locus also promote cell proliferation. KSHV miR-K12-1 targets p21 mRNA, which encodes an inducer of cell cycle arrest. EBER1 and EBER2 activate STAT3 expression through upregulation of IL-6 expression. The activated STAT3 downregulates expression of cell cycle inhibitors, p21 and p27, leading to release from cell cycle arrest. B) Induction of angiogenesis by pathogen-associated ncRNAs. A group of KSHV miRNAs, including miR-K12-1, -K12-3-3p, -K12-6-3p and -K12-11, accelerate anchorage-independent proliferation and angiogenesis by inhibiting THBS1 mRNA expression. TSBH1 acts through its receptors, CD47 and CD36, to inhibit angiogenesis. EBV miRNAs and EBERs are in blue font and KSHV miRNAs are in red font.

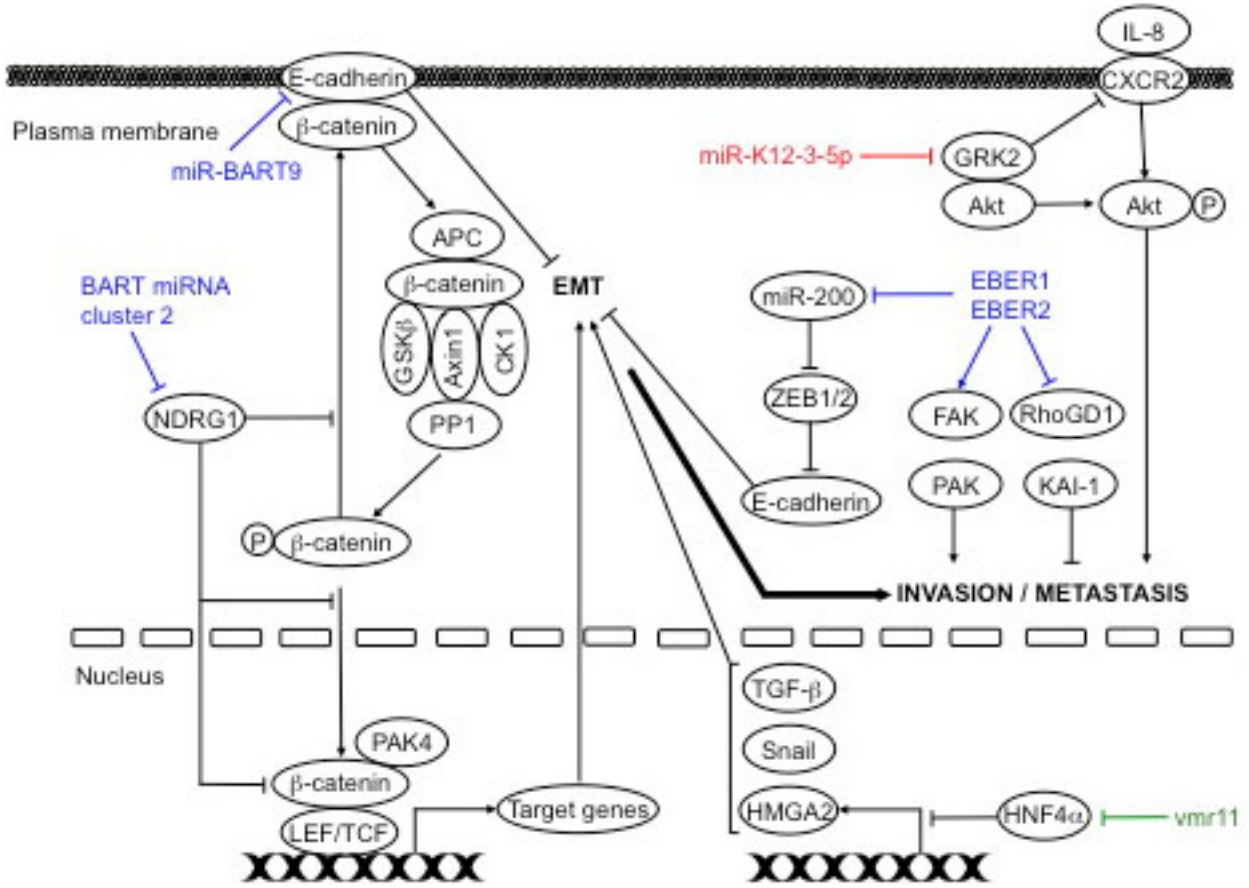

Figure 6. Activation of invasion and metastasis by pathogen-associated ncRNAs. EBV miR-BART9 promotes the migration of NPC cells by specifically inhibiting E-cadherin, resulting in a mesenchymal-like phenotype. EBV BART miRNA cluster 2 promotes tumor invasion and metastasis by targeting NDRG1 mRNA, which encodes a suppressor of metastasis. Reduced expression of NDRG1 allows nuclear translocation of phosphorylated beta-catenin, resulting in EMT with invasion and metastasis. EBV EBER1 and EBER2 induce the activation of pro-metastatic molecules, FAK and PAK1, along with downregulation of anti-metastatic molecules, RhoGD1 and KAI-1, which promote cell migration. Furthermore, EBER1 and EBER2 inhibit host miR-200, leading to inhibition of E-cadherin expression and EMT. By targeting GRK2 mRNA, KSHV miR-K12-3-5p promotes cell migration and invasion, which result from transduction of CXCR2 signaling that activates Akt phosphorylation. HCV vmr11 targets HNF4alpha mRNA, which causes expression of EMT regulatory genes: *TGFB*, *Snail* and *HMGA2*. Upregulated expression of these genes results in EMT. EBV miRNAs and EBERs are in blue font, KSHV miRNAs are in red font and the HCV miRNA is in green font.

EBV-positive NPC cells by activating invasion and metastasis.

It is thus concluded that following induction of chronic, tumor-promoting inflammation by EBV miRNAs, another set of EBV miRNAs downregulate the expression of anti-tumor suppressor genes and induce EMT activation, leading to the acquisition of cancer hallmarks relevant to tumor progression (Figure 6) (Table 2, 3 to 5 of cancer hallmarks).

3.2. KSHV miRNAs and oncogenesis

KSHV encodes 12 viral miRNA precursors, most of which are from a large intron in the KSHV latency-associated region (46, 65, 66). Like EBV, KSHV expresses miRNAs in latently infected B cells. These miRNAs contribute to viral oncogenesis by similar strategies to those of EBV; likewise, KSHV evades host immunosurveillance and inhibits apoptosis and lytic reactivation, thereby maintaining latent infection. This leads to the production of tumor-promoting inflammatory cytokines, as discussed for EBV (section *3.1.*) (42, 43) (Table 2, 10 of cancer hallmarks).

To commence the oncogenesis process, immunosurveillance is evaded by KSHV miR-K12-9 and -K12-5, which suppress the expression of IRAK1 (interleukin-1 receptor-associated kinase 1) and MYD88 (myeloid differentiation primary response protein 88) (67), respectively (Figure 1). These target molecules are essential for TLR7/8 (Toll-like receptor 7/8)- and TLR9-dependent recognition of viral ssRNA and unmethylated CpG oligonucleotides of microbial origin, respectively; therefore, they effectively downregulate type I IFN production in the infected cells (Figure 1). Furthermore, miR-K12-11 downregulates the expression levels of IKBKE (inhibitor of NF-kappaB kinase subunit epsilon) mRNA (also known as IKKepsilon (IkappaB kinase epsilon)), causing the deactivation of IRF3/7 (interferon

regulatory factor 3/7) in infected cells. These results reveal that KSHV infection can attenuate type I IFN responses, resulting in evasion of host antiviral innate immunity (68).

Resistance to apoptosis is another strategy evolved by EBV to enable persistence in host cells. Likewise, KSHV employs miRNAs for downregulating the apoptotic pathways. Using a microarray-based approach to identify target mRNAs, BCLAF1 (Bcl-2-associated factor) mRNA, which encodes a pro-apoptotic protein, was identified as a target of miR-K12-5, -9, -3 and -10b. The repression of BCLAF1 mRNA expression by these KSHV miRNAs enabled cells to overcome etoposide-induced caspase activation, resulting in inhibition of apoptosis (Figure 2) (69).

Virally encoded miRNAs can also prevent apoptosis in KS (Kaposi sarcoma) tumor-derived endothelial cells in response to TWEAK (tumor necrosis factor-like weak inducer of apoptosis) stimulation. For example, miR-K12-10a-mediated knockdown of TWEAKR (TWEAK receptor) mRNA protected KS cells from TWEAK-induced apoptosis (Figure 2) (70). In another study, Suffert and colleagues showed that multiple KSHV miRNAs; miR-K12-1, 3 and 4-3p, target caspase 3 mRNA, resulting in resistance to apoptosis (71). Furthermore, miR-K12-11 targets LDOC (leucine zipper down-regulated in cancer 1) mRNA, which encodes a factor responsible for apoptosis regulation (72). Thus, these KSHV miRNAs are relevant for inhibiting the induction of apoptosis, which constitutes one of the cancer hallmarks listed in Table 2, 6 of cancer hallmarks.

Following evasion of host immunosurveillance and inhibition of apoptosis, another set of KSHV miRNAs maintains viral latency. Deletion of a cluster of miRNAs in the KSHV genome (but not miR-K12-10 and -12) resulted in enhanced viral lytic replication as indicated by the increased levels of RTA mRNA and MCP (major capsid protein) mRNA as well as increased virion production (73). Because RTA and MCP mRNAs encode proteins responsible for KSHV lytic infection, these results suggest that viral miRNAs are enrolled to maintain viral latency in host cells.

Three ways to maintain latency by viral miRNAs have been proposed (Figure 3). Firstly, they suppress IkappaBalpha mRNA expression, resulting in suppression of lytic gene transcription. KSHV miR-K12-1 was identified as such an miRNA by neutralization using an antagomiR (73). The neutralization experiment caused increased levels of RTA and MCP mRNAs and of the viral lytic transcripts, ORF57 and PAN (73). Secondly, KSHV miR-K12-4 causes activation of DNMTs (DNA methyl transferases), resulting in inhibition of *RTA* gene expression. For this, miR-K12-4 inhibits the Rbl2 (retinoblastoma-like protein 2) mRNA, which encodes a repressor of DNMT (74). Thirdly, miR-K12-7 and -K12-9 target MRE-K12-7 and -K12-9 in the 3′-UTR of RTA mRNA, resulting in destabilization of the mRNA and inhibition of RTA mRNA expression (75). Thus viral miRNAs contribute to the maintenance of KSHV latency by repressing lytic gene expression.

As was discussed above for EBV oncogenesis, latent infection of KSHV can be followed by chronic, tumor-promoting inflammation (32, 41). Virally encoded miRNAs induce IL-6 and IL-10 secretion from infected human myelomonocytic cells (Figure 4) (76). This phenotype was mediated by miR-K12-3-5p and miR-K12-7, which target LIP (liver-enriched inhibitory protein) mRNA, encoding a negative transcriptional regulator of *IL-6* and *IL-10* genes (76). These data support a role for KSHV miRNAs in programming cytokines to establish a chronic inflammatory status in the host microenvironment (Table 2, 10 of cancer hallmarks) (41).

Apart from acting on the mRNAs encoding caspase 3 and IkappaBalpha (Figures 2 and 3, respectively) miR-K12-1 also targets p21 (cyclin-dependent kinase inhibitor) mRNA, which encodes a key inducer of cell cycle arrest (Figure 5A) (77). Indeed, ectopically expressed miR-K12-1 specifically inhibits the expression of endogenous p21 mRNA in KSHV-negative cells and strongly attenuates the cell cycle arrest that normally occurs upon p53 activation. Furthermore, stable knockdown of this miRNA in a latently KSHV-infected PEL (primary effusion lymphoma) cell line resulted in derepression of p21 expression and increased the efficiency of cell cycle arrest following p53 activation (77).

These data thus demonstrate that miR-K12-1 represses the expression of p21, a protein with known tumor suppressor function, and further suggest that this KSHV miRNA is likely to contribute to the oncogenic potential of KSHV, leading to evasion of growth suppressors (Table 2, 2 of cancer hallmarks).

Once miR-K12-1 together with -K12-3-5p and -K12-7 promote oncogenic proliferative signaling and induce tumor-promoting inflammation, respectively, in the KSHV infected host, a group of miRNAs, including miR-K12-1, -K12-3-3p, -K12-6-3p and -K12-11 further accelerate anchorage-independent proliferation and angiogenesis by inhibiting THBS1 (Thrombospondin 1) mRNA (Figure 5B) (78). This mRNA encodes a potent inhibitor of cell adhesion, migration and angiogenesis (78). Furthermore, by directly targeting GRK2 (G protein-coupled receptor kinase 2) mRNA, miR-K12-3-5p promotes cell migration and invasion, which result from transduction of CXCR2 signaling and activation of Akt phosphorylation (Figure 6) (79).

Although KSHV and EBV follow identical paths to execute viral oncogenesis, the miRNAs of

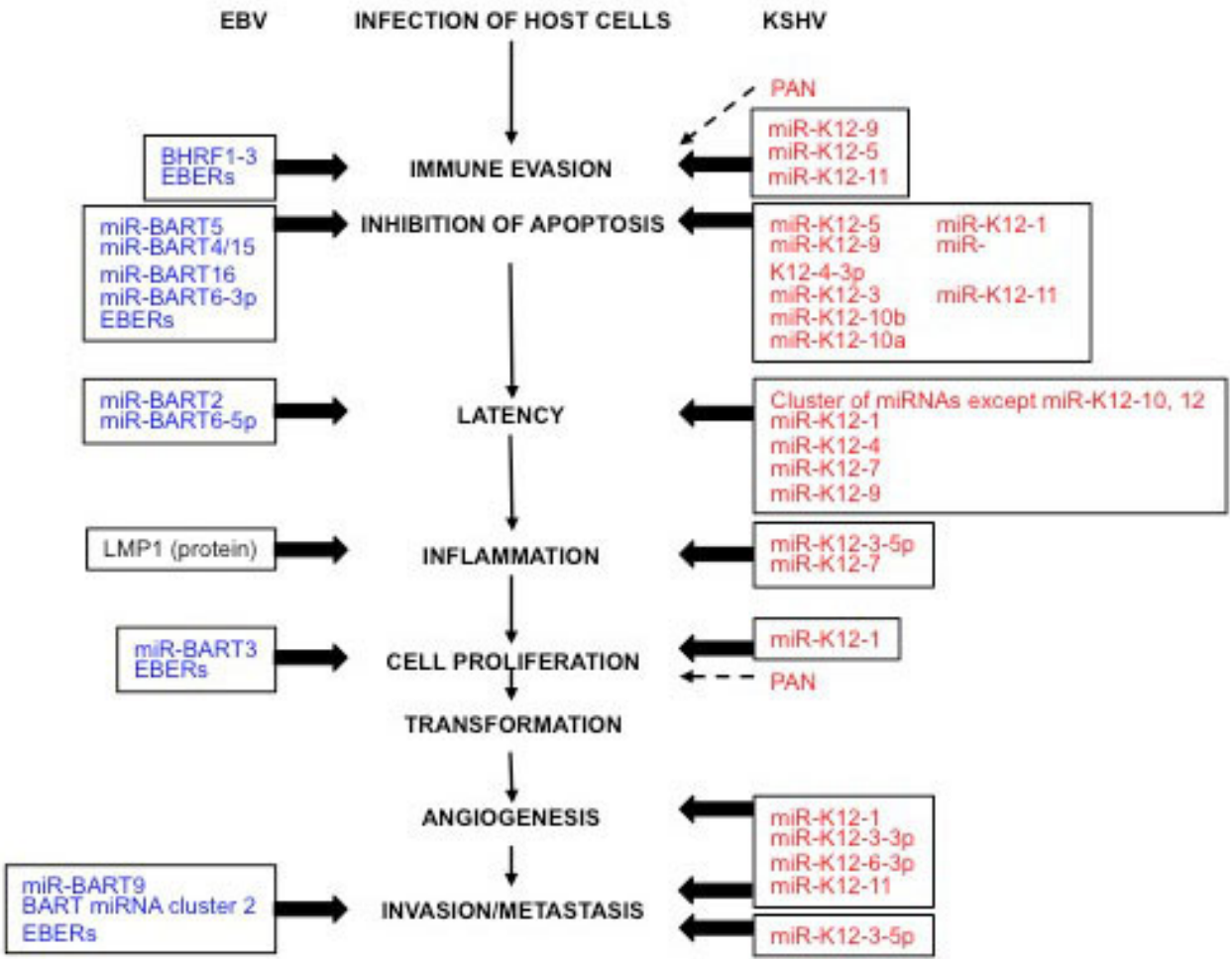

Figure 7. The pros and cons of EBV and KSHV miRNAs for viral oncogenesis. Although both KSHV and EBV follow identical processes to execute viral oncogenesis, the ncRNAs of the two viruses have different modes of action. Almost all of the KSHV miRNAs are involved in more than one oncogenic process, whereas EBV miRNAs are specific for one particular process. Furthermore, EBV employs EBER1 and EBER2 to complete some of the processes. The dashed lines indicate possible involvement by KSHV PAN. EBV miRNAs and EBERs are in blue font and KSHV miRNAs and PAN are in red font.

the two viruses have different modes of action. Almost all of the KSHV miRNAs are involved in more than one oncogenic process, whereas EBV miRNAs are specific for one particular process (Figure 7). The contrasting ways of executing oncogenesis between KSHV and EBV may reflect the different numbers of miRNAs that each herpes virus encodes. While EBV encodes 25 miRNA precursors, resulting in the production of 48 mature miRNAs, KSHV encodes 12 miRNA precursors, producing only 25 miRNAs (46, 80, 81). Furthermore, to assign particular roles to each miRNA, EBV employs the small ncRNAs, EBER1 and EBER2, which compensate for the EBV miRNAs that are involved in oncogenesis but are not sufficient to complete the processes (Figure 7) (see below).

3.3. HPV miRNAs and oncogenesis

HPV is a well-characterized human etiological agent that is directly linked to cervical cancer. Papillomavirus-encoded miRNAs in human cervical cancer and cell lines were first identified by Qian and colleagues (82).They established small RNA libraries from human HPV-associated cervical cancer lesions and HPV-harboring cell lines. They sequenced these libraries and discovered putative HPV-encoded miRNAs. Gene ontology analyses of the predicted cellular targets of HPV16-encoded miRNAs suggest that they might have pathological effects on cell cycle, cell migration, and cancer development (82).

4. ANOTHER CLASS OF ncRNAs ENCODED BY EBV INVOLVED IN ONCOGENESIS

As discussed in section *3.2.*, EBV encodes another class of ncRNA, EBER1 and EBER2 (167 and 172 nucleotides long, respectively) to complete viral oncogenesis. EBERs are the most abundant viral transcripts in latently EBV-infected cells (83), whose genes are separated by a 161 base pair intergenic segment and are transcribed from the same DNA strand (84).

EBER1 and EBER2 contribute to several features of EBV-based oncogenesis. Studies using cells derived from BL (Burkitt Lymphoma), revealed the functional correlation between EBER1 and EBER2 expression and their transformation capabilities, including oncogenicity in SCID (severe combined immunodeficiency) mice, and their ability to inhibit apoptosis via resistance to apoptotic inducers, such as cycloheximide, glucocorticoid, hypoxic stress, and upregulation of apoptosis inhibitor, Bcl-2 (Figure 2) (85). Subsequently, EBER1 was shown to inactivate the major IRG (interferon response gene) product, PKR (protein kinase R), enabling avoidance of host immunosurveillance (Figure 1) (86). A recent report further showed that gastric carcinoma cells stably expressing EBER1 and EBER2 have increased migration and invasion capabilities (53). These results thus suggested that EBER1 and EBER2 are closely involved in EBV oncogenesis, not only for transformation to malignancy, but also for the cancer initiation and progression processes, such as immune evasion, invasion and metastasis (53, 85, 86). In the following sections, we discuss how EBER1 and EBER2 contribute to EBV-dependent oncogenesis.

4.1. Molecular mechanisms of EBER1 and 2 action in viral oncogenesis

As discussed above, EBER1 and EBER2 play roles in various aspects of viral oncogenesis (87, 88). Firstly, to complete the immune evasion process, both EBV miRNAs and EBERs target IRGs but act on different molecules. While BHRF1-3 target chemokine CXCL-11/I-TAC mRNA to downregulate the CTL cytokine networks (48), EBER1 inactivates another and major IRG product, PKR (Figure 1) (86). EBER1 occupancy of the PKR dsRBD (double-stranded RNA-binding domain), affects its conformation and inhibits PKR dimer formation, resulting in failure to activate autophosphorylation (86). Although the authors did not examine the inhibitory double-strand RNA effect of EBER2 (86), another study using a dominant-negative PKR showed that both EBER1 and EBER2 conferred resistance to IFN-alpha-induced apoptosis via binding to PKR and inhibiting its phosphorylation (90).

Although in acutely infected cells, EBERs induce type-I IFN expression through recognition by the cytosolic sensor, RIG-I (retinoic acid-inducible gene-I) for EBER1 and 2 (52), and the cell surface sensor, TLR3, for EBER1 (Figure 1) (89), the EBV-enrolled small ncRNAs eventually enable evasion of the immune response by attenuating the major antiviral effector, PKR (90). These results thus strongly suggest that EBV can avoid innate and acquired immunity through the cooperation of EBER1 and BHRF1-3, resulting in apoptosis inhibition (Figures 1 and 7; Table 2, 6 and 8 of cancer hallmarks).

Secondly, in addition to the induction of cytokine expression by LMP1 (see section *3.1.*), EBER1 but not EBER2 also induced IL-10 expression (91), in a manner that depends on the RIG-I-mediated IRF3 signaling pathway (Figure 4) (52). IL-10 is a pro-oncogenic factor, which upregulates the apoptosis inhibitor, Bcl-2 (92-94). EBER1, thus, completes the apoptosis inhibition processes through two distinct targets; PKR and IL-10. IL-10 also exhibits another pro-oncogenic effect by promoting BL cell growth (91). Furthermore, a recent report by Banerjee *et al*, showed that EBER1 and EBER2 activated STAT3 expression through upregulation of another cytokine, IL-6. The activated STAT3 then downregulated the cell cycle inhibitors, p21 and p27 in a gastric carcinoma cell line (53). EBER1 and EBER2, thus, cooperatively complete cell proliferation processes by modulating IL-10 and IL-6 expression in collaboration with miR-BART3, which suppresses DICE1/INTS6 expression (Figures 5A and 7) (54).

Thirdly, Banerjee and colleagues (53) also showed that EBER1 and EBER2 activate the pro-metastatic molecules, FAK and PAK1, and also downregulate the expression of the anti-metastatic molecules, RhoGD1 and KAI-1, which promote cell migration (Figures 6 and 7).

Moreover, both EBER1 and EBV latency type I gene products (e.g. BARF0, EBNA1 (Epstein-Barr nuclear antigen 1), and LMP2A (Latent Membrane Protein 2A)) play an additional role in tumor cell invasion by synergistically downregulating the miR-200 family (95). The miR-200 family targets ZEB1 (zinc finger E-box-binding homeobox transcription factor 1) and ZEB2 mRNAs, which encode E-cadherin repressors. Upon inhibition of the miR-200 family in a gastric carcinoma cell line, the up-regulated repressors suppress E-cadherin expression, resulting in EMT (95). Indeed, transfection of *BARF0*, *EBNA1*, and *LMP2A* expression plasmids downregulated the transcription of pri-miR-200 RNAs, whereas EBER1 post-transcriptionally inhibited miR-200 action (95), possibly acting as a ceRNA (competing endogenous RNA) to sequester the miR-200 family (96, 97).

These results strongly suggest that, in contrast to KSHV-encoded miRNAs, EBV miRNAs require the EBERs to complete the oncogenic process (Figures 6 and 7).

5. KSHV lncRNA PAN AND ONCOGENESIS

In lytically infected cells, KSHV expresses a <1.1. kb lncRNA, PAN, which constitutes nearly 80% of total polyadenylated RNAs in the infected cells (<500,000 copies per cell) (98, 99). Recent publications have indicated potential functions of PAN in KSHV-mediated oncogenesis, particularly in the

processes of modulating host immune responses and cell proliferation.

Firstly, Rossetto and colleagues investigated the functions of PAN by isolating proteins with the lncRNA (100, 101). This proteomics study showed that PAN interacted with IRF4, which was further confirmed by a formaldehyde-based crosslinking assay (101). Expression of PAN reduced the activity of an IRF4-responsive promoter in a luciferase reporter assay, suggesting that PAN could negatively regulate IRF4 activity (101). To further elucidate downstream immune response genes under control of the IRF4-responsive promoter, Rossetto *et al* examined the expression profiles of the genes encoding human interferon-signaling and -response factors. RT-PCR analysis of a cell line constitutively expressing PAN RNA showed reduced levels of IFN-gamma, IFN-alpha16, IL-18 and RNase L mRNAs, suggesting that KSHV PAN RNA could modulate the expression of genes involved in immune regulation (101).

RNA-Seq analysis of cell lines that express PAN RNA further showed that transcription of genes encoding factors that regulate the cell cycle, immune response and inflammation was dysregulated, which caused an enhanced growth phenotype (102). These results thus suggest that KSHV PAN RNA may complement miRNA function to complete the viral oncogenesis processes including immune evasion and cell growth (Figure 7).

6. HTLV-1 BASIC LEUCINE ZIPPER FACTOR MRNA AND ONCOGENESIS

The HTLV-1 provirus is 9 kb and encodes multiple open reading frames that are flanked by two identical 750 bp terminal repeats at the 5′ and 3′ ends (103). The complementary strand of the HTLV-1 provirus also harbors the *HBZ* (HTLV-1 basic leucine zipper factor) gene, which encodes HBZ, a bZIP (basic leucine zipper) transcription factor that downregulates viral transcription (104).

Intriguingly, the HBZ mRNA also carries coding-independent regulatory functions (105, 106). The HBZ mRNA supports the proliferation of an IL-2-dependent T-cell line, Kit225. Although the precise mechanism of this action has not been clarified, the mRNA likely exerts its regulatory function by transcriptionally upregulating adenovirus E2F1 (E2 promoter-binding factor 1) mRNA, which can subsequently activate the transcription of downstream target genes to enhance cell proliferation (106). A recent study further reported that the regulatory HBZ mRNA also inhibits apoptosis in mouse CD4 T cells (105). HBZ mRNA increased transcription of the anti-apoptotic gene, *survivin*, which likely accounts for its anti-apoptotic effects. These two key functions indicate that the regulatory HBZ mRNA might contribute to the oncogenesis of HTLV-1 by sustaining proliferative signaling and resisting ATL (Adult T cell Leukemia) cell death (Table 2, 1 and 6 of cancer hallmarks).

7. *H. PYLORI* INFECTION AND ONCOGENESIS

Infection with *cagA* (cytotoxin-associated gene A)-positive *H. pylori* is causally associated with the development of gastric carcinoma, the third leading cause of cancer death (107-110). Dysregulation of SHP2 (Src homology 2-domain containing tyrosine phosphatase) by *H. pylori*-delivered CagA is considered to play a key role in the neoplastic transformation of gastric epithelial cells (111).

A recent report showed that CagA also targeted SHP1, the only homologue of SHP2 (112), resulting in the dephosphorylation of CagA that dampens its oncogenic action (113). Interestingly, *in vitro* infection of gastric epithelial cells with EBV caused *SHP1* promoter hypermethylation, which strengthened the phosphorylation-dependent CagA action by epigenetic downregulation of *SHP1* expression (113).

H. pylori and EBV are involved in roughly 90% and 10%, respectively, of gastric tumorigenesis (110, 114), which indicates that a considerable portion of EBV-positive patients may be superinfected with *H. pylori*. The *in vitro* experiment reported by Hatakeyama and colleagues (113), indicates that it is conceivable for gastric epithelial cells co-infected with the above two pathogens, EBV miRNAs and/or EBERs, to modulate DMNT action, leading to the promotion of neoplastic transformation through activated CagA protein function.

8. HCV miRNA AND ONCOGENESIS

HCV infection is responsible for 70-85% of worldwide HCC (hepatocellular carcinoma) (115). For the pathogenesis of HCC following HCV infection, a recent report showed that HCV vmr11 was sufficient to confer infected hepatocytes with invasive properties (116). To exert this oncogenic function, vmr11 targets HNF4alpha (hepatocyte nuclear factor 4alpha) mRNA, resulting in reduced HNF4alpha expression levels (116). Sustained loss of HNF4alpha protein expression in HCV-infected hepatocytes induces the expression of EMT regulatory genes; such as *TGFB* (transforming growth factor beta), *Snail* and *HMGA2* (high mobility group AT-hook 2), which are associated with reduced E-cadherin protein expression (Figure 6) (116). TGF-beta, a soluble growth factor having multiple functions at EMT, together with HMGA2, activates *Snail* expression (117). Snail is a negative transcriptional regulator of *CDH1* (Cadherin 1) (118);

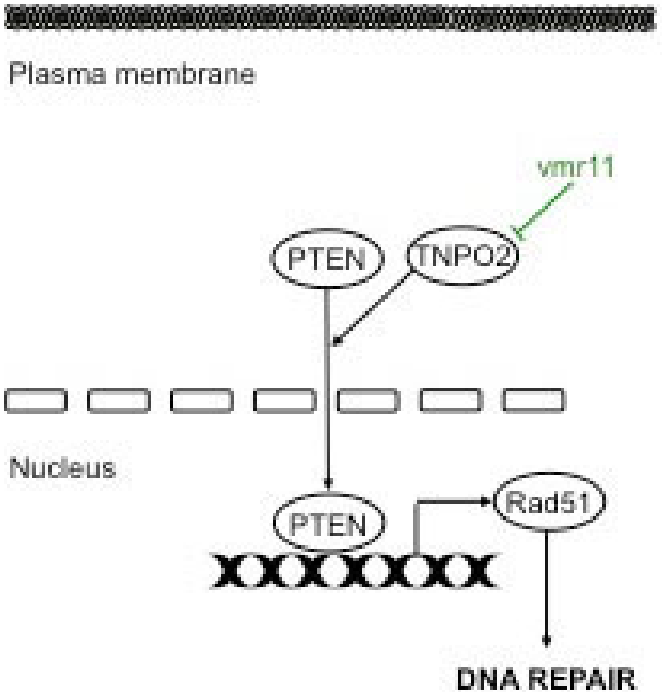

Figure 8. Chromosome breakage and translocation by pathogen-associated ncRNA. The HCV miRNA, vmr11, targets TNPO2 mRNA, which encodes a transportin for the nuclear import of PTEN. Nuclear PTEN acts on chromatin or the promoter of *Rad51*. Rad51 is critical for chromosomal stability via the control of DSB repair; therefore, vmr11-dependent nuclear exclusion of PTEN results in failure of DSB repair and chromosome breakage and translocation. The HCV miRNA is in green font.

therefore, the downregulation of E-cadherin protein results in EMT.

vmr11 also targets TNPO2 (Transportin-2) mRNA, resulting in restricted nuclear translocation of PTEN protein in HCV-infected human hepatocytes (119). This result was substantiated by the restoration of intracellular TNPO2 levels, which rescued the expression levels of nuclear PTEN. These results thus support a novel mechanism for regulating the expression levels of PTEN in the nucleus; a vmr11-dependent reduction of TNPO2 mRNA levels leads to the exclusion of PTEN from the nucleus in virally infected hepatocytes (119).

PTEN might be involved in the transcriptional regulation of *Rad51* by acting on chromatin or its promoter (120). Rad51 is critical for chromosomal stability, presumably through controlling DSB (double-strand break) repair (121). Therefore, the PTEN-Rad51 DNA repair pathway provides a mechanistic basis for a DSB repair defect in the nucleus of HCV-infected hepatocytes, which can give rise to chromosomal breakage and translocation (Figure 8). It is thus plausible that the nuclear exclusion of PTEN by vmr11 promotes genomic instability in HCV-infected hepatocytes, which would lead to the acquisition of invasion and metastasis capabilities (Table 2, 9 and 4 of cancer hallmarks) and cancer susceptibility (120).

9. PERSPECTIVES

The development of sequencing technologies and the evolution of bioinformatic methodologies revealed the presence of large numbers of ncRNAs encoded by oncogenic pathogens. This progress has deepened our knowledge of the regulatory functions of ncRNAs, leading to proposals of new forms of circuitry for ncRNA-dependent oncogenesis.

The inherent nature of pathogen-associated regulatory ncRNA circuitry may have important sequelae for viral and bacterial oncogenesis. ncRNAs deregulate and disrupt the function of a number of cellular factors, for example those responsible for the immunological monitoring that reduces pathogenic burden, for governing the apoptotic program, and for controlling the careful production and release of growth-promoting signals. Such deregulation ultimately leads to the hallmarks of cancer (31) that are generated during the multistep development of infectious cancers. The proposal by Hanahan and Weinberg, that the complexity of cancer can be reduced to six underlying principles or hallmarks (see Table 2) that govern the transformation of normal cells to cancer cells, has changed over the years. They later proposed four additional hallmarks: (1) abnormal metabolic pathways, (2) evading the immune system, (3) genome instability, and (4) inflammation (Table 2) (32). The new form of

circuitry for gene regulation by pathogen-associated regulatory ncRNAs discussed throughout this review generates the genetic diversity or even abnormality that underlies the acquisition of processes that form the cancer hallmarks.

ncRNAs are generally expressed in a tissue-specific manner and exhibit aberrant expression in cancers. Therefore, targeting and either downregulating or upregulating specific lncRNAs in malignancies may not have deleterious side effects on normal cells. Although the circuitry requires much investigation to fully determine the mechanisms of its action on pathogen-associated oncogenesis, it seems plausible that key pathogen-associated oncogenic ncRNAs and/or host tumor-suppressor ncRNAs, if any, provide new therapeutic targets for the treatment of pathogen-associated cancers.

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Abbreviations: ncRNA: non-protein-coding RNA; lncRNA: long non-coding RNA; HTLV-1: Human T-lymphotropic virus 1; HCV: *Hepatitis C virus*; HBV: *Hepatitis B virus*; HHV4: *Human herpesvirus 4*; EBV: Epstein-Barr virus; HHV8: *Human herpesvirus 8*; KSHV: Kaposi sarcoma-associated herpesvirus; HPV: Human papillomavirus; RISC: RNA-induced silencing complex; AGO: argonaute; MRE: miRNA response element; CTL: cytotoxic T lymphocyte; PUMA: p53 upregulated modulator of apoptosis; Bim: Bcl-2 interacting mediator of cell death; TOMM22: translocase of outer mitochondrial membrane 22; PTEN: phosphatase and tensin homologue deleted on chromosome 10; EBNA: EBV nuclear antigen; RTA: replication and transcription activator; Bcl-XL: B-cell lymphoma XL; cIAP: cellular inhibitors of apoptosis protein; GADD45beta: growth arrest and DNA-damage-inducible 45beta; BCL2A1: B-cell-lymphoma-2-related protein A1; SOD2: superoxide dismutase 2; TNF-alpha: tumor necrosis factor-alpha; EBER: EBV-encoded small RNA; DICE1: deleted in cancer cells 1; INTS6: Integrator complex subunit 6; NPC: nasopharyngeal carcinoma; TAM: tumor-associated macrophage; VEGF: vascular endothelial growth factor; NDRG1: N-myc downstream regulated gene 1; EMT: epithelial-mesenchymal transition; IRAK1: interleukin-1 receptor-associated kinase 1; MYD88: myeloid differentiation primary response protein 88; TLR: Toll-like receptor; IKBKE: inhibitor of nuclear factor-kappaB kinase subunit epsilon; IKKepsilon: IkappaB kinase epsilon: IRF: interferon regulatory factor; BCLAF1: Bcl-2-associated transcription factor 1; KS: Kaposi sarcoma; TWEAK: tumor necrosis factor-like weak inducer of apoptosis; TWEAKR: TWEAK receptor; LDOC: leucine zipper downregulated in cancer 1; MCP: major capsid protein; DNMT: DNA methyl transferase; Rbl2: retinoblastoma-like protein 2; LIP: liver-enriched inhibitory protein; PEL: primary effusion lymphoma; THBS1: thrombospondin 1; GRK2: G protein-coupled receptor kinase 2; BL: Burkitt Lymphoma; SCID: severe combined immunodeficiency; IRG: interferon response gene; PKR: protein kinase R; dsRBD: double-stranded RNA-binding domain; EBNA: Epstein-Barr nuclear antigen; LMP: Latent Membrane Protein; IL-6: Interleukine-6; CXCR4: C-X-C chemokine receptor type 4; RANTES: Regulated on Activation, Normal T Cell Expressed and Secreted; MCP1: Monocyte Chemotactic Protein-1; ZEB: zinc finger E-box binding homeobox transcription factor; ceRNA; competing endogenous RNA; HBZ: HTLV-1 basic leucine zipper factor; bZIP: basic leucine zipper; E2F1: E2 promoter-binding factor 1; ATL: Adult T cell Leukemia; SHP2: Src homology 2-domain containing tyrosine phosphatase; HCC: hepatocellular carcinoma; HNF4alpha: hepatocyte nuclear factor 4alpha; TGF-beta; transforming growth factor-beta; HMGA2: high mobility group AT-hook 2; CDH1: Cadherin 1; TNPO2: Transportin-2; RIG-I: retinoic acid-inducible gene-I; Bax: Bcl-2 associated X; IkappaBalpha: inhibitor of kappaBalpha

Key Words: Regulatory non-coding RNA, Oncogenesis, microRNA, Small ncRNA, Long ncRNA, Cancer hallmarks, Review

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