

# MicroRNAs as new immunity regulators in viral and bacterial infections

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**Keywords** microRNA, immunity, viruses, bacteria

**Abstract** MicroRNAs (miRNAs) – small, conserved RNA molecules, containing 22 to 25 nucleotides and occurring in the cells of living organisms. As regulatory molecules, they have enormous biological potential and can influence a number of cellular processes. In the context of immunology, the role of miRNAs as novel immunity regulators is invaluable. The miRNAs regulate immune phenomena at many levels - starting from the impact on the processes of maturation, proliferation and differentiation of the immune system cells, through the regulation of the secretion of their products, to the regulation of intracellular signalling pathways. In all these areas, the miRNAs can play the role of both an inducer and an inhibitor by appropriately increasing the intensity of or suppressing the immune processes they regulate. In the future, it will be possible to regulate the host's immune response to the pathogen thanks to the properly controlled expression of miRNAs in the immune system cells.

## Cząsteczki mikroRNA jako nowe regulatory odporności w infekcjach wirusowych i bakteryjnych

**Słowa kluczowe** mikroRNA, odporność, wirusy, bakterie

**Streszczenie** MikroRNA (miRNA), małe, konserwatywne 22–25 nukleotydowe cząsteczki RNA występujące powszechnie w komórkach żywych organizmów. Jako cząsteczki regulatorowe mają ogromny potencjał biologiczny i mogą wpływać na wiele procesów komórkowych. W kontekście immunologii nieoceniona jest rola miRNA jako nowych regulatorów odporności. MiRNA regulują zjawiska odpornościowe na wielu poziomach. Począwszy od wpływu na procesy dojrzewania, proliferacji oraz różnicowania komórek układu odpornościowego, przez regulację wydzielania ich produktów, po regulację wewnątrzkomórkowych szlaków sygnalizacyjnych. Na wszystkich tych polach miRNA może odgrywać rolę zarówno induktora, jak i inhibitora, odpowiednio zwiększając nasilenie lub wygaszając regulowane przez siebie procesy odpornościowe. W przyszłości dzięki właściwie pokierowanej ekspresji miRNA w komórkach układu odpornościowego możliwe będzie regulowanie przebiegu odpowiedzi immunologicznej gospodarza w odpowiedzi na patogen.

## Introduction

MicroRNAs (miRNAs) are small, conserved and non-coding sequences containing 22–25 nucleotides (Bartel, 2004). They are assigned a role in controlling the expression of genetic information in many physiological and pathological processes such as cell proliferation and differentiation, embryogenesis, DNA repair, inflammation, immunity, viral and bacterial infections, apoptosis or neoplastic processes (Ardekani, Naeini, 2010; Bartel, 2004; Das et al., 2016; Hukowska-Szematowicz, Deptuła, 2010; Mahesh, Biswas, 2019; Olejniczak et al., 2018; Poczęta et al., 2018; Świetlik, Szemraj, 2017). Moreover, these molecules play a part in intercellular signalling (Barbu et al., 2020). So far, more than 38.000 various miRNAs have been identified, the activities of which were distinguished in individual biological processes (Annon, 2020a). Nevertheless, a single miRNA molecule can influence the expression of several or several dozen different genes (Bartel, 2004). MiRNA influences the reading of the target mRNA by identifying complementary fragments at the 3' end of the UTR of the mRNA strand (Bartel, 2004). The mRNA reading is regulated by reducing the level of its transcription or by post-transcriptional mechanisms such as mRNA cleavage or its dissociation from ribosome subunits (Pong et al., 2018). MiRNA distinguishes between target mRNAs by using complementary sequences containing 2–8 nucleotides, located at the 5' end of the miRNA. These sequences are called seed sequences/ seed regions (Das et al., 2016; Jeker, Marone, 2015; Olejniczak et al., 2018; Pong et al., 2018). Those miRNAs that target the same mRNAs have the same seed regions (sequences) (Jeker, Marone, 2015). MiRNAs are presumed to control the expression of 30% to 60% of protein-coding genes in humans (Acuña et al., 2020; Das et al., 2016; Ojha et al., 2016). It was also found that a part of miRNAs can bind to the 5'-UTR fragment and to the ORF region, which increases the number of genes they regulate.

The expression of miRNAs can be regulated genetically or epigenetically (DNA methylation, modification of histone proteins) (Barbu et al., 2020; Das et al., 2016). MiRNA biogenesis takes place in several stages (Bartel, 2004; Olejniczak et al., 2018). The initial stages occur in the cell nucleus with the next stages taking place in the cytoplasm. MiRNA biogenesis begins with the transcription of genes encoding miRNAs via RNA polymerase II (RNA Pol II). As a result, the primary miRNA transcript (pri-miRNA) is produced. The resulting transcript is recognized by the Microprocessor complex consisting of the Drosha protein and DGCR8. After trimming by the Microprocessor, a miRNA transcript called precursor miRNA (pre-miRNA) is produced. Pre-miRNAs are transported from the cell nucleus to the cytoplasm by exportin-5 (XPO5). This process is catalyzed by RAN GTP hydrolysis. Then, the pre-miRNA binds to the Dicer protein and its partner protein TRBP and undergoes the process of converting into double-stranded miRNAs. So created molecule is loaded onto the Argonaute (Ago) and TNRC6A/B/C proteins to form the RNA-induced silencing complex (RISC) (Bartel, 2004). When all the above mentioned items are combined, one of the miRNA strands is discarded and degraded; the other becomes the mature miRNA molecule. RISCs and mature miRNAs combine complementarily with the target mRNA, resulting in gene silencing by degrading the mRNA or inhibiting its translation (Barbu et al., 2020; Dickey et al., 2017; Michlewski, Caceres, 2019; Olejniczak et al., 2018; Pong et al., 2018). There are also several alternative miRNA biogenesis pathways. Some of the miRNAs can be collected in the so-called clusters and transcribed together, others can be synthesized without the Dicer enzyme via the Ago2 protein (Jeker, Marone, 2015; Michlewski, Caceres, 2019; Olejniczak et al., 2018). However, these are not all of the possible alternative pathways for miRNA biogenesis.

MiRNAs control gene expression, but miRNAs themselves can also be regulated. The biogenesis of miRNAs may be affected by homeostasis abnormalities, which may interfere with its

production at every stage (Olejniczak et al., 2018). Stress or viral and bacterial infections are an example of factors causing the body imbalance (Drury et al., 2017; Olejniczak et al., 2018).

## Key miRNAs involved in immune regulation

As previously mentioned, miRNAs can affect many various processes. MiRNAs can regulate the mechanisms of both innate and adaptive immunity (Acuña et al., 2020). In the context of immunity, they, *inter alia*, influence the survival of the immune system cells, their differentiation and proliferation (Jeker, Marone, 2015).

MiRNAs affect the activity of many cells of the immune system, which can be observed, for example, in macrophages (Nazimek et al., 2015). MiRNA-17-5p, miRNA-20a and miRNA-106a regulate the biological activity of macrophages as early as in their differentiation and maturation phases. Also, miRNA-146a and miRNA-155 increase their expression during the differentiation of monocytes into macrophages, which shows they are necessary in this process. (Ahmed et al., 2016; Hukowska-Szematowicz, Deptuła, 2010; Nazimek et al., 2015). Interestingly, for example, the miRNA-146 molecule, the expression of which in macrophages is stimulated by the activation of TLR2, TLR4 and TLR5 receptors, inhibits the activity of macrophages M1, and thus also reduces an inflammatory response (Nazimek et al., 2015). The same miRNA molecule contributes to the immune tolerance of the body by inhibiting the production of pro-inflammatory cytokines in macrophages. MiRNA-155 is considered to be the key miRNA molecule involved in the regulation of immunity. This molecule, by targets and inhibits specific genes, affects a number of immune cells such as macrophages, B lymphocytes, T lymphocytes and their subpopulations and DC, NK cells. In these cells, it controls the secretion of inflammatory mediators (Dickey et al., 2017). It should be pointed out that the dysregulation of the above-mentioned processes can be affected by the development of inflammation caused by viral or bacterial infection present in the host organism (Das et al., 2016). In order to increase their pathogenicity and the chance of survival in the affected cells, pathogens, using the miRNAs they encode, cause changes in the mRNA expression of the infected cell (Das et al., 2016). This shows how pathogens themselves can influence the immune regulation and differentiation of immune cells in an infected organism. In the future, thanks to properly controlled miRNA expression in the cells of the immune system, it will be possible to regulate the host's time course of immune response to a pathogen (Barbu et al., 2020; Nazimek et al., 2015).

Several miRNAs are involved in regulating the maturation and differentiation processes of immunocompetent cells. A few types of miRNAs are involved in the development and activation processes of a single type of immune cells.

*MiRNA-146*. The production of miRNA-146 in macrophages is associated with the activation of TLR2, TLR4 and TLR5 receptors (Nazimek et al., 2015). MiRNA-146 inhibits the activity in of macrophages with M1 phenotype, which has also been proven in relation to other cells of innate immunity (Acuña et al., 2020; Nazimek et al., 2015). Moreover, in macrophages, miRNA-146 reduces the production of pro-inflammatory cytokines such as TNF- $\alpha$ , IL-1 $\beta$  and IL-6, thereby exhibiting a tolerogenic effect. Moreover, miRNA-146 was found to negatively affect IRAK1 and TRAF6, through which it affects the NF- $\kappa$ B and MyD88 signalling pathways (Ahmed et al., 2016; Barbu et al., 2020; Zhao et al., 2015).

*MiRNA-146a*. The expression of miRNA-146a has been shown to increase during the differentiation of monocytes into macrophages (Li et al., 2016; Nazimek et al., 2015). Increased production of this type of miRNA is induced during bacterial infection, in response to bacterial

lipopolysaccharide (LPS), and during interaction with IL-1 $\beta$  and TNF- $\alpha$ . Such overexpression may result in macrophages becoming tolerant to LPS, rendering them unable to participate in the immune response. The expression of miRNA-146a is also enhanced by contact with the *Candidia albicans* and *Listeria monocytogenes*, *Mycobacterium bovis* (Li et al., 2016; Nazimek et al., 2015). In infected cells, miRNA-146a, under the influence of *Mycobacterium tuberculosis*, suppresses the expression of inducible nitric oxide synthase (iNOS), which is responsible for inducing the production of nitric oxide (NO) in macrophages (Das et al., 2016; Li et al., 2016). This results in a reduction of NO production thereby favouring the survival of mycobacteria inside these cells (Li et al., 2016). The suppression of iNOS expression occurs by the suppression of NF- $\kappa$ B and mitogen-activated protein kinases (MAPK) pathways and reduction of the expression of TNF receptor-associated factor 6 (TRAF6) (Li et al., 2016; Zhang et al., 2019). However, the level of miRNA-146a in peripheral blood cells in patients infected with *M. tuberculosis* is reduced in mononuclear cells, which, *inter alia*, include B and T lymphocytes, NK cells and monocytes. It is worth emphasizing that within the same type of bacteria, the same miRNA molecule may activate different functions. Research also shows that miRNA-146a influences the host's immune response in viral infections (Zhang et al., 2019).

*MiRNA-150*. The production of this type of miRNAs in monocytes was reported, which resulted in a lower susceptibility of these cells to human immunodeficiency virus-1 (HIV-1) infection. It is one of the miRNAs that binds directly to HIV RNA (Ojha et al., 2016). MiRNA-150 influences the regulation of T lymphocyte metabolism and the cytokines produced by T lymphocytes (King et al., 2016). In Th1 lymphocytes stimulated by CD46, miRNA-150 is necessary for their regulation and activation and for the initiation of the IL-10 secretion process (King et al., 2016). MiRNA-150 regulates the c-Myb transcription factor (cellular Myb), which influences the development of B lymphocytes. An increase in the activation and proliferation of CD8<sup>+</sup> T cells is another process regulated by this molecule (Badalzadeh et al., 2019).

*MiRNA-155*. This molecule is referred to as the master regulator of inflammation (Mahesh, Biswas, 2019). The high expression of miRNA-155 was reported in monocytes, macrophages, T and B lymphocytes, NK cells and DC (Dickey et al., 2017; Herrera-Urbe et al., 2018; King et al., 2016). In the above-mentioned cells, miRNA-155 is responsible for regulating the secretion of chemokines, cytokines and transcription factors in such a way that the immune response is optimal (Dickey et al., 2017). An increased expression of miRNA-155 has been observed in response to contact with *Candidia albicans*, as well as in macrophages derived from mice after contact with LPS (*Listeria monocytogenes*, *M. tuberculosis*) (Das et al., 2016; Nazimek et al., 2015). In macrophages, miRNA-155 is one of several miRNAs that are responsible for modulating TNF- $\alpha$  secretion. In the same cells, the secretion of this miRNA induces the development of specific M1 phenotype, and additionally prevents the development of the M2 phenotype (Dickey et al., 2017; Nazimek et al., 2015). Blocking the M2 phenotype formation is associated with a reduction in the IL-13 receptor expression. In T cells, miRNA-155 causes an increase in IFN- $\gamma$  production and a decrease IL-2 production (Dickey et al., 2017). Moreover, it enhances the response of CD4<sup>+</sup> and CD8<sup>+</sup> T cells, which is dependent on IFN- $\gamma$  and is involved in the maturation of Treg lymphocytes. It was shown that in the absence of miRNA-155, T cell responses were reduced during infections caused by certain neurotrophic viruses (Dickey et al., 2017). Moreover, miRNA-155 affects the maturation of NK cells (Dickey et al., 2017). Its deficiency results in the production of less NK cells and has a negative impact on their survival (Dickey et al., 2017). Moreover, variable expression of this miRNA was reported during infection with HIV and IAV (Barbu et al., 2020; Chen et al., 2017; Zuo et al., 2017).

*MiRNA-223*. This molecule is responsible for inducing monocyte maturation (Ahmed et al., 2016). In addition, studies have shown that the expression of the *NLRP3*, which is also found in macrophages, is inhibited under the influence of miRNA-223. The protein encoded by this gene is responsible for maintaining the balance inside the cell. Together with the miRNA let-7i, it is responsible for regulating the TLR4 signalling pathway (Nazimek et al., 2015). Moreover, the production of miRNA-223 blocks the IL-1 $\beta$  production in macrophages (Nazimek et al., 2015). In CD8<sup>+</sup>T cells it increases the intensity of their proliferation and biological activity (Badalzadeh et al., 2019).

*Other miRNAs involved in immune regulation*. These include the miRNAs encoded by the Epstein-Barr virus (EBV) (Hartung et al., 2019; Wang et al., 2018; Zuo et al., 2017). HIV replication is inhibited by miRNA-133b, miRNA-138-5p, miRNA-326, miRNA-149-5p and miRNA-92a-3p (Balasubramaniam et al., 2018; Bernier, Sagan, 2018; Ojha et al., 2016). MiRNA-323, miRNA-491, miRNA-654, miRNA-584-5p and miRNA-1249 molecules reduce influenza A virus replication (Chen et al., 2017; Kumar et al., 2018; Zhao et al., 2015). MiRNAs belonging to the miRNA let-7 family are involved in the regulation of immunity in viral and bacterial infections (Ahmed et al., 2016; Rivera et al., 2016; Zhang et al., 2019). MiRNA-136 is responsible for the increase in the production of IL-6, IFN- $\alpha$ , IFN- $\beta$  and TNF- $\alpha$  (Zhao et al., 2015). MiRNA-301b reduces the influx of phagocytes into the inflammatory focus (Li et al., 2016). MiRNA-21, miRNA-146a and miRNA-155 affect the NF- $\kappa$ B transcription factor during infection with *Salmonella sp.* (Ahmed et al., 2016).

## The role of miRNAs in selected viral infections

### Epstein-Barr Virus (EBV)

Epstein-Barr virus belongs to the *Herpesviridae* family, and contain dsDNA genome (Annon, 2020b). EBV belongs to the group of oncogenic viruses. Studies on the presence of antibodies against EBV indicate that this pathogen is present in approximately 90% of the worldwide adult population (Hartung et al., 2019; Lewandowisz-Uszyńska et al., 2018; Wang et al., 2018). After entering the body, particles of this virus may not be completely destroyed, and as a result, remain latent in the body even for the host's entire life (Barbu et al., 2020; Wang et al., 2018; Zuo et al., 2017). As numerous studies have shown, the presence of latent EBV infection can result in the development of various malignant neoplasms, including Burkitt lymphoma, Hodgkin lymphoma, nasopharyngeal cancer and stomach cancer (Barbu et al., 2020; Wang et al., 2018; Zuo et al., 2017).

In 2004, EBV was the first virus found to encode miRNAs (Pfeffer et al., 2004). So far, EBV has been shown to encode 25 miRNA precursors and 44 mature miRNAs that can affect mRNAs of both host and virus cells (Bernier, Sagan, 2018; Wang et al., 2018; Zuo et al., 2017). Viral miRNAs are expressed from two regions of the viral genome, i.e. BART and BHRF1 (Hartung et al., 2019; Wang et al., 2018; Zuo et al., 2017). During a latent infection, the virus shows a reduced level of its own protein synthesis, but a high level of expression of non-coding RNA molecules, including miRNAs (Zuo et al., 2017). Studies show that EBV miRNAs affect the host's immunity-related genes (Wang et al., 2018). They are also responsible for maintaining latent viral infection. In addition, it has been observed that EBV miRNA biosynthesis is dependent on the host's transcriptional mechanisms and it does not show significant differences as compared to cellular miRNA synthesis (Wang et al., 2018; Zuo et al., 2017). The key mechanism which allows the virus to avoid the host's immune response is to prevent cells from presenting antigen, inhibit

T cell responses, and disrupt cytokine and chemokine signalling pathways (Wang et al., 2018). Another function of the miRNAs produced by EBV is to reduce the synthesis of viral membrane proteins. These proteins, i.e. latent membrane protein 1 (LMP1) and latent membrane protein 2A (LMP2A), are responsible for activating specific signalling pathways of the immune cells of the infected organism (Wang et al., 2018; Zuo et al., 2017). They are referred to as viral antigens that stimulate NF- $\kappa$ B signalling and the cytotoxic effect of CD4<sup>+</sup> and CD8<sup>+</sup> T cells (Bernier, Sagan, 2018). The LMP1 protein increases the proliferation and transformation of viral cells (Wang et al., 2018). The LMP2A protein exhibits the effect of antigen to which T cells respond (Wang et al., 2018).

EBV miRNA also regulates the host's innate immune response (Wang et al., 2018). One of the ways to control it is the effect of miRNA-BHRF1-3 on the inhibition of the activity of the C-X-C motif chemokine 11 (CXCL-11 chemokine) (Bernier, Sagan, 2018; Wang et al., 2018; Zuo et al., 2017). Under the influence of IFN, this chemokine engages and activates NK cells (Wang et al., 2018) and regulates the influx of T cells (Bernier, Sagan, 2018). Additionally, the interaction between CXCL-11 and C-X-C motif chemokine receptor 3 (CXCR3 receptor) (for which the chemokine is a ligand) is important from the viewpoint of Th1 effector cells. MiRNA-BART6-3p suppresses RIG-I protein signalling and thus also type I IFN reactions. The RIG-I protein belongs to the pattern recognition receptors (PRRs) (Wang et al., 2018). RIG-I also stimulates the type I IFN response, which affects the time course of viral infections, including EBV infections (Gołęb et al., 2018; Wang et al., 2018). Another miRNA, miRNA-BART2-5p, suppresses the expression of MHC class I chain-related molecule B (MICB) on the surface of cells containing EBV (Bernier, Sagan, 2018; Wang et al., 2018; Zuo et al., 2017). When the amount of MICBs on the cell surface is reduced it somehow protects the infected cells from the reaction of NK cells and T lymphocytes (Wang et al., 2018; Zuo et al., 2017). Moreover, miRNA-BART3-3p reduces the cytotoxic effect by suppressing the expression of importin 7 (IPO7) (Zuo et al., 2017). This protein influences the stimulation of T lymphocytes and immune tolerance. In addition, it has been observed in macrophages that after the decrease in the amount of IPO7 due to the effect of miRNA-BART3, the secretion of IL-6 is reduced (Zuo et al., 2017). EBV miRNAs can also control the expression of many cytokines (Wang et al., 2018). MiRNA-BHRF1-2-5p directly affects the IL-1 receptor 1 (IL1R1) and prevents the activation of IL-1 $\beta$  stimulated NF- $\kappa$ B. MiRNA-BART6-3p can regulate the expression of the receptor for the IL-6, which is involved in the regulation of the anti-infective response (Gołęb et al., 2018; Wang et al., 2018; Zuo et al., 2017). Moreover, IL-6 is a growth factor for B lymphocytes and has a stimulating effect on T lymphocytes. Furthermore, miRNA-BART1, miRNA-BART2, miRNA-BART22 and miRNA-BHRF1-2 inhibit the secretion of IL-12 (Wang et al., 2018; Zuo et al., 2017). This cytokine increases the secretion of IFN- $\gamma$  and TNF- $\alpha$  and is responsible for the activation of Th1 lymphocytes. The reduced activity of IL-12 caused by the above-mentioned miRNAs results in a decreased T cell response, differentiation and activation, thus increasing the survival of EBV-infected cells (Wang et al., 2018; Zuo et al., 2017). In EBV-infected cells, miRNA-BART20-5p and miRNA-BART8 affect the secretion of IFN- $\gamma$  (Zuo et al., 2017). It has also been shown that miRNAs produced by EBV regulate part of the genes responsible for antigen presentation to immune cells (Wang et al., 2018). The lysosomal enzymes of class II MHC cells, responsible for epitope modification, are often their targets. Their regulation is influenced by such miRNAs as: miRNA-BART1, miRNA-BART2 or miRNA-BHRF1-2. In turn, miRNA-BART1-5p affects lymphocyte antigen 75 (LY75) which is responsible for the presentation of the antigen on the surface of MHC molecules and for the stimulation of CD4<sup>+</sup> and

CD8<sup>+</sup> T cells. This may result in the avoidance of T lymphocyte responses by EBV-infected cells (Wang et al., 2018).

## Influenza Virus (IV)

Influenza virus belongs to the family *Orthomyxoviridae*, contain a single-stranded negative-sense RNA genome (Annon, 2020b). It causes respiratory symptoms, but also causes systemic symptoms by negatively affecting the respiratory system (Zhang et al., 2019). Due to the accumulation of numerous mutations in the viral genome during its replication, adaptive immunity is often insufficient to fight off infection (Brogaard et al., 2018). For this reason, IV present a new challenge to the immune system in each flu season. In humans, influenza A virus (IAV) is the most common cause of pneumonia-related death (Zhang et al., 2019). This virus is recognized by TLR-3, TLR-7, TLR-8 and RIG-I receptors (Brogaard et al., 2018; Kumar et al., 2018). In order to prevent an excessive immune response, the host organism produces factors that suppress signalling pathways such as suppressor of cytokine signalling 1–7 (SOCS1-7) and CUE domain-containing 2 (CUEDC2) (Kumar et al., 2018).

Comparative studies of miRNA expression in cells infected with IAV and control cells have shown an increase in the expression of microRNA- miRNA-21, miRNA-663b, miRNA-146a, whereas a decrease in the expression was reported for miRNA-211, miRNA-508-5p and miRNA-4298 (Zhang et al., 2019). These studies, indicated that, miRNA-146a has the greatest impact on IAV replication process. The said miRNA molecule contributes to an increase in viral replication in infected cells by suppressing the type I IFN (IFNs) response. Studies have shown that the decrease miRNA-146a expression in cells promotes the production of IFN- $\alpha$  and IFN- $\beta$ , the synthesis of which is stimulated by IAV (Zhang et al., 2019). MiRNA-146a and miRNA-146 modulate IFN synthesis by targeting the *TRAF6* and suppressing its expression (Chen et al., 2017; Zhang et al., 2019). Thus, miRNA-146a weakens the host's antiviral defence. In addition, miRNA let-7c, miRNA-33a and miRNA-302c have been shown to be involved in IV replication (Zhang et al., 2019). Furthermore, miRNA-485-5p (Kumar et al., 2018), miRNA-323, miRNA-491 and miRNA-654 (Chen et al., 2017; Zhao et al., 2015) inhibit IAV replication by interacting with the gene encoding PBI (Chen et al., 2017; Kumar et al., 2018). Moreover, miRNA-485-5p stimulates the antiviral response by increasing the stimulation of the signalling pathway mediated by the RIG-I receptor (Kumar et al., 2018). Studies have shown that during IAV infection, the miRNA-155 molecule acts as an immune regulator. The high expression of this molecule has been observed in macrophages (Chen et al., 2017). In these cells, miRNA-155, by affecting SOCS1 (on a feedback basis), increases IFNs signalling, which leads to the development of antiviral immunity. Studies have shown that during IAV infection, a reduction in miRNA-302a expression and an increase in the synthesis of interferon regulatory factor 5 (IRF-5) are observed (Chen et al., 2017). The latter factor is activated by the stimulation of TLR-7 or TLR-8 receptors. IRF-5 and plays an important role in the expression of type I IFN and pro-inflammatory cytokines IL-6, IL-8, IL-12 and TNF- $\alpha$ . Moreover, it is involved in the polarization of M1 macrophages. MiRNA-302a directly targets IRF-5 by suppressing its expression (Chen et al., 2017). It has also been observed that an increase in the amount of IRF-5 has a positive effect on the IAV replication process. During IAV infection, the reduction of miRNA-302a expression results in increased cytokine and chemokine synthesis and viral replication. The increased cytokine production leads to a "cytokine storm". During IAV infection, a decrease in the expression of let-7f miRNA has been observed, resulting in an increase in the production of IL-6 and IL-10 (Rivera et al., 2016). During infection with avian influenza

virus (H5N1), it was observed that this virus inhibited miRNA-324-5p expression (Kumar et al., 2018). This miRNA reduces replication of the influenza virus in infected cells by affecting the PB1 transcript. PB1 encodes one of the viral RNA polymerase subunits (Kumar et al., 2018). The host's miRNA molecules, i.e. miRNA-584-5p and miRNA-1249, target the gene encoding PB2 (the second subunit of viral RNA polymerase) thereby also negatively affecting its replication. According to studies, miRNA-324-5p also stimulates the host's innate antiviral immunity during H5N1 infection. This is because miRNA-324-5p targets the CUEDC2 transcript. CUEDC2 is the host's protein that affects the JAK-STAT signalling pathway. This pathway is responsible for the induction of type I and III IFN. Thus, CUEDC2 negatively influences the regulation of the antiviral response (Kumar et al., 2018). MiRNA-324-5p directly binds to the CUEDC2 inhibitor, suppressing its expression in the cell and increasing the body's immune response. Thus, this type of miRNA mediates in the increased synthesis of type I and III IFN during H5N1 infection (Kumar et al., 2018). In addition, miRNA-136 has also been shown to increase the production of IL-6, IFN- $\alpha$ , IFN- $\beta$  and TNF- $\alpha$  (Zhao et al., 2015).

### Human Immunodeficiency Virus (HIV)

The human immunodeficiency virus belongs to the *Retroviridae* family (Annon, 2020b). It is estimated that over 36 million people in the world are infected with HIV. The presence of HIV in the human body can lead to acquired immune deficiency syndrome (AIDS) (Balasubramaniam et al., 2018). The mechanism of viral pathogenesis is based on the attack and destruction of CD4<sup>+</sup> Th cells as well as monocytes, macrophages, DC (Balasubramaniam et al., 2018). So far, two types of virus have been distinguished: HIV-1 and HIV-2 (Barbu et al., 2020; Devadas et al., 2016; Flór, Blom, 2016). The HIV-2 type is less aggressive and is transmitted less frequently than the HIV-1 type (Devadas et al., 2016). In addition, a longer latency has been observed for HIV-2 type as compared to HIV-1 type (Devadas et al., 2016). In this study, most of the data collected relates to the HIV-1 type virus (hereinafter referred to as HIV) unless stated otherwise.

According to studies, viral replication in CD4<sup>+</sup> T cells does not start until their activation (Balasubramaniam et al., 2018). It is worth stressing that after activating infected cells, the amount of cellular miRNA negatively affecting viral RNA decreases in them. In studies on model cells, the effect of miRNA-132 on an increase in HIV replication in infected T cells has been observed (Balasubramaniam et al., 2018; Bernier, Sagan, 2018; Ojha et al., 2016). The increased expression of this miRNA also takes place in activated CD4<sup>+</sup> T cells (Bernier, Sagan, 2018). By directly affecting the viral RNA, MiRNA-133b, miRNA-138-5p, miRNA-326, miRNA-149-5p and miRNA-92a-3p reduce the virus replication by more than 40% (Balasubramaniam et al., 2018). In CD4<sup>+</sup> T cells, an increase in the expression of five cellular miRNAs, i.e. miRNA-28, miRNA-125b, miRNA-150, miRNA-223 and miRNA-382, that targets and inhibits viral mRNAs, has been observed (Balasubramaniam et al., 2018; Bernier, Sagan, 2018; Ojha et al., 2016). Upon activation of CD4<sup>+</sup> T cells, the expression of these miRNAs decreases, leading to reduced immunity of these cells to viral infection (Ojha et al., 2016). By affecting the mRNA of the virus, these particles contribute to reducing the amount of synthesized viral protein and progeny virions. The part of the miRNAs expressed in CD4<sup>+</sup> T cells targets mRNA encoding viral genes (*nef*, *vpr*, *vif* or *vpu*) and cellular factors (cyclin T protein and receptors necessary for virus to enter into the cell) (Ojha et al., 2016; Ortega et al., 2018). Cellular miRNA-29a, which affects the mRNA of the virus by suppressing its expression thus reducing its replication and infectivity, is also highly expressed in T lymphocytes infected with the virus (Balasubramaniam et al., 2018; Modai



et al., 2019; Ortega et al., 2018). Additionally, miRNA-146a/b increases during viral infection and reduces the NF- $\kappa$ B pathway signalling by targeting TNF receptor-associated factor 6 (TRAF6) (Barbu et al., 2020). Four of the five miRNAs mentioned above (excluding miRNA-223) were also detected in macrophages and monocytes (Nazimek et al., 2015). It was found that these molecules, as compared to macrophages, are more expressed in monocytes, which means that the latter are more resistant to HIV infections (Nazimek et al., 2015). The presence of two other miRNAs, i.e. miRNA-221 and miRNA-22, has been confirmed in macrophages. These miRNAs limit the possibility for HIV to enter the cell (Balasubramaniam et al., 2018). Research shows that miRNA-155 is also involved in controlling the spread of the virus, *inter alia*, by influencing the polarization of macrophages (Dickey et al., 2017). MiRNA-155 promotes macrophage differentiation towards the M1 phenotype, which is more resistant to HIV infection (Dickey et al., 2017). Moreover, miRNA-155 reduces the possibility of HIV binding to dendritic cells (Dickey et al., 2017; Ojha et al., 2016). The same miRNA inhibits the NF- $\kappa$ B pathway thus contributing to the maintenance of latent infection (Barbu et al., 2020). MiRNA-155 can influence HIV-1 replication by acting on factors involved in the development of infection in both the host and virus itself (Dickey et al., 2017). Increased expression of miRNA-155 has also been demonstrated after the stimulation of TLR3 receptors in macrophages (Dickey et al., 2017). Other studies have shown that this type of miRNA is involved in the transcriptional silencing of HIV-1 in T cells by acting on the host factor - tripartite motif-containing protein 32 (TRIM32) and E3 ubiquitin ligase. Through the agency of them, the factor NF- $\kappa$ B is stimulated, which affects the virus transcription. Moreover, the increased expression of miRNA-155 leads to a reduction of dendritic cell-specific intercellular adhesion molecule-3 grabbing nonintegrin (DC-SIGN) receptors on the surface of dendritic cells, which prevents the virus from binding to these cells (Dickey et al., 2017). MiRNA-155 may also bind to the HIV-1 genome and reduce the expression of viral genes (Dickey et al., 2017). HIV is presumed to encode its miRNAs (Balasubramaniam et al., 2018; Barbu et al., 2020). Five regions that can encode viral miRNAs have been identified in the viral genome. The miRNAs encoded from one of these regions are miRNA-TAR-5 $\beta$  and miRNA-TAR-3 $\beta$ . They are expressed in infected CD4<sup>+</sup> T cells. The function of these miRNAs is to prevent cell apoptosis and stimulate viral replication (Balasubramaniam et al., 2018; Barbu et al., 2020; Bernier, Sagan, 2018). However, the existence of these two types of miRNAs is debatable. Currently, researchers assume that HIV neither encodes any miRNAs nor strongly influences cellular miRNA expression, at least at the beginning of infection.

## The role of miRNAs in selected bacterial infections

### *Salmonella* Typhimurium

*Salmonella* is an intestinal gram-negative bacteria belonging to the *Enterobacteriaceae* family (Busse et al., 2012). It is classified as an absolute intracellular pathogen (Szewczyk et al., 2013; Zhou et al., 2018). Its presence in the body may lead to the development of typhoid fever or gastroenteritis (Naveed et al., 2017; Zhou et al., 2018). It is usually transmitted through food (mainly on products of animal origin contaminated with faeces) (Herrera-Uribe et al., 2018; Szewczyk et al., 2013). There are three main serotypes of *Salmonella*: Typhi, Typhimurium and Enteritidis (Zhou et al., 2018). This study deals with the serotype of *Salmonella* Typhimurium. This species of bacteria is most often isolated on products that are potential vectors of *Salmonella* infection (Herrera-Uribe et al., 2018). The bacterium under consideration is one of the causes

of salmonellosis in humans (Szewczyk et al., 2013). Studies show that abnormalities in miRNA function influence the pathogenesis of infection with this bacterium (Zhou et al., 2018).

According to research, bacteria of the genus *Salmonella* can regulate miRNAs in epithelial cells and in macrophages (Ahmed et al., 2016). In the above-mentioned cells, *Salmonella* Typhimurium changes the expression of miRNA-15, miRNA-21, miRNA-146a, miRNA-155 and let-7. In that case the expression of miRNA-146a is upregulated and the expression of let-7 is downregulated (Herrera-Uribe et al., 2018; Naveed et al., 2017). Mentioned molecules affect the genes that regulate the cell cycle, the proliferation of B and T lymphocytes, and the inflammatory response of the body (Herrera-Uribe et al., 2018). After detection, by TLR4 receptors, of LPS from *Salmonella* the expression of miRNAs from the miRNA let-7 family is reduced, *inter alia*, in macrophages (Ahmed et al., 2016; Huang et al., 2019; Naveed et al., 2017; Yao et al., 2015; Yao et al., 2016; Zhou et al., 2018). The reduced expression of the above miRNAs increases the production of IL-6 and IL-10, which are involved in immunity regulation (Ahmed et al., 2016; Naveed et al., 2017; Yao et al., 2015; Yao et al., 2016; Zhou et al., 2018). After infection with this bacteria, an increase in the expression of miRNA-155 in macrophages has been observed (Herrera-Uribe et al., 2018). On the other hand, after *Salmonella* Typhimurium infection the expression of miRNA-155 is reduced in macrophages, it's reduces the host's immune response through the influence of this molecule on lymphocytes and dendritic cells (Zhou et al., 2018). Studies have confirmed that in the absence of miRNA-155, the specific immune response is significantly reduced (Ahmed et al., 2016). This is due to aberrant antigen presentation by dendritic cells to B and T lymphocytes. The reduction of miRNA-155 synthesis in B cells also affects the levels of immunoglobulin G class (IgG1) antibodies produced by these cells. After *Salmonella* infection, three miRNAs: miRNA-21, miRNA-146a and miRNA-155 strongly affect the NF- $\kappa$ B transcription factor, thus reducing the regulation of B and T lymphocyte proliferation (Ahmed et al., 2016). It has been observed that miRNA-214 and miRNA-331-3p are involved in *Salmonella* Thypimurium infection, and they play a part in the regulation of the host immune response (Herrera-Uribe et al., 2018; Zhou et al., 2018). A decrease in miRNA-214 expression and an increase in miRNA-331-3p expression were demonstrated (Zhou et al., 2018). Moreover, it has been proven that during infection with *Salmonella* bacteria in human monocytes there is an increase in the expression of miRNA molecules such as: miRNA-23b, miRNA-24, miRNA-27a, miRNA-29 and miRNA-222 (Ahmed et al., 2016). In the case of *Salmonella* Typhimurium infection, it has been observed that the time course of the inflammatory response is regulated by TNF- $\alpha$  mediated miRNA-125a/b (Herrera-Uribe et al., 2018). These miRNAs have been shown to negatively affect TNF- $\alpha$  production (Herrera-Uribe et al., 2018; Yao et al., 2016). It has also been proved that miRNA125a/b affects proteins involved in the MHC class I antigen presentation. Proteins involved in regulation include proteasome subunit beta type-8 (PSMB8), protein disulfide isomerase family A member 3 (PDIA3) and heat shock protein 90 beta family member 1 (HSP90B1) (Herrera-Uribe et al., 2018). The PSMB8 protein is involved in the inflammatory response and cell death. MiRNA-125a/b regulates the secretion, by macrophages, of effector molecules such as nitrogen intermediates, reactive oxygen species, and cytokines - IL1 $\beta$ , IL6 or TNF- $\alpha$ . Moreover, the effects of miRNA-148a/b on the HSP90B1 protein and miRNA-1 on the PDIA3 protein have been observed (Herrera-Uribe et al., 2018).

### *Pseudomonas aeruginosa*

*Pseudomonas aeruginosa* belongs to the *Pseudomonadaceae* family of opportunistic gram-negative bacteria (Busse et al., 2012). This bacterium is the aerobic, which is most often isolated

from the genus of *Pseudomonas* (Zhou et al., 2018). This bacteria is one of the leading causes of contact lens-associated bacterial keratitis (Muraleedharan et al., 2019; Xu, Hazlett, 2019). Moreover, in immunocompromised persons or those suffered from cystic fibrosis, it also causes chronic and acute respiratory infections (Shin et al., 2017).

Studies have shown that miRNA-155 expression increases during *P. aeruginosa* corneal infection (Xu, Hazlett, 2019). Its presence increases the tissue susceptibility to the development of inflammation. MiRNA-155 reduces the ability of macrophages to phagocytose and inhibits intracellular killing processes (Xu, Hazlett, 2019). The effect of the miRNA-183/96/182 cluster on the time course of infection caused by *P. aeruginosa* has also been observed (Xu, Hazlett, 2019). During infection, lowering the activity of miRNA-183/96/182 leads to a reduction in the inflammatory response in the cornea (Muraleedharan et al., 2019; Xu, Hazlett, 2019). Whereas, a decrease in the activity of miRNA-183/96/182 or its absence results in the stimulation of the phagocytosis process and intracellular killing of bacteria in macrophages and neutrophils (Muraleedharan et al., 2019; Xu, Hazlett, 2019; Zhou et al., 2018). An increase in the activity of these mechanisms is caused by the influence of miRNA-183/96/182 on the increase of the efficiency of synthesis process of reactive oxygen and nitrogen species. It has also been observed that the miRNA-183/96/182 cluster increases the level of proinflammatory cytokines in macrophages in response to *P. aeruginosa* corneal infection (Muraleedharan et al., 2019; Xu, Hazlett, 2019). It has also been shown that this cluster is expressed in innate immunity cells and during the differentiation of Th17 lymphocytes (Xu, Hazlett, 2019). This cluster promotes Th17 lymphocyte response and stimulates the production of pro-inflammatory cytokines. The miRNA-183/96/182 cluster targets the *DAPI2* (which is synonym for the transmembrane immune signalling adapter (*TYROBP*) gene) whose macrophage expression contributes to the reduction of cytokine production in response to *P. aeruginosa* (Muraleedharan et al., 2019). The *DAPI2* is also found on the surface of NK cells. By lowering the cluster expression that occurs during the infection with the bacterium in question, the expression of the *DAPI2* increases thus resulting in extinguishing the immune response by reducing the production of cytokines by macrophages. Another gene that the miRNA-183/96/182 cluster targets is NADPH oxidase 2 (*Nox2*). The *Nox2* is an enzyme necessary for the production of reactive oxygen and nitrogen species (Muraleedharan et al., 2019). Pulmonary *P. aeruginosa* infection also leads to the lung tissue inflammation development (Li et al., 2016). Studies in mice have shown that during infection, the expression of miRNA-301b is increased under the influence of LPS (Huang et al., 2019; Li et al., 2016). The same studies have shown that after infection with the bacterium in question, miRNA-301b-m (chemically synthesized miRNA-301b) reduces the recruitment of neutrophils. Therefore, miRNA-301b is also presumed to inhibit the early recruitment of phagocytes to the focus of inflammation (Li et al., 2016). The appearance of neutrophils at the site of inflammation is associated with an increase in the immune response in this area. The same miRNA-301b-m decreased the secretion of pro-inflammatory cytokines, i.e. IL-4 and TGF- $\beta$ 1, by macrophage cells (Li et al., 2016). In the same study, miRNA-301b was found to target the c-Myb transcription factor (Li et al., 2016; Zhou et al., 2018). The c-Myb expression decreases after bacterial infection and is further decreased by the miRNA-301b activity. According to research, c-Myb influences the production of IL-4 and TGF- $\beta$ 1, and its lack suppresses their release (Li et al., 2016). Moreover, the same studies have shown that influx of CD4<sup>+</sup> T cells into the lungs under the influence of *P. aeruginosa* infection was inhibited by miRNA-301b-m. miRNA-301a is also presumed to produce similar effect as miRNA-301b on the release of IL-4 in macrophages (Li et al., 2016).

## *Mycobacterium tuberculosis*

*Mycobacterium tuberculosis* belongs to the *Mycobacteriaceae* family (Busse et al., 2012) and is one of the best studied intracellular mycobacteria. Approximately one third of the human population is infected with this bacteria (Kumar et al., 2015; Szewczyk et al., 2013; von Both et al., 2018). Tuberculosis caused by *M. tuberculosis* most often affects the lungs, although its extrapulmonary forms also occur (Szewczyk et al., 2013). Infection with these microorganisms occurs through droplets or dust particles (Szewczyk et al., 2013). Mycobacteria multiply in macrophage cells, which are subsequently destroyed and phagocytosed by subsequent macrophages and other phagocytic cells (Szewczyk et al., 2013). *M. tuberculosis* may remain latent in the host's organism (Kumar et al., 2015; Szewczyk et al., 2013). In order to increase survivability in infected cells, mycobacteria suppress the processes leading to phagolysosome formation in the cell (Szewczyk et al., 2013; von Both et al., 2018). In addition, *M. tuberculosis* developed other mechanisms for intracellular survival: suppression of antigen presentation and deregulation of class II MHC system (von Both et al., 2018).

Research shows that the regulation of immunologic factors is influenced by miRNA-223 (Zhou et al., 2018). This molecule modifies the time course of *M. tuberculosis* infection by regulating the influx of neutrophils to the site of inflammation. Its level in the blood of infected patients is significantly elevated (Das et al., 2016). It is also presumed that the increased expression of miRNA-223 lowers the level of chemokine (C-C motif) ligand 3 (CCL3), chemokine (C-X-C motif) ligand 2 (CXCL2) and IL-6 (Das et al., 2016). After infection with *M. tuberculosis*, miRNA-155 expression increases in macrophage cells and other affected cells (Ahmed et al., 2016; Das et al., 2016; Zhou et al., 2018). This miRNA increases the influx of macrophages to the site of infection and the production of reactive oxygen species, thereby reducing the intracellular survival of mycobacteria (Zhou et al., 2018). In addition, miRNA-155 stimulates apoptosis in infected cells through the agency of TLR2 and NF- $\kappa$ B signalling pathways. The same miRNA molecule may also have a favourable effect on the survival of mycobacteria in macrophages (Das et al., 2016; Zhou et al., 2018). This is, *inter alia*, achieved by inhibiting the expression of one of the zinc finger domains BTB or SHIP1 (SH2-domain containing inositol polyphosphate 5-phosphatase 1), which shows phosphatase activity (Zhou et al., 2018). Moreover, miRNA-155 increases survival and enhances the functions of T cells specific to *M. tuberculosis* infection (Zhou et al., 2018). It has also been observed that reducing the level of miRNA-155 in human macrophages inhibits the production of TNF- $\alpha$  (Ahmed et al., 2016; Das et al., 2016). Additionally, studies have shown that *M. tuberculosis* inhibits TNF- $\alpha$  production by upregulating miRNA-125b expression (Das et al., 2016). Studies have shown that *M. tuberculosis* inhibits miRNA let-7f expression (Ahmed et al., 2016; Das et al., 2016; Kumar et al., 2015; Zhou et al., 2018). The let-7f miRNA regulates the mRNA of the factor inhibitor NF- $\kappa$ B - A20. The A20 protein is a feedback inhibitor of the NF- $\kappa$ B pathway (Kumar et al., 2015). In this way, the tubercle bacilli increase their survivability in the affected cells (Das et al., 2016). The role of miRNA-144 in the immune response to mycobacterial infection was also demonstrated experimentally (Ahmed et al., 2016). MiRNA-144 reduces the synthesis of TNF- $\alpha$  and IFN- $\gamma$  and inhibits the proliferation of T lymphocytes. The MiRNA-146a expression is also increased during *M. tuberculosis* infection. This molecule, through the signalling pathways TLR/NF- $\kappa$ B and interleukin-1 receptor-associated kinase-1 (IRAK-1), reduces the secretion of pro-inflammatory cytokines: TNF- $\alpha$ , IL-1 $\beta$ , IL-6 and monocyte chemoattractant protein 1 (MPC-1) chemokine (Das et al., 2016). During infection with this bacterium, the levels of miRNA-26a and miRNA-132 are increased, which indirectly contribute to the reduction of IFN- $\gamma$

in macrophages. Additionally, an increase in the miRNA-206 expression has been observed, which increases the secretion of pro-inflammatory cytokines- IL-1 $\beta$ , IL-6, IFN- $\gamma$ , TNF- $\alpha$  and matrix metalloproteinase 9 (MMP9) (Das et al., 2016). It is presumed that *M. tuberculosis* increases the miRNA-99b expression in DC and macrophages, the presence of which in these cells suppresses the release of pro-inflammatory cytokines (IL-1 $\beta$ , IL-6, IL-12 and TNF- $\alpha$ ) and increases the severity of infection (Ahmed et al., 2016; Das et al., 2016; Zhou et al., 2018). In addition to the TNF- $\alpha$  receptor genes, MiRNA-99b also targets the tumour necrosis factor receptor superfamily member 4 (TNFRSF-4) genes (Das et al., 2016). Research confirms that *M. tuberculosis* avoids immune response by increasing the miRNA-381-3p expression (Das et al., 2016). MiRNA-381-3p reduces the amount of CD1 antigen on the surface of infected dendritic cells (Das et al., 2016). This antigen is responsible for the presentation of *M. tuberculosis* antigens to T lymphocytes (Das et al., 2016; Gołab et al., 2018).

## Conclusion and perspectives

This article shows that miRNAs affect a number of processes related to immune regulation during viral and bacterial infections. This affect cannot be clearly defined as negative or positive. As we showed in our work depending on the type of infected cell or the infectious agent, the same miRNA can have different effects. In addition, miRNAs represent an exceptionally promising research object due to the diversity of their biological potential. They can be used not only as diagnostic material, but also as a therapeutic objective in the treatment of various diseases. Research on the influence of miRNAs on the course of the immune response during viral and bacterial infections provides more and more new evidence that miRNAs can be used in the future in immunological therapies. In the future, these molecules may provide an alternative to the traditional treatment of bacterial infections with antibiotics. More and more studies report the possibility of inhibiting or even combating, by means of miRNA regulation, infections with bacterial strains resistant to antibiotics.

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