

n unique concept MIRNA in regulation of immune response against viral infection.

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ABSTRACT: MicroRNA (miRNA) square measure little non-coding molecules of polymer. they're regarding twenty two nucleotides long, fibre, and mediate post-translational regulation by the repression or degradation of courier RNA(mRNA). miRNA play a key half within the proliferation, differentiation and death of cells. virus infection is one in all the foremost common causes of human unwellness. Some studies have found that miRNA contains a terribly shut relationship with virus infection, that has an impression on microorganism replication, the reaction and antiviral immunity. Use of miRNA could become the cornerstone of recent strategies for the designation and treatment of virus infection. resistance is taken into account to produce the initial defense against infections by viruses, bacteria, fungi, and protozoa. Detection of the signature molecules of invasive pathogens by front-line defense cells via varied germline-encoded pattern recognition

receptors (PRRs) is required to activate living thing communication cascades that cause transcriptional expression of inflammatory mediators to coordinate the elimination of pathogens and infected cells. to keep up a fine balance between protecting immunity and inflammatory pathology upon infection, the innate communication pathways within the host got to be tightly regulated. MicroRNAs (miRNAs), a replacement category of little non-coding RNAs, are recently shown to be potent modulators that operate at post-transcriptional levels. Accumulating proof demonstrates that the involvement of microorganism-encoded and host miRNAs would possibly play instructive roles within the reaction upon infection. Here, we tend to discuss this information of miRNAs within the regulation of reaction against infections.

Keywords: : MicroRNA (miRNA), antiviral immunity, inflammatory pathology, post-transcriptional levels, reaction.

I. INTRODUCTION.

Viruses are tiny organisms that measure a few nanometers. They are made from genetic material inside a protein coating. Viruses

cause various infectious diseases like the communicable disease, respiratory disorder and warts. They additionally cause severe sicknesses like HIV/AIDS, Ebola, and COVID-19

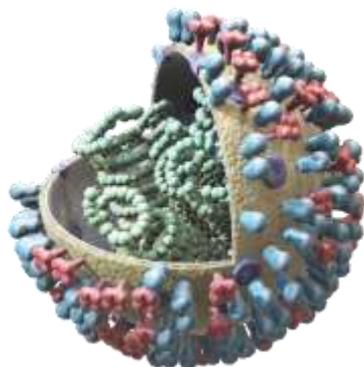


Fig1. 3-D model of virus.

Viruses are like hijackers. They invade living cells and use those cells to multiply and manufacture different viruses like themselves.

This may kill, damage, or amend the cells and cause you to get sick. Different viruses attack different cells in your body like your liver, system, or blood.

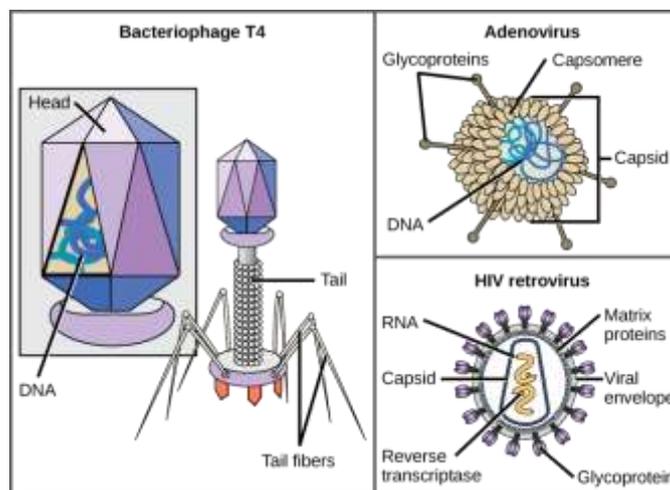


Fig2. Structure of Virus.

When you get a pandemic, you'll not invariably get sick from it. Your system is also able to fight it off. For most infectious agent infections, treatments will solely facilitate with symptoms whereas you look ahead to your system to oppose the virus.^[1,2] Antibiotics don't work for infectious

agent infections. There are antiviral medicines to treat some infectious agent infections.

Vaccines will facilitate forestall you from obtaining several infectious agent diseases. In fact, viruses are classified by the International Committee on Taxonomy of Viruses system and therefore the Baltimore organisation primarily in step with many composition characteristics.

The Baltimore classification depends on the ordering sort (DNA, RNA, fiber (ss), double-stranded (ds), etc.) and replication technique.

virus-induced diseases occur only unhealthful viruses enter the host's body once coming into the infectious virus particle to the host's cells. Most however not all unhealthful viruses will cause cytopathic effects within the host cell and typically cause death of the host cell. Some viruses don't cause changes in host cells and are latent and inactive.

Some viruses that aren't latent cause chronic or long infection. Despite the host defense mechanisms, the virus continues to duplicate within the host's body, and eventually causes chronic sickness. specifically, the liver disease {viral hepatitis} virus and viral hepatitis virus cause chronic hepatitis by causing liver inflammation in humans. alternative viruses cause cancer or serious diseases with a high morbidity.

The human papillomavirus (HPV) is that the most typical of those viruses, inflicting cervical cancer. though the general public with HPV infection don't develop cervical cancer,

some varieties of HPV, like varieties sixteen and eighteen, represent a significant risk issue for cervical cancer (16). The Ebola virus contains a high morbidity (50~89% counting on the virus subtype) and causes infectious agent viral infection in humans.

II. PATHOPHYSIOLOGY OF VIRAL INFECTION.

Pathogenesis is that the method by that associate infection ends up in malady. morbific mechanisms of infective agent malady embrace implantation of virus at the portal of entry, native replication, unfold to focus on organs (disease sites), and unfold to sites of shedding of virus into the atmosphere. Factors that have an effect on morbific mechanisms square measure accessibility of virus to tissue, cell status to virus multiplication, and virus status to host defenses. survival favors the dominance of low-virulence virus strains.^[3]

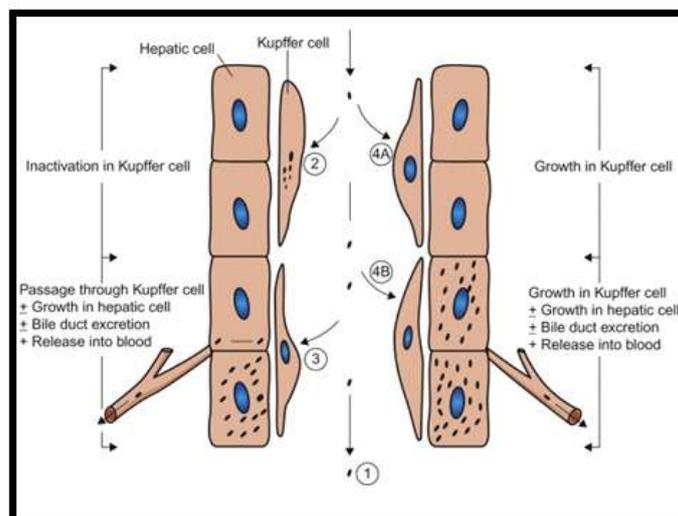


Fig3. Pathogenesis of viral infection.

Cellular pathological process^[4]

Direct cell injury and death from infection would possibly result from diversion of the cell's energy, shutoff of cell compound synthesis, competition of agent RNA for cellular ribosomes, competition of agent promoters and transcriptional enhancers for cellular transcriptional factors like RNA polymerases, and inhibition of the

drugs defense mechanisms. Indirect cell injury may result from integration of the infective agent ordering, induction of mutations within the host ordering, inflammation, and also the host reaction.

Tissue reaction

Viral affinity for specific body tissues (tropism) is decided by cell receptors for virus, cell

transcription factors that acknowledge infective agent promoters and attention sequences, ability of the cell to support virus replication, physical barriers, native temperature, pH, and element tension enzymes and non-specific factors in body secretions, and organic process enzymes and digestive juice within the channel which will inactivate some viruses.

✚ Implantation at the Portal of Entry.

Virions implant onto living cells chiefly via the metastasis, gi, skin-penetrating, and reproductive organ routes though different routes will be used. the ultimate outcome of infection is also determined by the dose and placement of the virus moreover as its infectivity and virulence.

✚ Local Replication and native unfold

Most virus varieties unfold among cells extracellularly, however some may additionally unfold intracellularly. institution of native infection could result in localized illness and localized shedding of virus.

✚ Dissemination from the Portal of Entry

Viremic: the foremost common route of general unfold from the portal of entry is that the circulation, that the virus reaches via the

lymphatics. Virus could enter the target organs from the capillaries by (1) multiplying in epithelium cells or mounted macrophages, (2) disseminative through gaps, and (3) being carried in a very migrating blood cell.

Neural: Dissemination via nerves sometimes happens with hydrophobia virus and typically with herpesvirus and enterovirus infections.

✚ Incubation amount

The time period is that the time between exposure to virus and onset of illness. throughout this sometimes well amount, implantation, native multiplication, and unfold (for disseminated infections) occur.

✚ Multiplication in Target Organs

Depending on the balance between virus and host defenses, virus replication within the organ is also spare to cause illness and even leading to death. Shedding of Virus Although the tract, channel, system tract and blood square measure the foremost frequent sites of shedding, numerous viruses is also shed at just about each website.

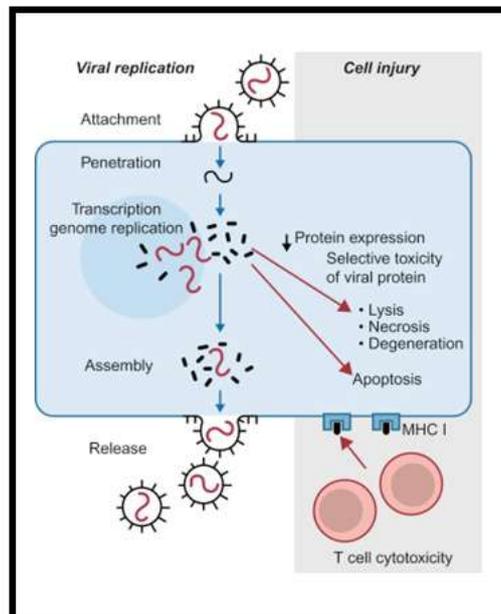


Fig3.1 Pathogenesis of viral infection.

✚ Congenital Infections

Infection of the craniate as a target “organ” is special as a result of the

virus should traverse further physical barriers, the first foetal immune and antiviral defense systems is also immature, transfer of the maternal

defenses area unit partly blocked by the placenta, the developing first-trimester foetal organs area unit susceptible to infection, and secretion changes area unit going down.

a. Defenses against viruses.

The body contains a range of defenses against viruses: Physical barriers, like the skin, that discourage straightforward entry. The body's immune defenses, that attack the virus. When a pestilence enters the body, it triggers the body's immune defenses.

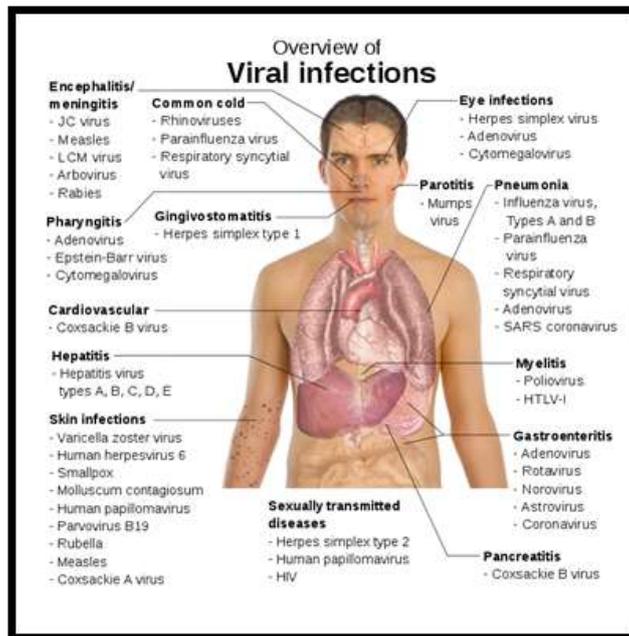


Fig 4. overview of viral infection.

These defenses begin with white blood cells, like lymphocytes and monocytes, that learn to attack and destroy the virus or the cells the virus has infected. If the body survives the virus attack, a number of the white blood cells keep in mind the interloper and square measure ready to respond additionally quickly and effectively to a later infection by a similar virus. This response is named immunity. Immunity also can be created by obtaining a vaccine.

III. INTRODUCTION TO MICRO-RNA

The advent of microRNA has probably uncovered a brandnew level of complexness to be thought-about for each organic process. Through the modulation of transcription and translation, microRNA alter the basal state of cells and therefore the outcome of stimulatory events.

The precise impact of the microRNA network and individual microRNA on cellular processes is {just is barely} just beginning to be compound. within the system, microRNA seem to own a key role within the early differentiation and effector differentiation of B cells.

In T cells, microRNA are shown to be key regulators of the lineage induction pathways, and to own a powerful role within the induction, operate and maintenance of the regulative T-cell lineage.

MicroRNA are necessary for control the differentiation of nerve fiber cells and macrophages via toll-like receptors, with responsibilities in suppressing effector operate before activation and enhancing operate when stimulation. [5]

Additionally to control key processes within the system, microRNA may additionally represent Associate in nursing archaic system themselves.

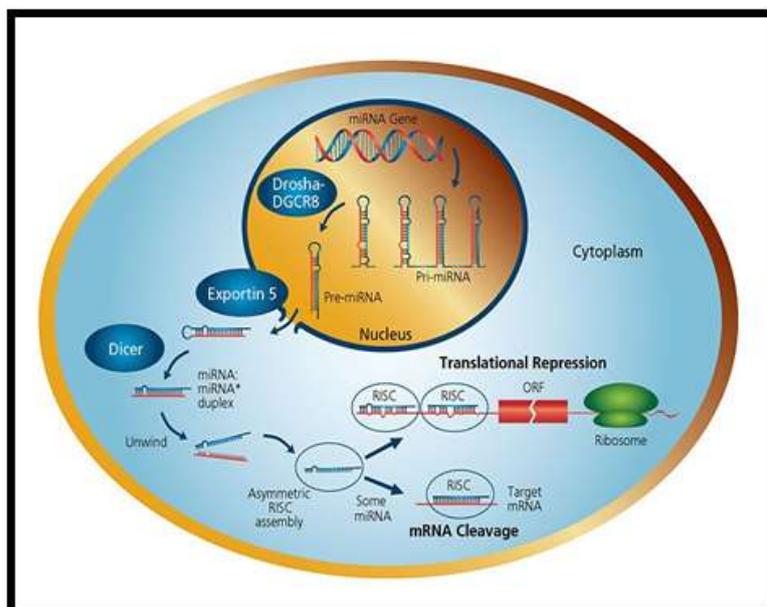


Fig5. micro-rna.

Little meddling ribonucleic acid of infectious agent origin has been shown to operate as Associate in Nursing living thing intercessor within the suppression of infection in eukaryotes as numerous as plants, insects, nematodes and fungi, and there's growing evidence that endogenous class microRNA will have same effects.

During the article they have a tendency to speculate that the anti-viral operate of microRNA drove the expression of various subsets of microRNA in several cellular lineages, which can have, in turn, junction rectifier to the myriad of roles microRNA play in lineage differentiation and stability.

Mature microRNAs (miRNAs) ar a category of present, little non coding polymer molecules, concerning 21–25 nucleotides long.

MicroRNAs are partly complementary to at least one or additional template RNA (mRNA) molecules, and their main perform is to downregulate organic phenomenon during a style of manners, as well as travel repression, mRNA cleavage, and deadenylation.

They were initial drawn in 1993 by Lee and colleagues¹, and additionally the term microRNA was coined in 20012. Thousands of miRNAs have ever since been legendary in various organisms

through random scientific research and sequence or procedure foresight.

The miRbase, hosted by the Sanger Institute provides miRNA word, sequence information, annotation and target prediction data.

The genes coding miRNAs are for much longer than the processed mature miRNA molecule. several miRNAs are noted to reside in introns of their pre-mRNA host genes and share their restrictive parts, primary transcript, and have an identical expression profile.

For the rest of miRNA genes that are transcribed from their own promoters, few primary transcripts are absolutely known.

MicroRNAs are transcribed by RNA enzyme II as massive RNA precursors known as pri-miRNAs and comprise of a 5' cap and poly-A tail.

The pre-miRNAs are then exported into the protoplasm by the karyopherin exportin five and Ran-GTP complicated. Ran (ras-related nuclear macromolecule) could be a tiny GTP binding protein happiness to the RAS taxon that's essential for the translocation of RNA and proteins through the nuclear pore complicated.

Once within the protoplasm, the pre-miRNAs endure a further process step by the ribonucleinase III accelerator mechanical device generating the miRNA, a double-stranded RNA aproximately twenty two nucleotides long.^[5,6]

Mechanical device additionally initiates the formation of the RNA-induced silencing complicated (RISC). RISC is liable for the sequence silencing determined thanks to miRNA expression and RNA interference.

IV. MICRO-RNA PATHWAY

MiRNA square measure tiny, organic process preserved, fibre, non-coding polymer molecules that bind target ribonucleic acid to stop supermolecule production by one among 2 distinct mechanisms.

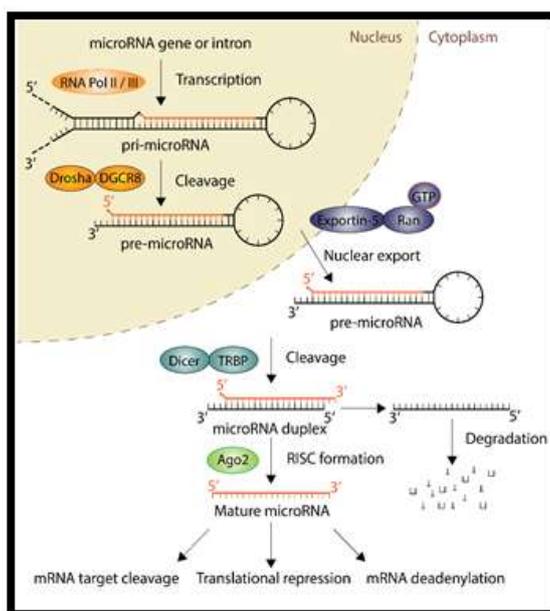


Fig.6. synthesis of miRNA.

The level of complementarity between the guide and ribonucleic acid target determines that silencing mechanism are going to be employed; cleavage of target template RNA (mRNA) with subsequent degradation or translation inhibition.

There is a cistrnal understanding of miRNA perform but the mechanistic detailing of miRNA biogenesis and gene silencing area unit still not clear.

Although the biological perform of known miRNAs is also unknown, examination of the expression profiles of those molecules provides data on their regulation and performance.^[7,8] Such observations have indicated that miRNA expression profiles area unit altered in specific tumors, implying that miRNA is also concerned in development of cancer and different diseases.

Despite the restricted information of those molecules, basic expression identification is proving to be clinically relevant to cancer designation, progressions and outcome.

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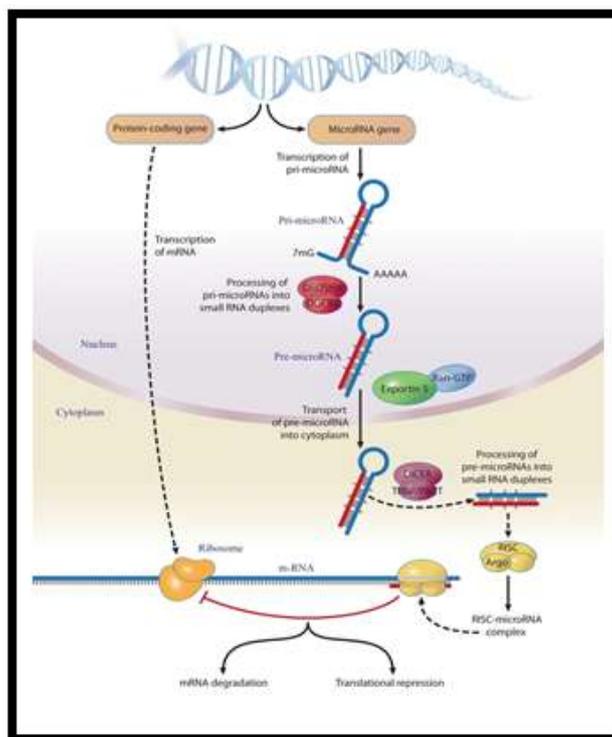


Fig7. Pathway of mi-rna.

Mature miRNA is generated through ballroom dancing cleavage of primary miRNA (pri-miRNA), that contains into the effector advanced RNA-induced silencing advanced (RISC). The miRNA functions as a guide by base-pairing with target messenger RNA to negatively regulate its expression. This new and exciting field of biological science continues to advance, having profound implications in drugs. Synbio Technologies offers a good vary of prime quality miRNA synthesis merchandise, together with miRNA mimics/inhibitors, miRNA agomirs/antagomirs and miRNA negative controls, etc. to support your miRNA practical analysis.

miRNAs square measure fiber, small, non-coding ribonucleic acid of twenty-two nucleotides that play vital roles as endogenous factor regulators by mediating translation repression or promoting degradation of target RNA. whereas the conventional expression and performance of miRNAs square measure very important for

physiological processes, aberrant expression of miRNAs has been evidenced to be closely associated with the incidence of varied cancers.^[8]

Perturbation of endogeneous miRNAs facilitate to check the perform of specific miRNAs and hold the potential for medicine.

V. EFFECT OF CELLULAR MIRNAS ON THE VIRUS LIFE CYCLE AND PATHOGENESIS.

Given the scope of miRNA-mediated cistron regulation within the mammalian system, it's expected that cellular miRNAs conjointly directly or indirectly have an effect on virus replication and pathologic process. microorganism genomic RNAs or mRNAs might have evolved to directly act with host miRNAs to facilitate bound steps of their life cycle.

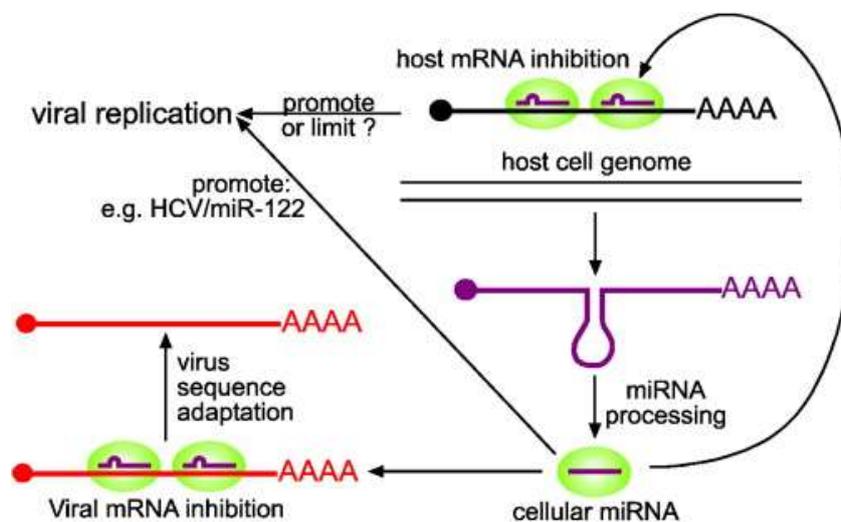


Fig8. Viral and cellular miRNA.

In various cases, such interactions would be restrictive and organism mRNAs might even be below selective pressure to avoid binding to abundant cellular miRNAs.

Finally, the cellular miRNA composition in infected cells is probably going to indirectly have an effect on viruses, because several pathways that promote or limit microorganism replication or the survival of infected cells area unit doubtless to be regulated by cellular miRNAs.

In either case, viruses might so gain a bonus by reshaping the cellular miRNA composition.

Several recent reports hint at the scope of microorganism interactions with host miRNAs and area unit mentioned below.^[9]

Viral miRNAs were discovered solely recently, and practical relationships between viruses and infectious agent or cellular miRNAs area unit solely currently setting out to be elucidated. Recent reports recommend that a minimum of some infectious agent miRNAs evolved to manage infectious agent organic phenomenon.

Different infectious agent miRNAs have an effect on cellular organic phenomenon by partaking in novel restrictive relationships or by mimicking cellular miRNAs and thereby utilizing predefined cellular restrictive networks. Conversely, cellular miRNAs will alter the infectious agent life cycle, strikingly exemplified by the very fact that host miR-122 facilitates HCV replication.

Some functions of cellular or infectious agent miRNAs in infected cells can doubtless end up to be vital for virus replication in vivo and should thus become targets for therapeutic intervention. On the opposite hand, the rising interface between viruses and miRNAs could uncover novel pathways that promote or limit virus replication, and this data might conjointly facilitate to guide drug style.

Antisense inhibitors of miRNA perform, that area unit bioavailable invivo, like antagomirs, might represent a decent start line for the event of miRNA repressive medicine. Antisense inhibitors targeting cellular miRNAs would be foretold to own aspect effects, looking on the perform of the restrained miRNA, since these inhibitors would conjointly disrupt the cellular functions of those miRNAs.

An alternate strategy can be to disrupt the interaction of cellular or infectious agent miRNAs with just one or few of their cellular or infectious agent target sequences.

As for different antiviral medicine, there's an opportunity of the virus turning into resistant, e.g., by mutation of the infectious agent miRNAs or infectious agent binding sites for cellular miRNAs. this is often a specific concern for viruses with high mutation rates, like HIV-1 or HCV. during this case, miRNA-based medical specialty, like different antiviral medicine, would doubtless be best once employed in combination.

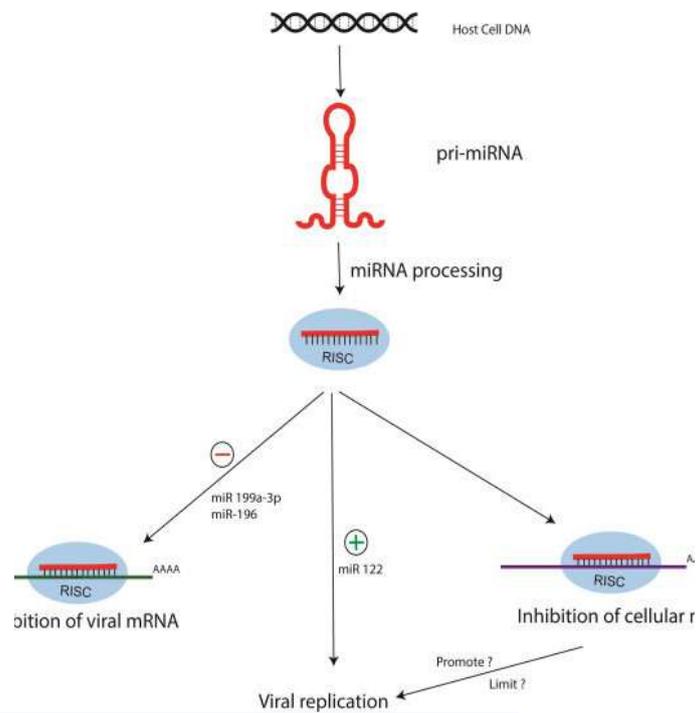


Fig9. Mechanism of cellular miRNA.

VI. MIRNA IN IMMUNITY. (INNATE AND ADAPTIVE)

MicroRNA have long been famous for his or her role in organ development, cellular differentiation, equilibrium and functioning. [10,11] a lot of recently, studies conducted by several teams have incontestible that miRNA are polar in each accommodative and natural immunity, as well as dominant the

differentiation of varied immune cell subsets also as their immunologic functions.

1. Adaptive immunity.

miRNA in adaptive immunity includes the following :-

- MicroRNA in B cells
- MicroRNA in conventional T cells
- MicroRNA in regulatory T cells

| | Function | miRNA |
|------------------------|---|---|
| Innate immunity | Granulocyte development | miR-155, miR-223 |
| | Monocyte development | miR-155, miR-17-92 |
| | Neutrophil function | miR-223 |
| | Macrophage activation | miR-155, miR-146a, miR-21 |
| | Dendritic cell function | miR-155 |
| Adaptive immunity | T cell development | miR-181 |
| | B cell development | miR-150 |
| | T cell proliferation | miR-182, miR-214 |
| | Th1, 17 cell differentiation | miR-155, miR-210, miR-326 |
| | Tfh cell differentiation | miR-10a, miR-17-92 |
| | Treg cell function | miR-155, miR-146a |
| | CD8T cell function | miR-155 |
| | B cell function | miR-155, miR-150 |
| Immunological diseases | Autoimmunity | SLE miR-23b, miR-146a, miR-125a, miR-21, miR-148a, miR-155, miR-15a |
| | | RA miR-23b, miR-146a, miR-155, miR-223 |
| | | MS miR-155, miR-326, miR-23b, miR-124 |
| | Infectious disease | miR-155 |
| Immune cell malignancy | miR-15a, miR-16, miR-17-92, miR-155, miR-223, miR-29b | |

Fig 10. Tabular data of miRNA in immunity.

1.1. MicroRNA in B cells

The essential role of miRNA in B-cell differentiation was first unconcealed in mice with a hematopoietic defect in Ago2, cryptography AN past macromolecule indispensable for miRNA biogenesis and performance.¹⁹ Deficiency of Ago2 didn't affect the generation of early pro-B cells, however considerably impaired more pre-B-cell differentiation and also the succeeding peripheral B-cell generation. In agreement with this, a subsequent study wherever the entire miRNA network was ablated by using the B-cell-specific deletion of a conditional factor of mechanical device has incontestible that B-cell differentiation is sort of utterly blocked at the pre-B-cell transition, a minimum of partly as a results of the deregulation of a pro-apoptotic molecule. Furthermore, mechanical device deficiency in B cells conjointly resulted in sustained terminal deoxynucleotidyl enzyme expression throughout B-cell maturation, fixing the generation of the protein repertoire. Whereas these findings provided important insights on however the miRNA network may impact B-cell differentiation and performance,

recent studies have begun to explore the role for individual miRNA in controlling completely different aspects of B-cell biology.

1.2. MicroRNA in conventional T cells

Unlike B-cell differentiation, wherever there's a block in a very specific organic process stage, the impact of T-cell-specific miRNA ablation is muted.

In mice with a deficiency in mechanical device in early T-cell progenitors (under the lck-driven cre transgene) the chances of various double-negative, double-positive and also the CD4-CD8 lineage (i.e. whether or not the transitioning cells became CD4 or CD8 single positives) choices additionally seems to be intact, albeit with a 10-fold reduction in total thymocyte numbers past the double-negative stage or else, later deletion of mechanical device with a CD4-drive cre transgene leads to smaller reductions within the variety of total thymocytes, at the single-positive stage though the precise molecular mechanism for the discrepancy between these studies remains not well characterised. The differential response within the numerical impact on T-cell differentiation reckoning on the temporal order of mechanical device excision suggests that miRNA don't have a non-redundant role in any specific organic process event, however rather produce a delayed

numerical reduction because the results of diminished proliferation and accrued status to death.

This numerical loss of thymic and peripheral T cells is also mediated partly by loss of miR-1792, as position expression of this miRNA cluster leads to Associate in Nursing growth of each CD4 and CD8 T cells the simplest proof for miRNA taking part in a job in specific organic process stages of T-cell differentiation is from miR-181, which, furthermore as reducing the quantity of T cells in haematogenic over-expression systems, will increase the sensitivity of T-cell receptor signalling.

It will this through the down-regulation of multiple phosphatases concerned within the attenuation of signal transduction events downstream of the T-cell receptor, and in doing therefore will increase the potency of each positive and negative choice.

1.3. MicroRNA in regulatory T cells^[12]

One set of T cells that heavily believe miRNA for generation and performance area unit the Forkhead box p3 (Foxp3)-dependent Treg cells, together with each thymic-derived and peripherally elicited Treg cells.

Each the thymic and peripheral induction of Treg cells is increased by miRNA. within the thymus, mice with either mechanical device or Droscha ablated mistreatment the CD4-driven cre transgene have a discount in thymic Foxp3+ Treg disproportionate thereto of alternative T-cell subsets.

Likewise, within the outer boundary miRNA additionally play a crucial role for the generation of adaptive Treg, as an absence of mechanical device ends up in a dramatic reduction of Foxp3 induction in T cells upon remodeling growth factor- β stimulation, as mentioned higher than.

This numerical scarcity results in spontaneous disease later in life. Additionally, miRNA play an important role in dominant Treg perform. Depletion of miRNA inside the Treg lineage ends up

in fatal pathology indistinguishable from that in Treg-deficient mice.

Moreover, whereas each the physiological state and suppressor capability of Dicer-deficient Treg cells were markedly reduced beneath non-inflammatory conditions, beneath inflammatory conditions Treg cells entirely lost their restrictive capability and anergic profile.

2. Innate immunity.

Recently, many efforts have additionally been created to demonstrate the role of miRNA in innate immune cells. For example, miR-223 has been shown to push granulopoiesis in vitro. furthermore, mice lacking miR-223 develop a lot of inflammatory respiratory organ lesions and tissue destruction upon toxin challenge as a results of hyperfunctional neutrophils. In macrophages and nerve fibre cells (DCs), miRNA have a vital role among the maturation of cells into the active lineage through toll-like receptors (TLR).

Stimulation with interferon- β and TLR ligands causes miR-155 induction, via every the nuclear factor- κ B pathway and Jun N-terminal protein pathway. The implication of miR-155 being concerned within the TLR-induced matter presentation pathway was confirmed by a study showing that miR-155-deficient DCs square measure unable to induce economical T-cell activation in response to antigens owing to impaired matter presentation capability and cost simulation activity.

SOCS1 could be a factual miR-155 target, so it is worth noting that SOCS1 negatively regulates the antigen presenting capability of DCs. liberation of SOCS1 in the absence of miR-155 may so account for the impaired DC perform. The miR-146 is additionally concerned in the TLR signalling loop.

Each miR-146a and miR-146b are transcriptionally up-regulated once lipopolysaccharide (LPS) stimulation, however solely mature miR-146a is generated (providing another example of the complicated nature of the regulation of miRNA expression)

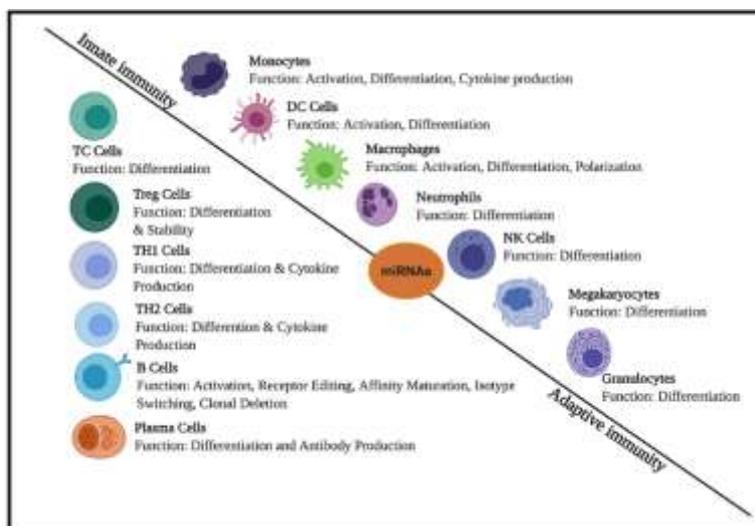


Fig10.1 miRNA adaptive and innate immunity

VII. MIRNAS IN THE MODULATION OF AN IMMUNE RESPONSE AGAINST VIRAL INFECTION. (MOA)

miRNAs are a unit a replacement category of organic process little non-coding polymer (snc-RNA) molecules with AN calculable size of twenty-two nucleotides (nt). miRNAs regulate organic phenomenon post-transcriptionally by the formation of incomplete base-pairs and attaching to sequences within the 3' untranslated region (UTR) of genes.^[12,13]

Consequently, this might either induce sequence degradation or repress sequence translation so preventing macromolecule accumulation.

on condition that miRNAs are unit capable of influencing important proteins and molecules concerned in signalling pathways and might target transcription factors with sturdy restrictive result on the response.

It had been determined that miRNAs have a major role in system activation and cellular differentiation. a lot of recently, miRNAs are shown as a completely unique category of regulators of assorted immune

and biological responses like signal transduction, apoptosis, carcinogenesis, biogenesis, cell growth and development and even responses to virus infection.

Moreover, miRNAs are unit concerned within the management of Natural Killer (NK) cells stimulation, perform and survival, and has incontestible a capability to delete Dicers or Dgcr8 not absolutely.

A lot of specifically, in mice, it's been shown that miR150 is crucial within the regulation of maturation and development of NK cells, whereas the miR-181 is twelve answerable for human NK cells maturation, activation and performance by activating Notch signal.

Further, once mouse NK cells were treated with IL-15, this resulted in AN alteration within the expression of various miRNAs. Among miRNAs, once miR-223 was down-modulated, it had been found that there was AN upregulation of its target sequence, granzyme B. Also, it's been shown that once miR-155 is correctly regulated, it will turn out protecting immune effects, whereas once miRNA155 is deregulated it might stimulate malignant transformation.

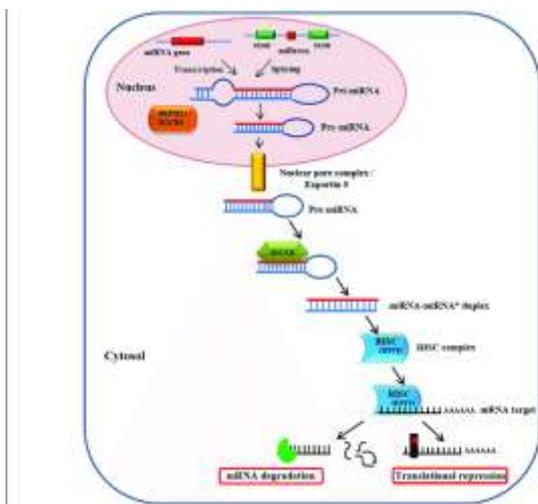


Fig 11. Mechanism of action of miRNA.

Vital analysis findings by Dickey et al have advised that miR-155 is a vital transforming gene in chicken lymphomas and was, later on, found that it's conjointly expressed in abundance in mammals with organic process cancers, thereafter, it had been classified as immunoregulatory noncoding polymer in macrophages and B lymphocytes.

These crucial discoveries elucidated that miR-155 is regulated by and plays a major role inside heterogeneous styles of the active immune cells that embrace varieties (differing types (differing kinds) of T and lymphocyte types, nerve fiber cells and NK cells.

Moreover, proof has shown that miR-155 expression is increased throughout the activation of T cells, B cells, nerve fiber cells, and macrophages. In addition, miR-155 regulates the expression of various macromolecule and signal molecules that have a job in dominant the response. Adore its established roles on modulating the response, many styles of analysis have disclosed that miR-155 is important in activating and dominant the response to viruses.

In an experimental work done by Trotta et al. to assess the result of miR-155 on human NK cells that were infected by lentivirus in vivo, they discovered that the NK cells that are activated by IL-12 and IL-18 had an increased expression of miR-155, conjointly they discovered a vital correlation between IL-18 with and therefore the levels of miR-155 and IFN- γ .

Thus, it had been projected that miR-155 would possibly play a job as a stimulator of IFN- γ production and once the miR-155 expression was down-regulated, there was a decline in IFN- γ levels. IFN- γ could be a archetypical protein that's secreted by NK cells and that they have a vital role in dominant the tumor immunity and protection from inflammation.

It's evident that IFN- γ deficiency may end up in an exceedingly bigger risk of infection and malignancy, whereas overexpression of IFN- γ may end up in reaction disorders. Given miR-155 have incontestible a vital role in craft CD4+ reactions in models of pathology, thus, many papers on viruses and response highlighted the importance of miR-155 in intensification the responses of CD8+ lymphocyte. what is more, various researches discovered that miR-155 is crucial for ample CD8+ lymphocyte activity, protein secretion, proliferation, and management of inflammation. The results of those reports enforce the importance of miR-155 in optimizing response when virus infection. Moreover, many reports shed the sunshine on the opposite aspects of the role of miRNAs as important controls of the interaction network between host-pathogen.

Though the involvement of many miRs may be a part of a bunch defence mechanism to limit the replication and proliferation of being. apparently, the host miRNAs pathway may be conjointly manipulated by the

viruses to facilitate infectious agent replication and dissemination.

These observations support a model wherever miRNAs may be wont to target infectious agent organic phenomenon, management inflammation and modulate immune activity.

VIII. MIRNAS TARGETING VIRAL INFECTION.

In recent years, the role of miRNAs within the development of immune responses in infective agent infections has been an issue of large analysis interest.

Various studies indicate that miRNA will be derived from Associate in Nursing intronic region of writing and non-coding genes, Associate in Nursing exonic region of non-coding genes, and intragenic regions.

In addition to the many eukaryotic cellular miRNAs, miRNAs of infective agent origin (also referred to as v-miRNAs) are discovered which will perform as post-transcriptional cistron regulators to host still as infective agent genes. [14,15]

8.1. Targeting the Viral Gene Expression.

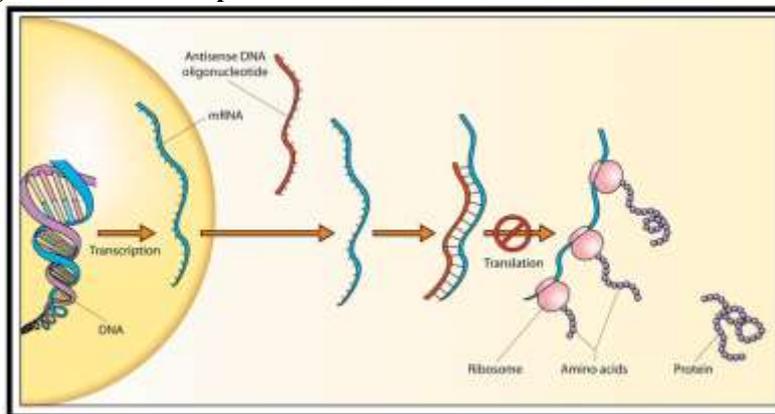


Fig12. Viral Gene expression.

EBV-encoded blue blood miRNAs play a key role in maintaining latency and dominant the infectious agent life cycle. Blue blood miRNAs like miR-BART16, miR-BART17-5p, and miR-BART1-5p target the 3' UTR of the LMP1 cistron and negatively regulate LMP1 supermolecule expression.

LMP1 is capable of inducement cell growth and proliferation, however overexpression of LMP1 may result in inhibition of growth and caspase-mediated cell death. Therefore, the

One of the main functions of microorganism miRNAs involves targeting microorganism organic phenomenon to regulate latency or as a switch from latency to activation.

SV40-encoded microRNAs regulate microorganism organic phenomenon and cut back condition to cytotoxic T cells. HSV1-induced latency is driven by latisimus dorsi (Latency Associated Transcript), that encodes for non-coding RNAs like miR-H2-3p and miR-H6.

These miRNAs target microorganism reactivation factors ICP0 and ICP4, that area unit essential in dominant microorganism reactivation from latency of HS1. Similarly, for HSV-2, miR-I, miR-II, and miR-III expressed by latisimus dorsi cut back the expression of ICP34.5, a key microorganism neurovirulence issue.

miR-I is additionally expressed in human sacral dorsal root ganglia of neurons latently infected with herpes simplex virus, suggesting the role of v-miRNAs in herpes simplex virus latency in human neurons.

downregulation of LMP1 expression could favor EBV-associated cancer development by exerting tight management on LMP1 expression.

The EBV-encoded miRNA miR-BART2 inhibits the infectious agent transition from the latent to the lytic a part of the life cycle by suppressing the infectious agent DNA enzyme BALF5.

Infectious agent miRNAs don't seem to be detected within the majority of RNA virus

families, largely thanks to the unavailability of the host machinery needed for miRNA biogenesis.

Tiny infectious agent RNAs (svRNAs) are known in respiratory illness virus infections that play a task in change the infectious agent enzyme from transcription toward ordering replication by interacting with the enzyme machinery. However, whether or not svRNAs target infectious agent or host transcripts is unknown. mistreatment in silico tools, the HIV-1 ordering was putatively shown to encipher 5 pre-miRNAs.

Supported the mature miRNA sequence deduced from the pre-miRNAs, these miRNAs were computationally foretold to focus on an

oversized set of host cellular genes to determine a good cellular environment for infectious agent replication.

8.2. Targeting the Host Cellular Genes

Evidence has been accumulating for v-miRNAs modulating the host reaction to alter a good animate thing milieu.

To date, studies of v-miRNAs targeting host cellular genes are principally targeted on KSHV and herpes virus infections (Table 1). Host target cellular genes are known with the assistance of organic phenomenon identification in HEK293 cells, ectopically expressing the KSHV miRNA cluster.

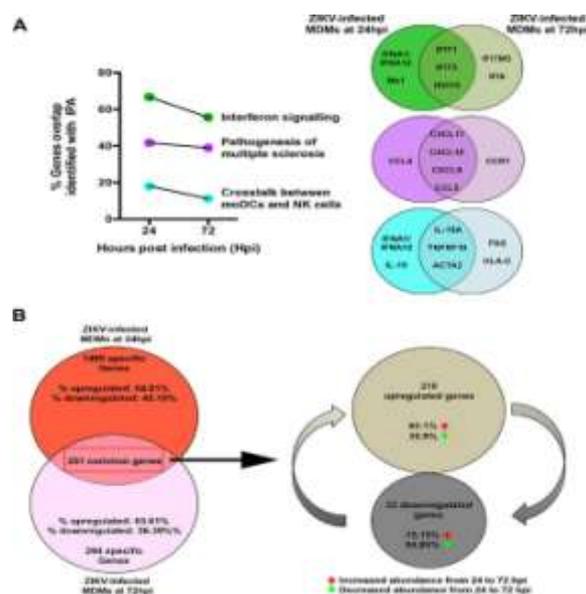


Fig.12.1 virus targeting the Host Cellular Genes.

KSHV miRNA suppressed the expression of thrombospondin one (THBS1), robust growth suppressor, and anti-angiogenic issue. KSHV miR-K12-1 controls cell survival and proliferation by targeting p21, a key growth suppressor and inducer of cell cycle arrest. miR-K5, along-side K12-9 and miR-K12-10b, targets Bcl-2-associated issue (BCLAF1), a glorious apoptotic issue.

Additionally, KSHV v-miRNAs cut back expression of C/EBP β p20 (LIP), a glorious negative regulator of IL6 and IL10 cytokines, to manage the protein sign in infected cells.

KSHV miR-K1 manage the NF- κ B pathway by exactly targeting I κ B. Suppressing I κ B enhances NF- κ B activity and inhibits infective agent lytic replication. KSHV miR-K12-10a suppresses the expression of TWEAKR (TNF-like weak inducer of necrobiosis receptor), whereas miR-K12-9 and miR-K12-5 target the TLR/Interleukin-1R sign pathway by targeting IRAK1 and MYD88, thereby dominant inflammation.

KSHV infective agent miRNAs additionally modulate the host organic phenomenon to regulate pathologic process. miR-K12-6 and miR-K12-11 direct the transcriptional reprogramming in latently infected

cells by targeting the cellular transcription issue MAF. Many KSHV infective agent miRNAs target malignant neoplasm (Rb)-like supermolecule a pair of (Rb1-2), a negative regulator of DNA methyltransferases, to keep up latency.

Exploitation Ago2-based RIP-Chip in multiple white cell|lymphocyte|lymph cell} lines latently infected with KSHV or stably transduced to precise ten KSHV miRNAs known genes concerned in lymphocyte activation and pre-mRNA splice like LRRC8D and NHP2L1, severally.

HCMV miRNAs are shown to focus on host genes concerned within the antiviral reaction. miR-UL112 blocks the natural killer (NK) cell-mediated recognition of virus-infected cells by inhibiting the expression of MICB, a stress-induced substance essential for NK-cell activity.

Suppression of MICB leads to slashed binding to the NKG2D receptor, thereby resulting in slashed killing of virally infected cells by NK cells. curiously, MICB expression is suppressed by KSHV miR-K12-7 and EBV miR-BART2 by binding to completely different sites within the within the, light a typical strategy for immune evasion normally employed by multiple DNA viruses.

To boot, HCMV miR-US4-1 targets the endoplasmic reticulum-resident aminopeptidase ERAP1, that is needed for MHC category I substance presentation on CD8 T cells, leading to less clearance of infected cells by HCMV-specific cytotoxic T cells.

Multiple lines of evidence have strengthened the “classical” hypothesis of v-miRNAs solely originating from DNA viruses; however, some non-canonical miRNA-like RNA fragments have been detected during RNA virus infections.

While the major functions of v-miRNAs across divergent virus families have been broadly attributed to immune evasion, autoregulation of the viral life cycle and tumorigenesis, there is still a broad gap in annotating the exact molecular determinants underlying these functions.

IX. THERAPEUTICALLY ENHANCING MIRNAS IN VIRAL INFECTION.

Viruses are obligate animate thing parasites. They lack the essential machinery needed for his or her replication. Thus, viruses adopt many clever methods to make sure the success of their replication during a appropriate host, one in all that is manipulation of the host miRNAs to switch the cellular setting for his or her own profit.^[15,16]

Some DNA viruses are capable of secret writing their own miRNAs to modulate each the microorganism and cellular supermolecule expression so as to produce a good setting for microorganism replication.

Respondent back, sure host miRNAs alter the cell organic phenomenon to defend the cells against the infection by meddlesome with microorganism p proteins or alternative cellular factors as a kind of immune reaction against these explicit viruses.

Therefore, the connection between viruses and miRNAs is difficult, to mention the smallest amount. Since miRNAs play essential roles in microorganism infections, they're thought of to be promising therapeutic targets in infectious diseases.

Their endogenous nature, small size, and versatile perform create miRNAs excellent candida tes, as they'll trigger lower immunogenic responses and have fewer facet effects than siRNAs.

In sight of the present information concerning the roles of {various} microorganism and cellular miRNAs in various microorganism replication cycles, we have a tendency to believe that manipulation of those miRNAs can have a promising therapeutic role in infectious diseases. Currently, there are over 700 miRNAs encoded by the human ordering alone.

New therapeutic approaches square measure desperately required for serious diseases, as well as cancer, vessel diseases, infectious agent infections, and others. A recent direction in drug development is that the utilization of nucleic acid-based therapeutic molecules, like antisense oligonucleotides, ribozymes, short intrusive polymer (siRNA), and microRNA (miRNA).

miRNAs square measure endogenous, short, non-coding polymer molecules. Some viruses code their own miRNAs, that play polar roles in infectious

agent replication and immune evasion methods. Conversely, viruses that don't code miRNAs could manipulate host cell miRNAs for the advantages of their replication. miRNAs have so become engaging tools for the study of infectious agent pathologic process. Lately, novel therapeutic methods supported miRNA technology

for the treatment of infectious agent diseases are progressing speedily.

Though this new generation of molecular medical care is promising, there square measure still many challenges to face, like targeting delivery to specific tissues, avoiding off-target effects of miRNAs, reducing the toxicity of the medication, and overcoming mutations and drug resistance.

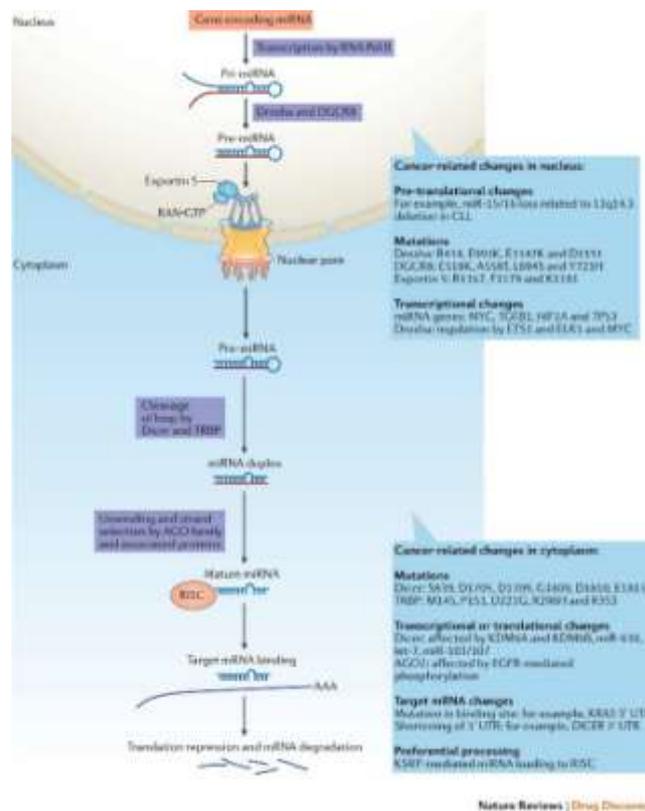


Fig.13. therapeutically enhancing miRNAs.

In Human polyomaviruses (HPyVs) area unit a bunch of oncogenic, circular, non-enveloped, double-stranded deoxyribonucleic acid (dsDNA) viruses. Five polyomaviruses are found to infect humans. Of specific interest area unit 2 strains of those viruses, named (according to the initials of the primary affected patients) Bk virus (BKV) and James ravine virus (JCV).

In Human papillomaviruses (HPVs) also are oncogenic viruses. they're typically related to totally different types of each benign and malignant tumors, particularly those touching the skin and also the reproductive organ tract. These viruses area unit typically classified, on the idea of

their virulence, into either low- or high-pathogenic variants.

In Adenoviruses area unit a bunch of non-enveloped dsDNA viruses. Over fifty serotypes are known in numerous clinical diseases, like metabolic process, duct, urogenital, and eye diseases. Animal virus typically encodes many tiny non-coding polymer molecules referred to as virus-associated RNAs, like VA1 and VA2.

In Herpesviruses area unit a bunch of swallowed dsDNA viruses, classified into 3 subfamilies (α , β , and γ). they're characterised by induction of latent infections in their target hosts.

In Human herpes virus (HCMV) could be a herpes viruses touching humans, and may end in acute or latent infections. the shape of infection mostly depends on the immune standing of the affected host. It is fatal in immune-compromised patients, like those with AIDS or recent organ transplants. it's going to even be to blame for birth defects and noninheritable abnormalities in pregnant ladies.

In herpes is another oncogenic virus touching humans. it's typically related to induction of latent infection in additional than ninety fifth of affected patients. In most cases, benign tumors develop; in some cases, however, malignant tumors may additionally develop, like Hodgkin's cancer, T-cell cancer, cavity cancer, and stomachal growth.

In KSHV is one in every of the gamma-herpes viruses teams and is typically related to Kaposi's cancer infection, from that it noninheritable its name. Like different herpesviruses, KSHV typically induces latent infections. In The human immunological disorder virus (HIV) order encodes many vital genes, like Nef, Vef, Tat, and Vpu. Bioinformatic analysis suggests that the HIV order encodes 5 pre-miRNAs, that area unit processed into 10 mature miRNAs, however their definite functions area unit still not well known.

➤ Limitations of the Therapeutic Potential of miRNAs

As we've got mentioned on top of, there are some promising results supporting the event of miRNAs for the treatment of many infective agent infections, and a few of those miRNA-based medicine have reached the trial stage.

Despite this nice progress, their clinical applications ar still hampered by many challenges. within the following section, we tend to in brief discuss this obstacles or limitations facing miRNAs-based antiviral medical care.

Delivery of miRNAs victimisation microorganism vectors typically leads to the event of immunologic response against the microorganism vector.

Basically, the delivery vector can stimulate AN innate immunologic response within the varieties of cytotoxic T-lymphocytes, body

substance neutralizing protein against their microorganism capsid proteins, and cytokine-mediated inflammatory responses in vivo.

Correlation between the immunologic response to the animal virus capsid supermolecule and also the concentration of the microorganism vector has been reported; this interaction is sometimes related to undesirable aspect effects within the host, particularly if the construct moves from the target tissue into the blood circulation.

• Lack of Targeted miRNA Delivery Systems.

The targeted delivery of siRNA, miRNA, and alternative nucleic acid-based therapies is another major concern of mistreatment these molecular therapeutic approaches. In distinction to the nice progress in native administration of each siRNA- and miRNA-based therapies within the eyes, lung, and vagina, general delivery to focus on organs like the liver, heart, and bowel continues to be undergoing improvement.

It's attention-grabbing to notice that some studies have shown success in administering siRNAs via the neural structure route; but, the danger is that foreign supermolecule could also be delivered to the CNS.

• Lack of Established miRNA Standard Analysis Techniques.

Several laboratory techniques — like period of time PCR, micro-array analysis, Luminex bead arrays, Northern blotting, in place hybridizing, formol fixation, and paraffin embedding — are presently in use in miRNA detection and quantification. However, all of those techniques still need more optimisation.

Once they're optimized, a transparent selection for sensitivity and specificity can emerge, and this approach can permit early and sensitive detection of miRNA expression in several malady syndromes. this may have an excellent impact on the first pursuit of significant microorganism diseases.

• Off-Target Effects and Unidentified Targets of miRNAs

The off-target effects of siRNAs were one in every of the main issues in earlier studies exploitation each siRNA and shRNA technologies in sequence medical aid.

As a replacement sequencing of molecular gene medical aid, miRNAs would be expected to own a high degree of specificity for his or her targets. However, since miRNA action relies on imperfect base pairing with the target sequence in most circumstances, the specificity are going to be not up to that of siRNA.

This prediction has been confirmed by recent clinical trials, followed up by microarray analysis, that discovered attainable off-target effects of miRNAs. Another study exploitation the mixture of bioinformatics and microarray analysis, found that exploitation either the siRNA or the miRNA may lead to off-target silencing. additionally, in vivo studies have discovered that one miRNA might target many genes at a similar time, and also the targets aren't clearly known. this implies various modes of action of a given single miRNA.

On the opposite hand, one sequence could also be regulated by many miRNAs, indicating that the mode of action is a lot of sophisticated than expected. Since drug therapies should exactly target the virus in question and zilch else, an oversized endeavor is required to collect all attainable data relating to all targets of every miRNA that's being thought-about for drug development.

- Mutations and Resistance.

Although the presently used infectious agent vectors in miRNA delivery square measure non-pathogenic, there's continuously the likelihood of mutations among those infectious agent vectors.

These mutations might not solely end in abnormal organic phenomenon of the infectious

agent miRNA construct however can also cause doable insertion of vectors into the human order, increasing the chance of cancer.

Moreover, the targeted viruses (especially the ribonucleic acid viruses) square measure at risk of mutation, which can drive drug resistance.

There square measure presently 2 doable approaches to overcome these issues: one is that the targeting of cellular factors that square measure essential for virus replication or use of over one miRNA for identical target gene; the opposite doable resolution is that the targeting of many preserved regions of the infectious agent order by totally different siRNAs or miRNAs.

X. MIRNAS AS BIOMARKERS IN VIRAL INFECTION.

In the pursuit of advance diagnostic tests for infectious disorder, some categories of molecules are scrutinized as prospective biomarkers.

Tiny (18–22 nucleotide), non-coding polymer transcripts known as microRNAs (miRNAs) have emerged as promising candidates with intensive diagnostic potential, because of their role

in various diseases, antecedently established strategies for quantitation and their stability at intervals biofluids. ^[17] Despite efforts to spot, characterize and apply miRNA signatures as diagnostic markers in an exceedingly vary of non-infectious diseases, their application in communicable disease has advanced comparatively slowly.

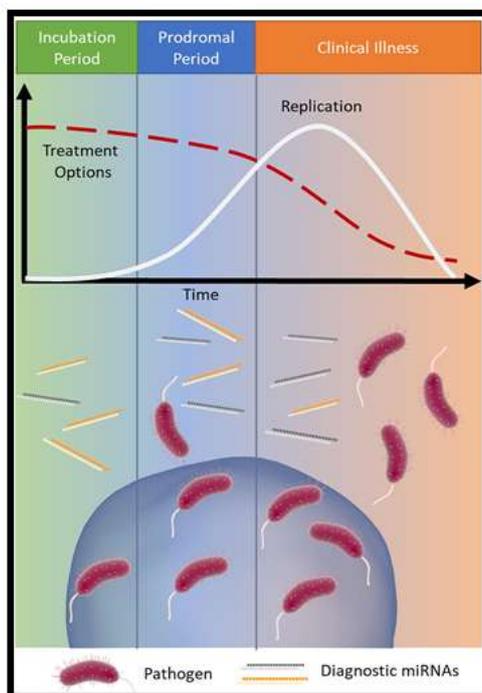


Fig 14. Biomarkers in miRNA.

Here, we tend to define the advantages that miRNA biomarkers supply to the identification, management, and treatment of infectious diseases.

Investigation of those novel biomarkers may advance the employment of personalised medication in communicable disease treatment, that raises vital concerns for corroboratory their use as diagnostic or prognostic markers.

Finally, we tend to discuss new and rising miRNA detection platforms, with a spotlight on speedy, point-of-care testing, to gauge the advantages and obstacles of miRNA biomarkers for communicable disease.

Currently, miRNAs are profiled as potential biomarkers in: Hendra virus, HIV, TB, malaria, and Ebola.

Additionally, current humour miRNAs are accustomed to distinguish latent and active TB, to get early prognostic signatures of infection, and as

biomarkers of malady severity in hepatitis caused by serum hepatitis and C virus.

In some cases, miRNAs were ascertained before malady onset, even before the microorganism may well be detected, and before the onset of seroconversion. While self-limiting conditions or those who need stripped intervention like the respiratory disorder might not take pleasure in development of miRNA platforms, others, specifically those with an outsized international impact, current lack of diagnostic tools, or long incubation periods would profit the foremost from such technology.

The potential of miRNAs in malady makes a myriad of enhancements conceivable as well as early detection, microorganism identification, detection of latent infections, measuring of treatment effectuality, prediction of malady outcomes and host response, and guiding best therapeutic choice still as companion nosology.

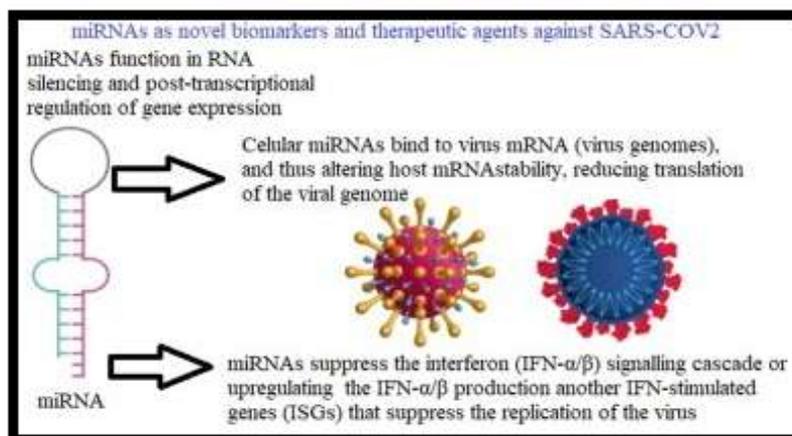


Fig14.1 Biomarkers in SARS-COV2.

An assay of current study and bioinformatic access shows that the examined potential of human miRNA interactions among the SARS-CoV-2's genome and confront the miRNA target sites to seven other coronaviruses showed that pathogenic human coronaviruses had miRNA signatures that differ from non-pathogenic human coronaviruses; Although much of the research on SARS-CoV-2 is primary. A set of lone miRNAs was identified for COVID-19 whereas SARS and MERS had their own different signatures.

XI. CONCLUSION AND FUTURE PROSPECTIVE.

Viruses are a unit among the foremost common causes of human diseases. attributable to the distinctive biological properties of viruses, there's no effective and specific antiviral medical care accessible to this point. many vaccines and antiviral medication have

shown a restricted degree of efficaciousness for prevention and treatment of some microorganism infections. However, high mutation rates change microorganism diseases to emerge and reappear often. Thus, new methods for drug and immunizing agent development should be devised to fight the threat of microorganism diseases to human health.^[18] Recent advances within the understanding of miRNA structure, function, and notably their association with the molecular pathological process of a range of advanced diseases, have served as a theoretical basis for drug development.

On the one hand, as key factors for microorganism replication and latency, miRNAs are ideal targets for inhibition. during this regard, construction of mRNAs that contain multiple tandem bicycle binding sites of a given miRNA could also be helpful to provide decoys or 'miRNA sponges' to inhibit the perform of a particular miRNA.

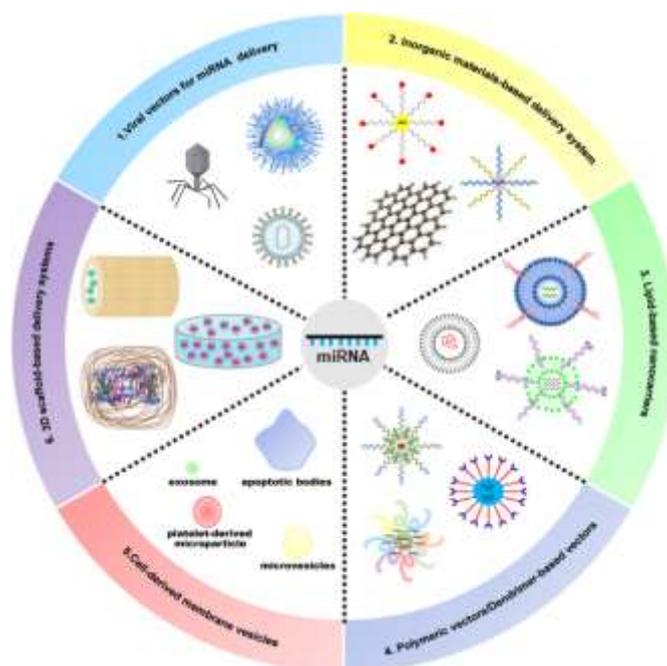


Fig15. Recent progress in miRNA.

Additionally, with chemicals synthesized antisense polymer oligomers ('antagomirs') targeting a miRNA of interest might be even be a promising approach to inhibit miRNA activity. On the opposite hand, ^[19,20] miRNA expression vectors will be wont to overexpress specific miRNAs to attain a semipermanent result of reversing the imbalance of miRNA expression caused by infection. Further, introduction of pre-

miRNA mimetics for transient replacement is another choice for investigation. In summary, though there area unit several limitations nowadays, we tend to believe that with the fast progress in miRNA analysis, these tiny molecules can become a useful target and a useful gizmo for basic analysis and drug development.

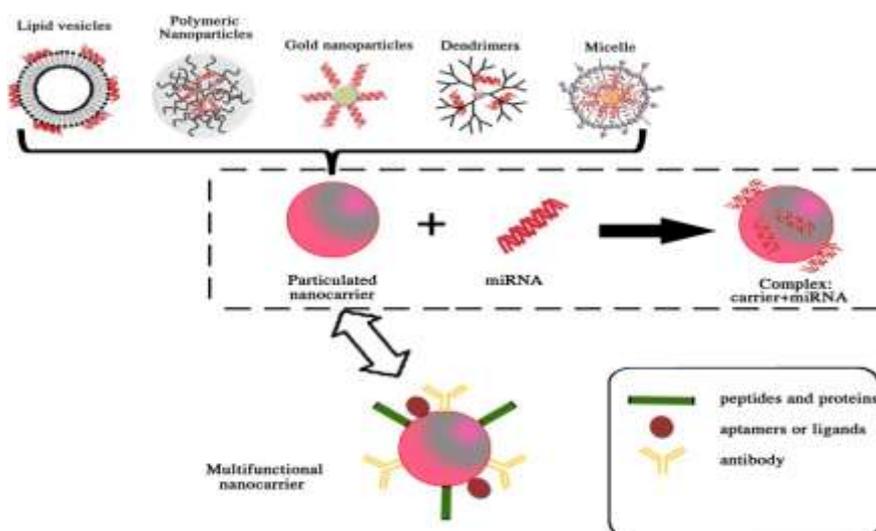


Fig15.1. Recent progress of miRNA in cancer.

It's expected that AN miRNA-based antiviral medical care can become accessible for clinical application within the close to future.

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