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Introduction of miRNA, their impact on host immunity and antibiotic/other drugs resistance

Nisar Fatima[1*], Dr. Ammara Saleem[2], Muhammad Furqan Akhtar[3], Muhammad Ammar Nawaz[4]

[1] Riphah Institute of Pharmaceutical Sciences, Lahore, Pakistan
[2] Faculty of Pharmaceutical Sciences , Govt College University, Faisalabad, Pakistan
[3] Faculty of Pharmacy, Riphah Institute of Pharmaceutical sciences, Lahore, Pakistan
[4] Departmemt of Marine Science, China University of Geosciences, Wuhan China.

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***Corresponding author:** Muhammad Ammar Nawaz
Departmemt of Marine Science, China University of Geosciences, Wuhan China.

Abstract

Riboswitches that are also called as microRNAs are small RNA that falls under category of non coding metaphorically sequences that are conserved which get produced in a number of tissues as well as cells which perform a major role that involves physiological and pathological outcomes of the body. There are some evidences provided by researchers for the implication of miRNAs in infectious diseases caused through bacteria by manipulating inflammatory responses, cell penetration, apoptosis and tissue proliferation. The review gives major discussion for the part of miRNAs in progression of infection and their impact on host immunity to improve the diagnosis, prevention and treatment strategies for the patient.

Keywords: *Riboswitches, microRNAs (miRNAs), non-coding RNA, bacterial infections, inflammatory response, cell penetration, apoptosis, tissue proliferation, host immunity, diagnosis, treatment strategies.*

Introduction:

Pathogenic bacteria are naturally capable to enter, survive and replicate within the host body. Owing to pathogenicity, many of these bacteria are responsible to infect human and other mammals deadly. Bacterial infections are widely spread and become epidemic or pandemic.

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The host immune systems are naturally embellished to cope with the pathogenic bacteria. - The immune system of host uses many types of regulators as defence that fight against the pathological processes that are being carried out by the bacteria that may affect the biological processes within host body. The lymphocytes, innate lymphoid cells, neutrophils along with macrophages are summed up together to form innate immunity within the host body that lead to phagocytosis of the phagocyte. As a reaction of phagocytosis, cytokines are released that are responsible for overcoming the inflammation process. A series of inflammatory reactions and signalling pathways are activated as a result of interaction between particular pathogen associated molecular patterns (PAMPs) with cell surface receptors like toll like receptors (TLRS) and NLRs, known as pathogen recognition receptors (PRRs)[i,ii]. This whole process is refer to as adaptive response of immune system which is instigated to remove pathogen from the host body[1iii]. The elimination of whole of the pathogenic bacteria from the body causes production of immune-regulatory cytokines with negative properties which allows Th2 cells to function in order to overcome this immunological response of body that may cause intense reaction or tissue damage[iv].

Table no. 1: Mechanism of Resistance developed by Bacteria

1	**On Genetic Basis**
a	**Mutational Resistance:**
	Bacteria produce genetic mutation in host cells making them unable to respond to antibiotics
b	**Horizontal Gene Transfer:**
	Introduction of foreign DNA causes bacterial volition and ultimately antibiotic resistance
2	**Mechanistic Basis of Antibiotic Resistance**
a	**Molecule of Antibiotic undergoing modification:**
	Chemical moiety is added to the bacterium that allows it to alter or inactivate the drug structure with production of enzymes.
b	**Decreased antibiotic penetration and efflux:**
	The decrease in the uptake of antimicrobial agent can result in preventing the bacteria from entering into the intracellular or into the periplasmic target region.
c	**Altered target site:**
	The alteration in target site with the help of bacteria results in the decrease in affinity for molecules of antibiotic which in returns causes it to hinder in entering targeted binding area.

Studies carried out Recently, various studies have explored the substantial defensive role of microRNAs (miRNAs) against bacterial infection within the body of hosts[v]. Micro RNAs (miRNAs) are small noncoding RNAs, consisting of about 22 nucleotides that are encoded through genomes. The miRNAs are responsible for post transcription repression of the expression of cellular mRNAs. In addition to gene regulation, miRNAs have also involved in targeting vast cellular processes and molecular pathways of individual's body. In human, almost 38,589 unique miRNA (according to miRBase database) are reported till date and almost 50% are present on vulnerable sites on chromosomes used for some kind of alterations like deletion, augmentation and rearrangements. The miRNAs take part in processes occurring at cellular level like cell cycle progression, escalation, metabolism, apoptosis, and stress tolerance besides, more than 60% of human protein coding genes are controlled by miRNAs. The abberent expression of miRNA responsible for various diseases. They also use as communication link between two cells.Moreover, it is considered as good biological marker in diagnosis of various diseases because of their secretion in extracellular fluid.

The RNA Polymerase II is responsible for transcription of these miRNA genes into a pri-miRNA which is a primary precursor that processed in two of the stages in presence of catalytic enzymes such Drosha and Dicer, which belong to RNAse III family. The first step takes place within the nucleus; a microprocessor complex is formed as a result of binding of the enzyme named Drosha with DGCR8, which is a RNA binding protein. As a result pri-miRNA is processed into a hairpin precursor (70 nucleotide) which is transferred to the cytoplasm with the help of Exportin 5. Cleavage of pre-miRNA takes place with the help of RNAase III enzymye Dicer into mature miRNA that is of 20 nucleotides approximately.

The miRNA then complexed with RNA induced silencing complex (RISC) by RNA processing proteins (AGO1 and AGO2) afterward it can bind to target transcripts through base pairing at their 3̀ untranslated regions (UTR). The translational repression may take place as a result of partial or improper binding of thea miRNA with that of the target mRNA conclude in degradation at the post transcriptional levels. many of the miRNAs have the capability bind to the 5′ untranslated region (5′-UTR) as well as to sites which are coding sequence of amino acid (CDS) of their target mRNA. One mRNA can result in the modulation of number of miRNAs, whereas a single miRNA in return have capability of causing expression of several target mRNAs.

MiRNAs are seen to play critical role in regulation of biological processes, like proliferation, differentiation, autophagy as well as metabolism with many other responses involving immune system. This impairment of a physiological regulatory mechanism can also be correlated with many of the diseases, that include cancer, autoimmunity, and cardiovascular diseases. This review discusses the impact of miRNA on immune system of the host as well as it discusses the role of miRNA during antibiotic resistance. Not only are this but miRNAs responsible for increasing the immunity of the host by interfering with the mechanism of different types of cells of immune system and resulting in beneficial roles. It is also stated through studies that miRNAs causes innate immunity within the hosts. miRNAs will also be playing significant role in future by marking a difference by allowing generation of personalized drugs as many of these miRNAs are being used as a biomarker for a specific disease[vi].

Impact of miRNA on the immune system of host

miRNA are beneficial in development of a organ, differentiation of cells, homeostasis as well as functioning. Through recent studies it has been made clear that miRNA plays an important role in immunity categorized as adaptive and innate, that includes the control of the differentiation process involving various cells of immune system affecting the functions at immunological level

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miRNA effecting the B-cells

The miRNA function was studied in the mice for differentiation of the B cells, the mice were represented with Ago2 that is defect involving haematopoietic system; the Ago2 was encoded with the protein that was indispensable for miRNA biogenesis as well as function[vii]. It was seen that the deficiency of Ago2 caused impairment in pre-B-cell differentiation rather than affecting the process that generates pro B cells at early stage which in return effected the generation of the succeeding peripheral B cell. A study was carried out in which all of the miRNA system was removed with the help of the B cell by specifically deleting the conditional allele of *Dicer*[viii]. This demonstrates that the process of differentiation of B cell is on whole hindered at the stage of transition occurring from pro B cell to pre B cell; it is done on partial status because of the deregulation undergoing upon pro apoptotic molecule that is Bim. It is seen that the deficiency of Dicer within the in B cells caused expression of deoxynucleotidyl transferase through whole process of maturation of B cell, this results in alteration in generation of antibody. This resulted in the findings that show the impact of miRNA system on B cell function as well as differentiation. Studies are being carried out to evaluate the role of every single miRNA that impacts the biology of B cell. For example, absence of miRNA 17~92 is shown in the aberrant Bim expression when B cells that were deficient in Dicer were observed[ix]. An increase in Bim expression is seen due to loss of miRNA 17∼92 leads and there is observed the development occurring due to the transition that causes conversion of pro B cells to pre B cells that is same as that of B cells that are deficient in Dicer[x]. It is seen that enhancement in B cell proliferation and survival takes place due to ectopic over expression of miR-17∼92. Similarly, it is also observed that miR 181 also has a positive impact on the regulation of differentiation of B cell. Expression of ectopic miR 181 causes a significant increase of the $CD19^+$ B cells which in return causes decrease in the number of T cell. The miR-150 also causes affects on the differentiation as well as maturation response of B cells[xi]. In early B cell progenitors, the low level of miR-150 expression is shown and expression of ectopic miR 150 has shown an impact on development of the B cells at pro stage to B cells at pre stage transition going on that is caused by c Myb targeting , which is the transcription factor. As opposite patterns of expressions are seen in miR-150 and c-Myb, the mice that are deficient in c-Myb but showing over expression of miR-150 shows phenotypes that can be compared in differentiation of B cells[xii].

The miR-155 is found in over expressed in humans with B cell related malignancies which are found to control the biology of the B cells without causing damage to the earky differentiation of B cells[xiii]. Pre leukemic proliferation was noticed in B cells with lineage due to restricted expression of B cell of miR155 transgene, these results in progression towards a severe malignancy of B cell, which did not caused any type of abnormality in differentiation of B cell mice deficient to miR-155[xiv]. However, it is observed that these cells have the capability to cause impairment in the ability that causes differentiation into germinal centre cells and also to go through the process of switching of the class of immunoglobulin. Despite the process through which miR-155 cause impairment of response of germinal centre is not clear, but impairment of switching of immunoglobulin class the result from the expression of the deregulated activation induced cytidine deaminase (AID)[xv]. it was observed that mice that have disrupted binding sites of miR 155 at the site 3' untranslated region[xvi] for AID has deregulation of its expression quantitatively and certain results are obtained effecting functions of switching of class as well as maturation that is similar as in the mice that is deficient in miR-155[xvii].

miRNA effecting the conventional T-cells:

The miRNA function in T cell is much different from that of the role in differentiation of B cell. It is seen that an intact percentage of varying double negative, double positive and the lineage of CD4 to CD8 [xviii] is shown in mice which is Dicer deficient in early stage of T cell progenitor, approximately reduction up to 10 folds is seen in total number of thymocytes that past the double negative stage[xix]. It was seen later that deletion of the Dicer with that of the CD4 drive transgene caused a decrease in total number thymocytes[xx], which is expressed at the single positive stage. According to the study results it is observed that the response in terms of differences caused a numerical impact differentiation of T cells with the timings of the Dicer which shows that miRNA have not significant role in development rather it decreases frequency of cell proliferation and death[xxi]. The miRNA has shown significant role in development of differentiation of T-cell through decreasing percentage for T-cell in excessive expression of haematopoietic systems that causes increase in sensitivity in signalling the receptors of T cells. The role of miRNA can be seen through miR 181 performing specific function in development stages of differentiation of T cells[xxii], it not only causes increase in the sensitivity of T cells towards signalling receptors but also causes reduction in the count of T cell that causes over expression of hematopoietic system[xxiii]. This is carried through the phenomena of down regulation of number of phosphatases that are responsible for attenuation of transduction of signals that causes down streaming of the receptors of T cells which in return results in increasing efficiency of positive as well as negative selection[xxiv].

Secondarily, the specific function to miRNA is prominent; along this an important role is its ability to generate different type's lineages of T helper (Th) and function of T cell. Th 1 induction is seen as well as impairment of induction of Th 17 in non polarizing conditions within the T cells that are deficient of Dicer[xxv]. Other than deleting the whole network, it was seen that miR 155 deficiency resulted in promotion of induction of Th2 in presence of the conditions favouring non polarization.[xxvi] In correspondence to the functions of T cell, miR-101 was seen playing important role in Icos undergoing the post-transcriptional modulation[xxvii]. Missing of miR 101 in mediated regulation, an increase embodiment of native T-cells is seen that results in the effecting the T cell like phenotypes which in return causes autoimmunity. Studies are still being performed to identify the role of miRNA that are specific for differentiation and functioning of the T cells.

miRNA effecting the regulatory T cells:

Forkhead box p3 (Foxp3)-dependent Treg cells[xxviii] are the sub types of T cells that depends upon miRNA for their generation as well as functioning, this includes both the Treg cells that are derived through thymic as well as periphery induction. miRNA is responsible for both types of induction of Treg cells that is thymic as well as peripherally[xxix].

miRna also play significant role in control of the function of Treg. When miRNA is being depleted from the lineage of Treg, this fatal autoimmunity which is not distinguishable to that of the mice which is deficient in Treg.the suppressor capacity along with homeostasis capacity of the Treg cells is observed to be reduced which are deficient in Dicer, under non-inflammatory

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conditions[xxx]. From this data we can evaluate that miRNA plays an important role as guardians for stable Treg functional programme in the conditions that challenge the lineage. The specific miRNA that is responsible for the control of Treg cell function needs yet to be identified; miR 155 is responsible for the reduction of homeostasis in Treg cells that are deficient in Dicer[xxxi]. The miR-155 in return is regulated directly through Foxp3 which is difficult to maintain for the heightened responsiveness of Treg cells that is required for the survival as well as growth factor that is interleukin-2, this is conducted through the targeting the suppressor acting upon cytokine signalling 1 (SOCS1)[xxxii], that will also work out in fitting to the healthy environment. miRNA which is responsible for enhancement of the suppressive function as well as lineage stability is yet to be identified.

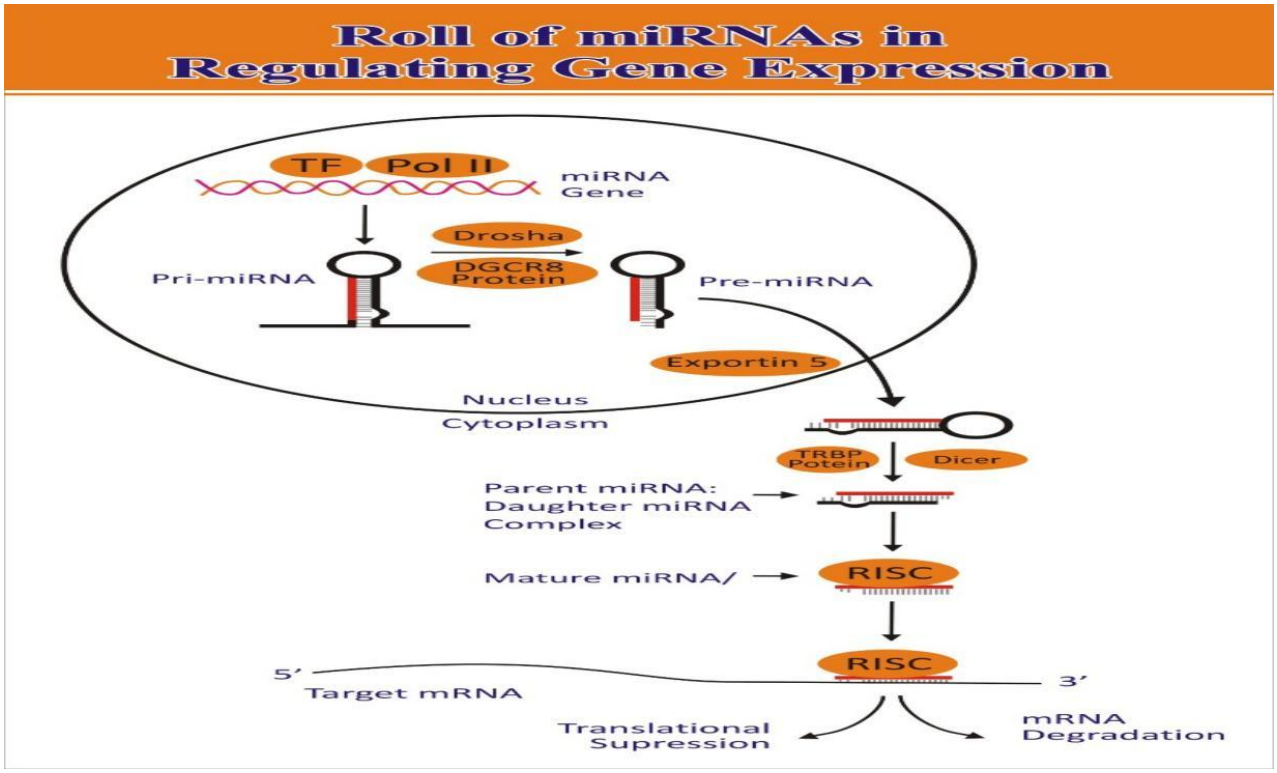

Fig 1: Overall silencing phenomenon exhibited by miRNA in regulating Gene expression

miRNA causing the innate immune system

Many studies are carried out in regarding specifying role of miRNA that is involved in innate immunity of cells, as it plays significant role in innate immunity. One such example includes in vitro promotion of granulopoiesis by the miR 223[xxxiii]. it is seen that the mice that are deficient in miR 223 tends to develop a large number of inflammatory lung lesions as well as tissue destruction of tissue which depends upon endotoxin challenge that occurs in result of hyper functional neutrophils[xxxiv].

It is observed in macrophages as well as dendritic cells (DCs) that miRNA plays a significant function for maturation of macrophages as well as dendritic cells into active lineage with the help of toll-like receptors (TLR)[xxxv]. Stimulation of induction of miR 155 occurs by both the interferon-β as well as TLR using the pathway involiving nuclear factor-κB along with pathway of Jun N-terminal kinase[xxxvi], due to the implication of miR-155 because of their involvement in the TLR-induced antigen[xxxvii] presentation pathway, it was confirmed through studies that DCs which are deficient in miR 155[xxxviii] were not able to cause induction in activation of T cell efficiently, which occurs as a response to the antigens because of the impaired presentation of the antigens in capacity and co-stimulation activity . miR-146 tends to involve in signalling of the loop for TLR. miR-146 as well as miR-146b are transcriptionally regulated upwards after causing stimulation of lipo-polysaccharide (LPS)[xxxix], still the maturation of miR-146a occurs only which provides with another example the regulation of miRNA expression with complex nature. Increase in expression process for miR-146a leads to decrease in expression of major key components that are IRAK1 and TRAF6 which are part of TLR signalling cascade. miR-146a plays an important role of effectors for the negative feedback mechanism that is driven to reduce the response TLR, which causes to prevent the excess of the inflammation. miR 125b which undergoes down regulation is shown in macrophages due to stimulation of LPS other than miR 155 and miR 146. miR-125b targets the gene of TNF-α[xl] which is tumour necrosis factor, due to this it is suggested that regulation showing downward graph for miR-125b is necessary for the generation of inflammatory response by the macrophages due to stimuli caused by microbes[xli].

Responses Shown by miRNA to Bacteria affecting its pathogenicity:

Despite the wide range of bacterium that occurs harmless and even are beneficial towards hosts, pathogenic bacteria forms main stream agents to numerous related diseases throughout the globe, diseases occurring as food borne due to L. monocytogenes and species of Salmonella[xlii], H. pylori causing stomach cancer and ulcers related to peptic disturbances whereas tuberculosis is associated with M. tuberculosis. To assure their survivability and replication over time, pathogenic bacteria exploit an open variety of function related to host cells by delivering proteins having effectors properties upon cells of host. Controlling manufacturing of miRNA resulting as infection by pathogenic bacteria is caused to emerge a distinct part for the response of host as result of infection, involving a unique strategy including molecular level that is manipulated by bacteria in controlling functions of host cells. The recent literatures on the regulation of host miRNAs by different pathogenic bacteria[xliii] are discussed in the literature given below and also seen in figure 1.

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L. monocytogenes

L. monocytogenes falls in category of Gram positive bacteria which functions as facultative pathogenic infecting through intracellular resulting in gastroenteritis in healthy person, serious infections are seen in person that have immuno-compromised systems and also in pregnant women. Entrance in vesicles or cells that are phagocytic or nonphagocytic in nature[xliv], L. monocytogenes rapidly exits through vacuole with bacteria in function regulated through formation of pore toxin listeriolysinO (LLO) that travels inside cytoplasm of host cell which effectively spreads along neighbouring cells[xlv]. This property of food borne pathogenic microorganism is utilized as representative phenomena in considering the behaviour of Gram-positive bacteria in regulation of expression of miRNA within infected cells of hosts.

L. monocytogenes have ability to invade miRNA-mediated host cell interrupting defense mechanism. miR-146b, miR-16, let-7a1, miR-145 along with miR-155 observed sufficiently to be impaired upon exposure to infection caused by Listeria in cells of epithelial origin. L. monocytogenes tends to cause changes for miRNA expressions within macrophages, demonstrated by Schnitger et al. miR-146a, miR-155, miR-125a-3p/5p along with miR-149 falls under the category of miRNAs[xlvi] that are altered mostly. . Lind et al. showed that CD8+ T cells having miR-155 deficiency displayed unresponsiveness to the signalling of AKT molecule after T-cell receptor (TCR) cross-linkages responses to L. monocytogenes infection. This states that miR-155 is necessary for inducing a proper CD8+ T-cell response[xlvii]. Whereas, miR-29 reduced immune responses of natural killer cells i-e CD4+ T cells and CD8+ T cells upon L. monocytogenes infection by invading IFN-γ. In contrast, macrophages with miR-21 inhibit the uptake of listeria monocytogenes to control infection by impairing the intracellular function. Archambaud et al. stated that intestinal micro biota could significantly alter the gut miR-143, miR-148a, miR-200b, miR-200c, and miR-378 responses[xlviii] upon oral infection by Listeria.

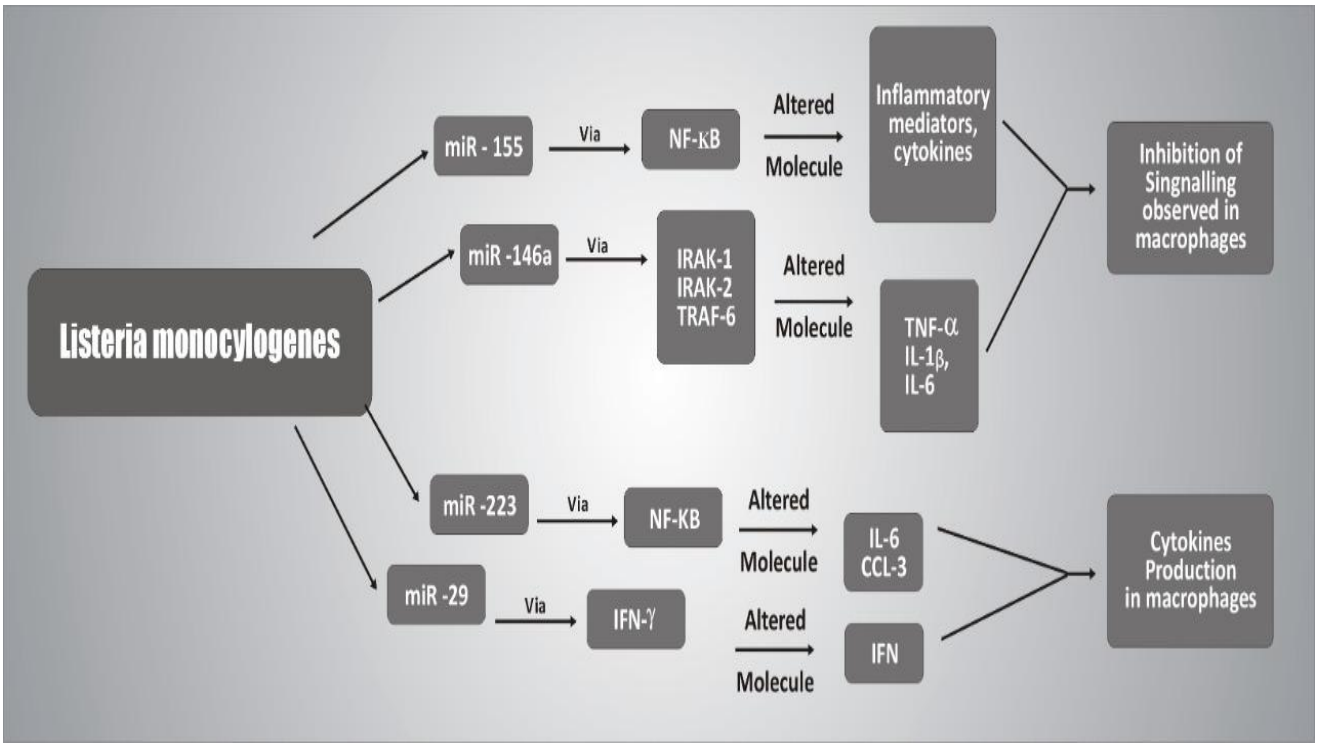

Fig 2: A view of mammalian host that is selected for miRNAs controlled by L. Monocytogenes

S. Typhimurium

S. Typhimurium is broadly categorized under Gram-negative, that is of facultative character and is intracellular pathogenic bacteria, and is categorized as common causative agents of gastric infections in human. S. Typhi is reported to infect both; phagocytic as well as non-phagocytic cells living in the Salmonella containing vacuole known as SCV[xlix]. Invading into host cells along with replication process occurring intracellular, Salmonella is capable of secretion of approximately 30 effectors proteins into cytoplasm of host cells via two of distinguishing type-III secretion systems (T3SS)[l]. Effectors proteins secreted by salmonella are responsible for regulation of numerous pathways within host cells that acts as essential requirement for infection to spread productivly. Modification of miRNA residing in host, functions by Salmonella infection was firstly explained through macrophages of mouse, NF-jB regulating miRNAs miR-155, miR-146a/b as well as miR-21 were tend to induced strongly invasion[li]. Following of miRNAs have been shown up regulation in human monocytes. Members of miRNA let-7 family have been shown to down regulated by Salmonella infection residing macrophages as well as epithelial cells, which indicates suppression of this miRNA family consisting of a common pathway leading to infection in phagocytic/non-phagocytic cells by Salmonella. The let-7 family is responsible for invasion of two of immunomodulatory cytokines that are; the pro-inflammatory cytokine IL-6 and anti-inflammatory cytokine IL-10[lii]. Hence, Salmonella infection is observed to cause trigger in expressing both the cytokines by inhibiting let-7 family, which in return causes balance within inflammatory response. It has been recently discovered that Salmonella also is responsible for down regulation of miR-15 family in HeLa cells[liii]. It is seen that over expression of miR-15 family causes inhibition of Salmonella infection very efficiently, by implementing suppression of Cyclin D1 (CCND1), which is a protein that is used in transition phase of G1/S. It is thus concluded that salmonella is responsivle for triggering of progression of cell cycle by down regulating miR-15 family which in return causes bacterial replication[liv].

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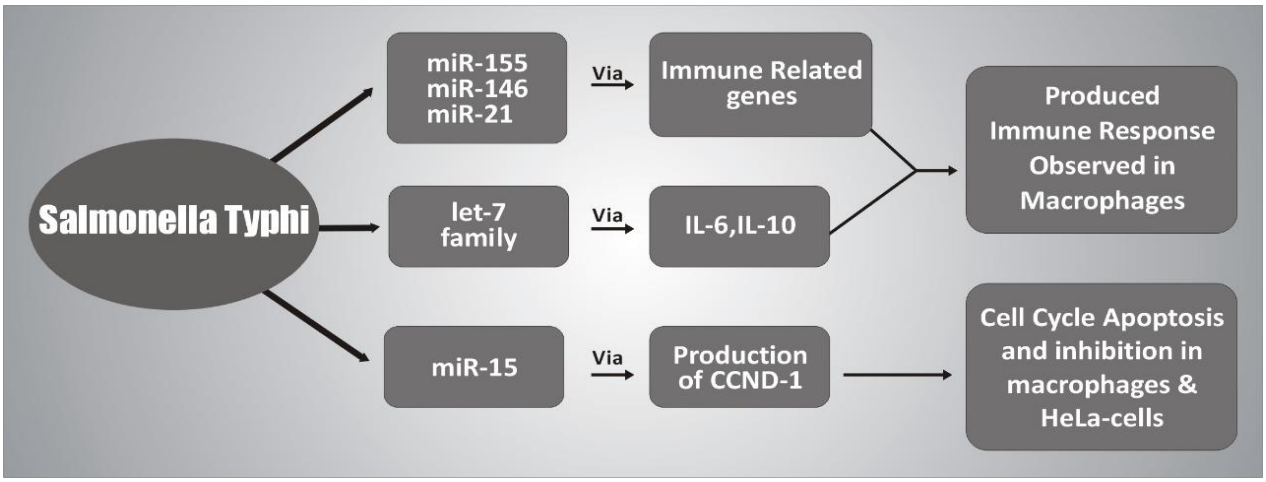

Fig 3: A view of selected host mammalian miRNAs controlled by Salmonella Typhi

H. pylori

H. pylori, a widespread categorized under Gram negative pathogenic microorganism which is estimated to be chronically infective in the mucosa of gastric cavity of approximately more than half of world's population and it is categorized as the primary reason causing gastritis, peptic ulcer and cancer in gastric cavity. H. Pylori provided with sample model for first time as evidence in mammalian host miRNA which was used as control during infection[lv]. Zhang in his study disclosed the fact that H. Pylori cause increase expression of miR-21 during its infection and provided with observation that miR-21 causes triggering of proliferation within host cell, it alos showed that miR-21 could cause association of H. pylori infection with gastric cancer propagation. Through many studies it is reported that miRNA associated with immune system i-e miR155 has seen to be up regulated by H. pylori infection, this study is applicable to in vitro which includes epithelial cells, lymphocytes and macrophages as well as in vivo which includes human biopsies carried out with help of infected cells of gastric mucosa[lvi]. miR-155 expression was depending upon LPS signalling through TLR4 as well as subsequent pathway activation regulated by NF-jB, also on toxins of bacteria which are secreted by type IV secretary system, specially including vacuolating toxin A known as VacA and c-Glutamyl transpeptidase[lvii].

Surprisingly, mice deficient in miR-155 unable in controlling infection resulting from H. pylori due to impairement of response of Th1 and Th17, but showing low chances to get infected by H. pylori resulting in gastritis or gastric cancer. Expression of miR-155 causes negative regulation of releasing IL-8 that is induced by infection; this indicates that miR-155 can act to negatively regulate small changes within inflammatory responses towards H. pylori. miR-155 is involved in targeting genes resulting in DNA damage in macrophages, on other hand can also increases resistance to apoptosis which occurs as result of damage to DNA caused by H. pylori[lviii]. miR-146a and NF-jB-dependent miRNA have also been noted to be induced as a result of H. pylori infection, both in vitro and in vivo. This miRNA also regulates inflammatory responses against H. Pylori negatively through modulation of IRAK1, TRAF6 and PTGS2[lix]. Alike miR-155, miR-146a also functions in negative feedback loop which causes to regulate responses as a result of inflammation caused by H. pylori. With the involvement of miR-155 and miR-146a/b, H. pylori causes response to Gram positive and Gram negative bacteria which causes down regulation of let-7 miRNA family. H. pylori cause decrease in expression of let-7, both in vitro and in vivo, with its factor responsible for virulence that is CagA[lx]. This leads to the de-suppression of their target molecule i-e TLR4 and thus induces the NF-jB inflammatory response. Balance of moderate level within expression process of miR-155, miR-146a/b and let-7 family is therefore crucial for controlling inflammation due to *H. pylori*[lxi].

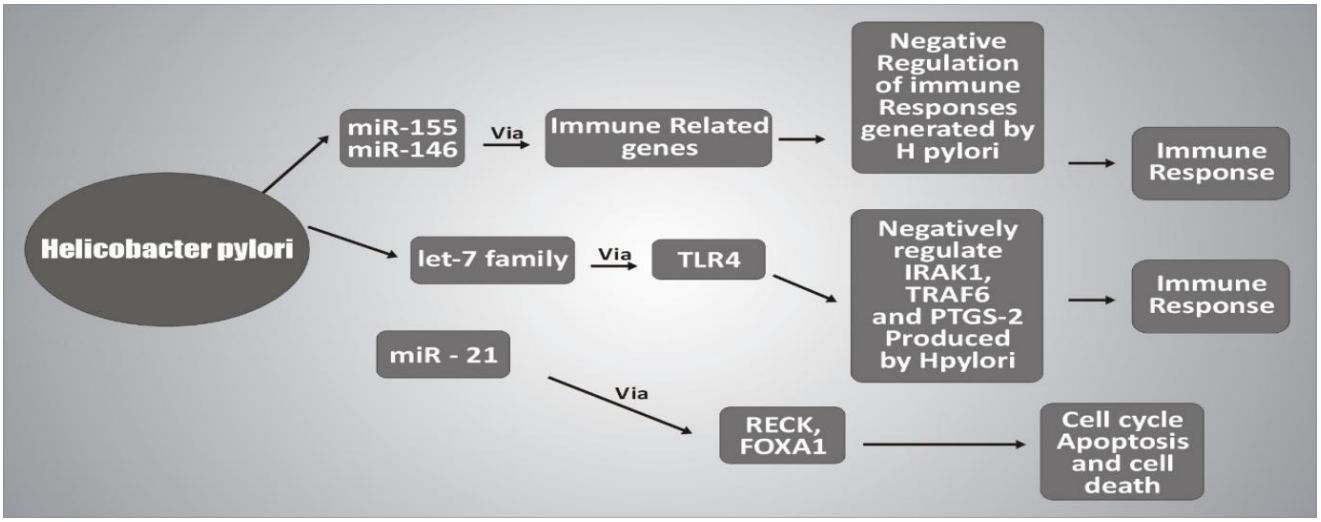

Fig 4: A view in selected host mammalian miRNAs controlled by Helicobacter pylori

Mycobacterium species

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Tuberculosis abbreviated ad TB has always been a major concern for health residing in public throughout the world, careful estimations according to studies indicates about third part of the population worldwide is prone to be infected by M. tuberculosis; around 1.5 million deaths are linked with it occur throughout the year. Genus Mycobacterium embraces species with high pathogenic microorganisms such as the root cause of TB or M. tuberculosis, and Mycobacterium leprae which is responsible for leprosy, on other hands includes opportunistic microorganisms such as *Mycobacterium avium*, that are able to infect individuals that are immunocompromised. Mycobacterium species like other pathogenic bacteria can regulate production of miR-155 upon infection. Mycobacterium bovis infection shows increase production of macrophages with help of TLR2 and NF-jB signalling, which inreturn causes progression of increased apoptosis of cells that is infected. A study showed a corresponding relationship in Mycobacterium virulence capacity[lxii]. This study revealed the differential induction of TNF-a, miR-155 and miR-125b. This showed that miR-125b directly invades TNF-α, opposite to this, miR-155 stimulates synthesis of TNF-α via SHIP1[lxiii]. Lipomannan, a compound secreted from both virulent (*M. tuberculosis*) strains leads to down-regulation of TNF-α, however, secreted from a virulent (*M. smegmatis*) strains lead to up regulation of TNF-α. This regulation depends upon a balance in miR155 and miR125b. miR-155 is produced in large quantities by M. tuberculosis , whereas miR-125b in low quantities and vice versa with M. smegmatis[lxiv]. But this remains unclear that either the induction on miR155 is beneficial to combat Mycobacterium infection or not. For instance, in some cases miR155 up-regulation caused activation of pathway that signals AKT which is essential for survival of M. tuberculosis[lxv]. Whereas other conditions shows that miR155 up-regulation produces killing effects on M. tuberculosis by inducing autophagy in cells via suppression of a negative regulator Rheb and components of mTOR pathways[lxvi].

miR-142-3p is also regulated differently by infection. For instance, it is strongly expressed upon infection through M. tuberculosis or M. smegmatis infection that affects macrophages causing reduction in the uptake of bacteria in phagocytic cells by invading N-Wasp[lxvii]. It contrast the production of miR142-3p is reduced by M. bovis, inducing activation of NF-jB cascade[lxviii]. Sometimes Mycobacterium infection modulates the production of the miRNAs miR-21 and miR-146a that are linked to immune system. For instance, M. bovis induced miR-21 production via NF-jB pathway in T-cells and dendritic cells (DC) that blocked IL-12 expression[lxix]. Increased production of miR-21 induced apoptotic damage to DC, via Bcl2. M. bovis may cause decreased response to antimycobacterial th1 agents by increasing production of miR-21. M. leprae can continue its virulence by increasing miR-21 production within monocytes and macrophages that show vitamin D dependent killing. Because this miRNA can cause inhibition of synthesis of two peptides that are dependent upon vitamin D, hence these cells lost their antimicrobial capability. Despite this expression of miR-99b by M. tuberculosis in macrophages decreases inflammatory response because substances i-e TNF-α acts as a substrate for miR-99b, whereas the inhibition of miR-99b causes increased inflammation[lxx].

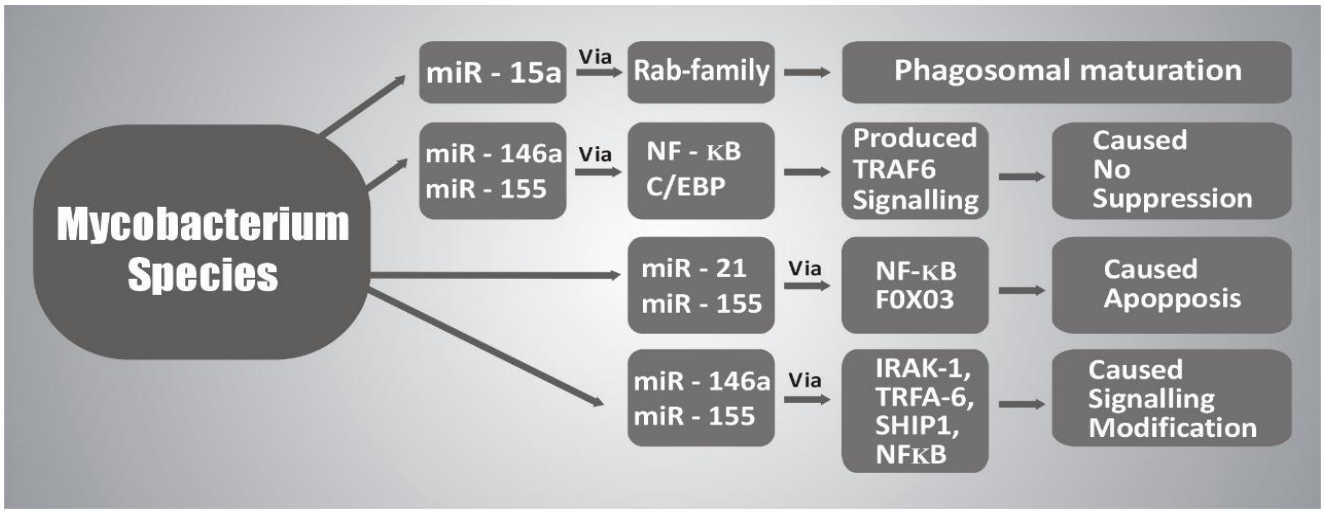

Fig 5: A view of selected host mammalian miRNAs controlled by Mycobacterium Species

miRNAs causing Immune Evasion:

miRNAs that target the Viral Gene Expression

The important function of viral miRNAs is to target the expression of viral gene viral that targets to control the latent phase of expression phase. miRNAs that are SV40 encoded is responsible for regulation of expression of viral genes and also causes reduction to susceptibility of viral genes towards cytotoxic T cells[lxxi]. LAT (that is Latency Associated Transcript) is drives HSV1 induced latency that is encoding miR-H2-3p and miR-H6 that falls under non-coding RNAs[lxxii]. These miRNAs targets the factors ICP0 and ICP4 that are responsible for the virus reactivation, these factors plays key role in reactivation of virus from latency of HSV-1[lxxiii]. Similarly, miR-I, miR-II, and miR-III expression through LAT takes place for HSV-2 which in return reduces the expression of ICP34.5 which is an important neuro-virulence factor[lxxiv]. miR-I that is expressed within human sacral dorsal root ganglia of neurons is latently infected by HSV-2, that suggests the function of v-miRNAs in latency of HSV-2 within human neurons.

miRNAs with therapeutic potential:

Tackling the diseases caused by viruses and cancer associated to viral factors is a major challenge for the world. Various studies have proved the identification of miRNAs to target in order to treat number of diseases. Antagomirs that are so designed to isolate within the host miR-122 is known to involve in HCV infection enters into the phase II clinical trials on human and are showing significant effects opposite to the infection[lxxv]. Similar techniques can be used to target v-miRNAs within DNA virus infection, with the help of inhibitors or antagomirs that are sponge based. The idea of development of antagomirs for v-miRNAs that to cellular

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miRNAs is much supported as this causes reduction in side effects that may be represented within humans and this may also help in the delivery that is non toxic or site specific[lxxvi]. The mice that are affected with cytomegalovirus (MCMV) infection receiving antagomirs in response to MCMV v-miRNAs had shown a reduction in occurrence of the disease, MCMV[lxxvii]. In a similar study, it was shown that gold nanoparticles that contained anti-EBV-miR-BART7-3p had shown to therapeutically deliver anti-miRNAs against the EBV-miR-BART7-3p, which caused inhibition of the tumorigenicity in EBV-positive cells of mice[lxxviii].

By the usage of EBV promoters that are EBER2 promoter, it was seen that miRNA sponge was expressed to some of the specific genes with silence property within cells infectyed with EBV that can be helpful for targeting the EBV positive NPC cells[lxxix]. v-miRNAs were used as biomarkers in a number of infectious diseases caused by viruses. was found to be present in the sera of EBOV infected patients presented with miR-VP-3p[lxxx] in their sera which was absent in healthy patients, this detection of v-miRNA in the infected serum caused the identification of presence of RNA of viral genome that served as biomarker to perform primary diagnosis at early stages in EBOV [lxxxi]. Similarly HCMV that encodes miR-US4-1 is used as a biomarker for treatment of IFNα whose potency is detected in the serum of hepatitis B patients[lxxxii]. Other than these many v-miRNA adapters (HSUR2) were also discovered that uses miRNA that targets the transcripts through the process of alternative base pairing. These Inhibitors which are used against these adaptors of supportive v-miRNAs can be used[lxxxiii]as an alternative to therapeutic procedures[lxxxiv]. Finally, the critical design along with the validation the studies that are carried upon using miRNA within cell lines as well as animal models can guide in identification of novel therapeutic candidates in order to carry out the treatment in future.

miRNA and antibiotic/other drug resistance:

One of the significant study is the importance as well as of non coding region that is encoding miRNA. These encoding regions of miRNA can be studied to predict the response of drug that is its resistance to the body reactions. Through the study it is discovered that first miRNA which shows drug resistance is miR 24[lxxxv], many of other miRNA are also identified that have association with drug resistance. This information of resistance associated with miRNA and drugs can be utilized for designing of drugs in order to achieve increased efficacy along with safety which in return will help in benefits in terms of health as well as economy. miRNAs are categorized as beneficial therapeutic agents as the show there expression in malignant cells that in normal cells. Significant advantages along with limitations have been observed in re expression therapy of miRNA[lxxxvi]. The identification of role of miRNA for drug resistance have brought a significant change towards diagnosis techniques as these encoding regions of human genome that are used by miRNA can be utilized to predict the response of a drug. The target sites of the drugs can be altered by using the decrease levels of miRNA and drug resistance can be conferred. It can be seen through the example that miR-24 cause regulation of the expression of the gene named *DHFR*[lxxxvii], which is the target of methotrexate which is anticancer drug, and this regulation is done through binding to 3′-UTR. Thus, a new phenomenon of over expression of targets as well as drug resistance is shown due to amplification of gene that results in over expression of DHFR and loss in function of miRNA. This all in returns establishes a connection between the drug resistance and miRNA. miR-24 also found to act as independent suppressor of tumor of p 53[lxxxviii], other than this drug resistance was also observed related to loss of miRNA 24 as well as it also give advantage in terms of growth to the cells which are immortalized and can induction of neoplastic transformation[lxxxix]. Through all these studies carried out a prominent study related to drug resistance is observed related to cell transformation that occurs as a result of loss in function of miRNA[xc].

The results of all the studies draw the conclusion that levels of miRNA can be the major factor that is used to determine the sensitivity as well as resistance of the drug. miRNAs have been found to be associated with the sensitivity as well as resistance of different types and different classes of drugs used in chemotherapy in which many antibiotics are also used. Through literature the drugs whose resistances are observed through miRNA are methotrexate, nogamycin, camptothecin, TRAIL, doxorubicin (DOX), tamoxifen, paclitaxel, cisplatin, vinblastine, hydroxyurea, microtubule targeting agents, gefitinib, lapatinib, mitoxantrone, interferon and 5-fluorouracil. The DNA intercalating properties of the two drugs that are camptothecin and nogamycin were observed to be effected by two miRNAs that are miR-21 and miR-34a. The resistance of the chemptherapeutic drug Nogamycin was observed due to the over expression of miRNA 21 in the following three lines of cancer cells; A549 which is non-small-cell lung[xci], SNB-19 which is glioma and OVCAR-3 which is ovarian cells. On the other hand, miR-192 and miR-140 are identified to show chemotherapeutic reisitance towards the drugs including methotrexate and 5-fluorouracil.

miR-451 is also seen to cause regulation of gene that is associated with *mdr1*. Sensitivity towards DOX is seen due to the over expression of miR-451 in MCF-7/DOX-resistant cells. Down regulation of capase 3 is also seen as a result of over expression of let-7a which in return caused resistance of DOX in the A431 cell line. miRNA 21 has been studied to show multidrug resistance including DOX and paclitaxel and some of the proteins that are involved in hyaluronan induced CD44 pathway.

miR-130a is a member of miRNAs family that is down regulated in the cell line causing drug resistance which targets the gene named *M-CSF* that is a well known factor causing in the ovarian cancer. miR-214 causes activation of Akt pathways by regulation of PTEN levels at the site 3’ UTR which is associated to survival of ovarian cancer cell as well as resistance of cisplatin. miR-15b and miR-16 showed down regulation in the resistant human gastric cancer cell line SGC7901/VCR with multi drug resistance that is developed through modulation in expression of BCL2.

The level of p27 was found to be decreased due to a significant increase in the expression of miR-221 and miR-222 that caused TRAIL resistance. miR-221 and miR-222 also caused regulation of p21 as well as estrogen receptor α that is linked with the resistance to were with tamoxifen (antiestrogen) that is being used in breast cancer cell lines. According to the analysis down through computation it was observed that deregulation of miRNAs are seen in in the antiestrogen resistant MCF-7 cells that are estrogen receptor positive. A marked increase in the accumulation intracellular in vinblastine as well as hydroxyurea was observed due to down regulation of miR-27a or that of miR-451[xcii]. miR-27a was also shown to be associated with the poor prognosis involving chemotherapy that is based upon platinum that is carried out in patients of ovarian cancer. miR 200c when over expressed caused reduction in the expression of TUBB3 as well as it causes restoring of its sensitivity towards anticancer agents that are

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targeting the microtubules. miRNA 125b is responsible for induction of resistance towards withdrawal of androgens within LNCaP cells through regulation of BAK1 which is involved in apoptosis induced by drugs[xciii].

Over expression of miR-205 causes the down regulation of HER3 in SKBr3 which are human breast cancer cells, and chemosensitivity gefitinib and lapatinib is improved[xciv]. miR 21 makes target of LRRFIP1 which is an inhibitor of signalling of NF-κB, and it causes resistance of VM-26 resistance within the glioblastoma cells. miR 519c and miR 328 are the two miRNAs which are responsible for inhibition of expression of ABCG2 and it was also associated to the sensitivity of drug sensitivity. miR 328 also was associated to the resistance caused by mitoxantrone within breast cancer cells[xcv]. miR 155 out of all miRNAs was identified to cause regulation proliferation as well as growth of Waldenstrom macroglobulinemia cells through inhibition of pathways of the MAPK/ERK, PI3K/AKT and NF-κB and its also been linked to the poor prognosis with that of Waldenstrom macroglobulinemia drugs[xcvi]. Individuals who represents with chronic hepatitis C shows decrease in levels of miR-122 due to which they respond poorly towards the interferon therapy[xcvii]. These miRNAs discovered can be used as the prognostic markers for specific drugs within the clinic.

Resistance to Macrolide Antibiotic:

An alteration to this attenuation pathway is known to be involved in controlling transcription process rather than translation mechanism and used to synchronize the expression of the genes for macrolide resistance coded by *ermK* and the *mef-mel (msr)* set of genes in *Bacillus* and *Streptococcus* species of microorganism[xcviii]. During the absence of macrolide antibiotics, transcription process seizes at the terminator edge present in the principal segments of the resistance genome. Antibiotic-induced ribosome obstruction inside the short leader/principal gene *orfs* enhances the production of anti-terminator structure permitting the RNA-polymerase enzyme to continue transcription process. A parallel process is thought to regulate *vmlR* and *bmrCD*[xcix], both encode ABC-transporters converse antibiotic resistance in *Bacillus subtilis* microorganism. In this situation, committed leader peptides are easy to detect. Being distinctive to old systems, the expression of *bmrCD* gene is regulated through a transcription attenuator system that is located on the ascending portion on the *bmrB* gene. Expression of the translation process of bmrB *gene* is necessary for *bmrCD* regulation indicating that it over rules the function of a leader peptide gene[c].

Resistance to Amino glycosides:

Currently, there was an RNA component declared to interact readily with amino glycoside antibiotics to attain a regulated production of directive encoded amino glycoside acetyl- or adenyl-transferases[ci]. This interaction was supposed to induce a conformational/structural change in the Principal RNA, thereby disclosing the RBS (RNA binding site), which is confiscated in a stem-loop during the absence of a ligand. However, this mechanism involving the characteristics of a genuine riboswitch is still behind the curtain[cii].

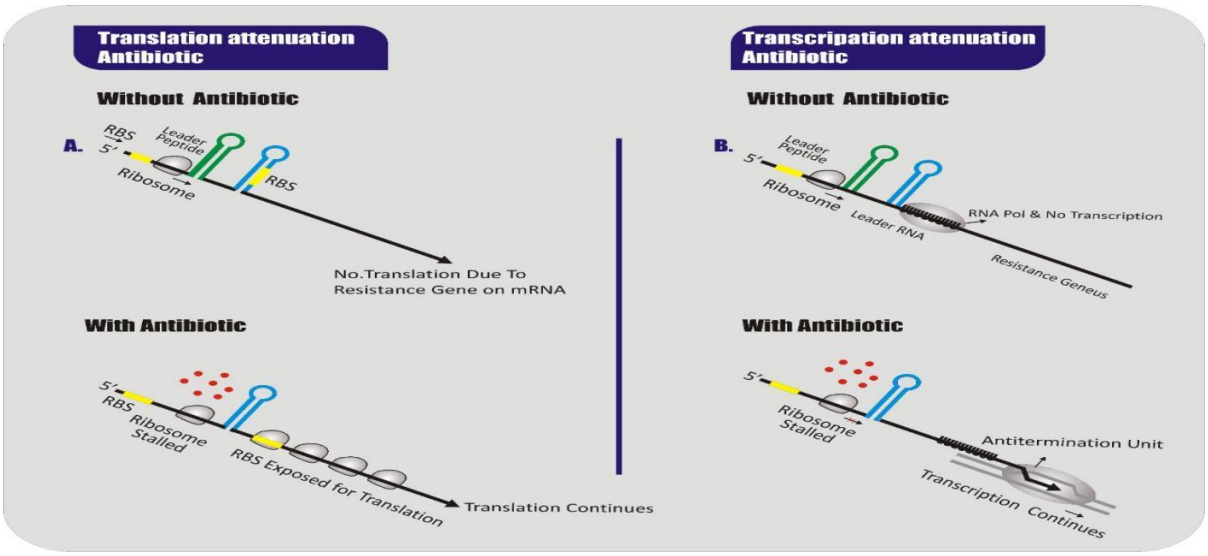

Fig 6: Antibiotic Resistance genes Regulation by attenuating RNA. (A) Translation attenuation regulating antibiotic. Short *orf* is encoded by *ermC* which is a resistant gene. Secondary structure is winded up due to translation of *orf*, which causes supersession of the translation of the resistant gene through confiscation of the RBS. This process causes the alternate structure to form that allows ribosome to reach up to RBS which than causes translation of the resistant gene. **(B)** Transcriptional attenuation regulating antibiotic resistance. Translation of the principal *orf* in the case of ermK or other attenuators causes the termination of the RNA-polymerase at an inborn terminating portion. Antibiotic-induced ribosome compartment that is induced by antibiotics within *orf* causes formation of an anti terminator portion that allows RNA-polymerase to continue the process of transcription despite the terminator.

Attenuating RNA to control Antibiotic Resistance:

Through the recent past years, an increasing number of studies showed that mechanisms that are involved in controlling the antibiotic resistance at the post-transcriptional level. This type of controlling mechanism produces an abrupt response, which is advantageous when antibiotic concentration increases rapidly. Mechanisms involved in attenuating RNA are known to be associated with expression of resistance genes to existence of associated antibiotics[ciii]. Most importantly, attenuating translation mechanism is not simply the result of translation inhibition *alone* as every different attenuator possesses a high selectivity and responds to only to the relevant subset of antibiotics. Binding of the antibiotic to the ribosome involved in translation process changes the attributes of the ribosomal enzyme complex called "peptidyl transferase center" in a drug-specified manner, thereby it

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inhibits peptide bond-formation between different set of combinations of amino acids that are present in the principal peptide chain[civ].

List of Regulatory RNA's involved in Antibacterial Resistance and Increasing Susceptibility through various mechanisms

Riboswitch/ Gene	Name	Organism	Mechanism	Resistance/ Induction	Reference
bmrCD	ABC exporters	*Bacillus subtilis*	Member of heterdimer family of ABC exporters having impaired bindingsite for nucleotides.	Antibiotics targeting the ribosome	Reilman et al., 2014
ermK	Multidrug resistance Protein	*Bacillus spec*	Controlling transcription at 235 rRNA through methylation and causig resistance to macrolides and Streptogramins.	MLS_B	Kwak et al., 1991
lmo0919	Listeria monocytogene Protein 0919	*Listeria monocytogenes*	Causes alternation of ABC transporter gene at transcription level.	Lincomycin	Dar et al., 2016
mef/mel **(*msR*)**	Mocrolide efflux Protein	*Streptococcus*	Controls MFS efflux at transcription.	Macrolides	Chancey et al., 2015

Table no 1
Antibiotic resistance developed by Transcriptional Attenuation

Table No. 2

Antibiotic resistance developed by Translational Attenuation

Riboswitch/ Gene	Name	Organism	Mechanism	Resistance/ Induction	Reference
aac/aad	Aminoglycoside acetyl transferase	Various species	Riboswitch controlling translation of aminoglycoside acetyl- or adenyl-transferase genes	Aminoglycosides	Jia et al., 2013
cat	Chloramphenicol	Various species	Encodes bacterial enzyme that transfers acetyl group from acetyl-CoA to chloramphenicol.	Chloramphenicol	Schwarz et al., 2004
cmlA	Chloramphenuol acetyl Transferase 2	Various species	When combined with chloramphenicol causes chemical modification of cys-26 export genes.	Chloramphenicol	Schwarz et al., 2004
ermC **(A, B)**	Adenine N-6-methyltransferase gene	Various species	It causes demethylation of adenine residue at 23S rRNA subunit, resulting low affinity of ribosomes to macrolides.	MLS_B	Ramu et al., 2009
fexA	Florfenicol – chloramphenicol resistance gene	*Staphylococcus lentus*	Causes efflux of chloramphenicol and florfenicol by attenuating translation.	Chloramphenicol, florfenicol	Schwarz et al., 2004

Conclusion:

It is concluded through the studies conducted that miRNAs have significant role in boosting up the immunity under certain circumstances. This can be achieved by targeting the coding sequences with which they can pair and cause reduction of the aggravated response of the immune system by altering the binding mechanism of the cells that make up immune system.

It is seen that the association between miRNAs and drug resistance can be used in achieving personalized result of a medicine for a specific individual with a certain clinical ailment[cv]. Above of the discussion shows that miRNAs can play a significant role in the drug resistance. The miRNAs can be well used as prognostic tools for the drugs that can be used in development of the molecular assays which will than allow the detection of response of drugs as well as to tailor the dosage of the drugs. It will also help in providing and designing a personalized therapy or can also allow to

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initiate a preventative measure[cvi]. The implication of miRNA personalized medicine for specific individual can be obtained when the clinical practice, researchers, policy-makers, governments and pharmaceutical companies will work in correspondence to each other by characterizing the disease as well as drug response by using miRNAs as the biomarkers, and the knowledge obtained is than integrated for the prediction of response of the drug studied clinically[cvii], which is than availed in eliminating the adverse drug reactions[cviii]. These miRNAs can also be used specifically for the treatment of the disease such as different types of cancers and many of its members have the potential to interact with antigens responsible for causing cancerous cells and in return reducing the chances of the disease prevalence within the effected body.

This project involving the human genome is stepping towards an advance era which will be able to provide project the personalized medicine. miRNAs can be used as a source to study the basis of a disease and also can help in diagnosis as w ell as prognosis of it[cix]. The features of miRNAs that involves relationship of it with that of the drug response will help in providing clear understanding of pharmacological response of a drug which can help in revolutionizing the discovery of drugs as well as their developmental process[cx]. The vast and clear understanding will help in better development of the drugs according to the personal factors for a specific treatment that will provide with great success and will also enable the maximum possibility of personalized medicine in upcoming era of medicine.

Conflict of interest

Authors declare no conflict of interest.

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