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Review article

Circular RNAs as a novel layer of regulatory mechanism in multiple sclerosis

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ABSTRACT

Multiple sclerosis (MS) is believed to be an autoimmune disease of the central nervous system (CNS) in which autoreactive immune cells recognizing myelin antigens lead to demyelination and axonal injury. Mechanisms inducing and controlling the pathogenesis of MS have not been fully elucidated. Recent studies suggest an important role of epigenetic processes during the development of MS. One of the most significant discoveries in the field of epigenetic contribution to immune response has been the recognition of a group of microRNAs (miRNAs). These single-stranded non-coding RNA molecules regulate the expression of genes encoding proteins and have already been shown to be involved in pathogenesis of MS. Some miRNAs enhance generation of pro-inflammatory immune cells by promoting Th1 and Th17 pathways and others contribute to regulatory and tissue repair processes. The miRNA-dependent controlling process of autoimmune reactions is highly complex because of miRNA redundancy and multitarget nature of most of these molecules. Recently it was discovered that circular RNAs (circRNA) representing a new class of RNA possess a unique ability to control miRNAs by blocking their activity. CircRNAs are called natural miRNA "sponges" as the single circRNA molecule is able to neutralize several miRNAs and thus might determine the availability of miRNAs for their posttranscription regulation. Thus, circRNAs emerged as critical factors in epigenetic regulation of many human diseases including MS. In addition, in contrary to other RNA species they are very stable in the blood and other biological fluids and thus might be considered as a candidate for a biomarker of MS.

1. Introduction

Despite the unequivocal progress that has been made in the understanding of the immunology of MS in recent years, the precise mechanisms underlying the development of autoimmune demyelination continue to be clarified. In light of the relative failure in the search for genetic contribution to MS (Munoz-Culla et al., 2013) the interest in studies on MS predisposition has shifted to environmental and epigenetic factors (Kucukali et al., 2015; Ridolfi et al., 2013). Although several processes and factors linked with environment impact on MS are being extensively investigated and numerous interesting correlations have been found these mechanisms are still not explaining the emergence of this condition (Alrouji et al., 2018; Guan et al., 2019; Leichsenring et al., 2018; McLaughlin et al., 2018; Tiwari et al., 2018). Therefore epigenetic factors draw a lot of attention for the analysis of autoimmune demyelination. An important epigenetic mechanism depends on endogenous posttranscriptional regulation. One of the most significant discoveries in recent years in this field has been the recognition of a group of small non-coding RNA molecules named microRNAs (miRNAs). These are single-stranded non-coding RNA molecules, 21–23 nucleotides in length that regulate the expression of genes encoding proteins and are involved in multiple basic biological processes. Several recent studies implicated miRNAs in the pathogenesis of MS (Guerau-de-Arellano et al., 2012; Selmaj et al., 2017; Zeng et al., 2014) and EAE (Mycko et al., 2012; O'Connell et al., 2010). However, one of the major problems in miRNA study and the understanding of their contribution to the disease mechanisms is their high redundancy in biological activity as well as their capabilities to target several transcripts. Thus, it would be very advantageous to identify a molecular mechanism controlling miRNA availability for their posttranscriptional regulation. Recent studies suggest that such a miRNA controlling mechanism might be provided by circular RNA (circRNA), another group of novel RNA molecules. CircRNAs have been described several years ago but only recently has their biological significance been confirmed in many studies on human diseases including autoimmune conditions. In addition to their important role in the posttranscriptional regulatory processes, circRNAs have also been proposed as a candidates for disease biomarkers based on their unique stability in the blood and other biological fluids. With an increasing need for a solid and reproductible biomarker of MS the circRNAs properties might be of particular relevance to this disease.

In this review, we shall evaluate the role of circRNAs in the pathogenesis of MS and will highlight their potential to serve as biomarkers in this disease.

2. Circular RNAs biosynthesis and structure

CircRNAs are a novel and unique class of endogenous RNAs whose

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discovery added another layer of amazing complexity to human genetics. The existence of circRNAs, described as single-stranded covalently closed RNA molecules was first reported by Sanger et al. (1976). It was demonstrated that plant pathogenic viroids were unable to be enzymatically labeled at their 5′ or 3′ ends thus suggesting their closed structure (Sanger et al., 1976). In 1979 it was established by electron microscopy that eukaryotic RNAs can also exist in circular form (Hsu and Cocaprados, 1979). The first detection of circRNA in humans was the hepatitis delta virus (HDV) (Kos et al., 1986). In the 1990s a handful of endogenous circular RNAs were reported, including DCC (Deleted in Colorectal Carcinoma) (Nigro et al., 1991) and ETS-1 transcripts (Cocquerelle et al., 1993). Nevertheless, at that time those transcripts did not receive much attention due to their low abundance. They were found to be expressed at much lower levels compared to the dominant canonical linear isoform. Therefore, initial circRNAs were considered as by-products of RNA splicing or regarded as a splicing error (Chen et al., 2016b; Cocquerelle et al., 1993). Subsequently it was discovered that the circular mouse Sry transcript (Capel et al., 1993) was expressed at higher levels than its corresponding linear form. Before the new era of RNA detection by high throughput sequencing methods only a few more circRNAs were identified e.g.: cytochrome P450 2C24, human cytochrome P450 2C18 (Zaphiropoulos, 1993) and human dystrophin genes (Surono et al., 1999), INK4/ARF (Burd et al., 2010) Fmn (Chao et al., 1998). In past years the interest in circular RNAs has resurfaced. High-throughput sequencing of ribosome-depleted RNA combined with developed computational tools enabled detection of numerous circular RNAs in all organisms (Jeck et al., 2013; Memczak et al., 2013; Salzman et al., 2012; Wang et al., 2014).

Until recently circRNAs were considered non-protein coding and classified as a subclass of long noncoding RNAs (lncRNAs). However, it has been demonstrated that a group of circRNAs are associated with ribosomes and can be translated challenging a dogma of their non-proteing coding nature (Pamudurti et al., 2017). circRNAs consist of covalently closed loops lacking the terminating 5′-cap and 3′-poliadenylated tail. They result from non-canonical alternative splicing. It is a process in which a downstream 5′ splice site (splice donor) is joined to an upstream 3′ splice site (splice acceptor) (Jeck and Sharpless, 2014; Wilusz, 2015) (Fig. 1). The biogenesis of circRNAs is not fully understood, but it is suggested that there are four paths involved in formation of circRNAs: exon skipping (also called 'lariat intermediate' or 'lariat-driven' circularization), intron pairing (also called direct back-splicing), protein factors associated circulation path and spliceosome-dependent circulation path. These mechanisms promote the biogenesis of circRNAs that can be summarized by the term "back-splicing"(Dragomir and Calin, 2018).

The most common classification of circRNA is the one focusing on their origin. Accordingly circRNAs can be categorized into three types: exonic circRNAs (ecircRNAs), intronic circRNAs (ciRNAs) and exon-intron circRNA (EIcircRNAs). EcircRNAs includes all circRNAs that are exclusively composed of one or more exons. They represent the largest class of circRNAs. Most ecircRNAs comprise between one and five exons (Memczak, Jens, 2013). The length of ecircRNAs can range from hundreds to thousands of nucleotides (nt), while their average estimated length is around 547 nt (Guo et al., 2014). Most often, the exons that participate in circRNA formation are long and may be three times as long as an average expressed exon (Jeck, Sorrentino, 2013). Most ecircRNAs are located in cytoplasm (Zhang et al., 2018b). CiRNAs are a much smaller fraction of circRNAs. They are composed of two or more connected introns. They often possess lariat-like structures with 2′-5′-phosphodiester bond. CircRNAs that originate from intron circularization predominantly localize in the nucleus. It may suggest possible differences in function between intronic and exonic circRNAs (Zhang et al., 2013). Exon-intron circRNAs consist of introns that have been retained between circularized exons. They are localized in nucleus and it is hypothesized that they may promote transcription (Li et al., 2017b). Beyond the above, another classification was proposed based on the relationship of circRNA to adjacent coding RNA. Here circRNAs are classified into five types: exonic, intronic, antisense, sense overlapping and intergenic (Liu et al., 2017). Overall circRNA appear as a complex group of transcripts probably reflecting their non-uniform biological role.

3. Circular RNA function

Research on circRNAs became particularly interesting in recent years with constantly growing scientific information revealing their unique features and their role in different biological processes. Aberrant expression of many circRNAs has been detected in several human

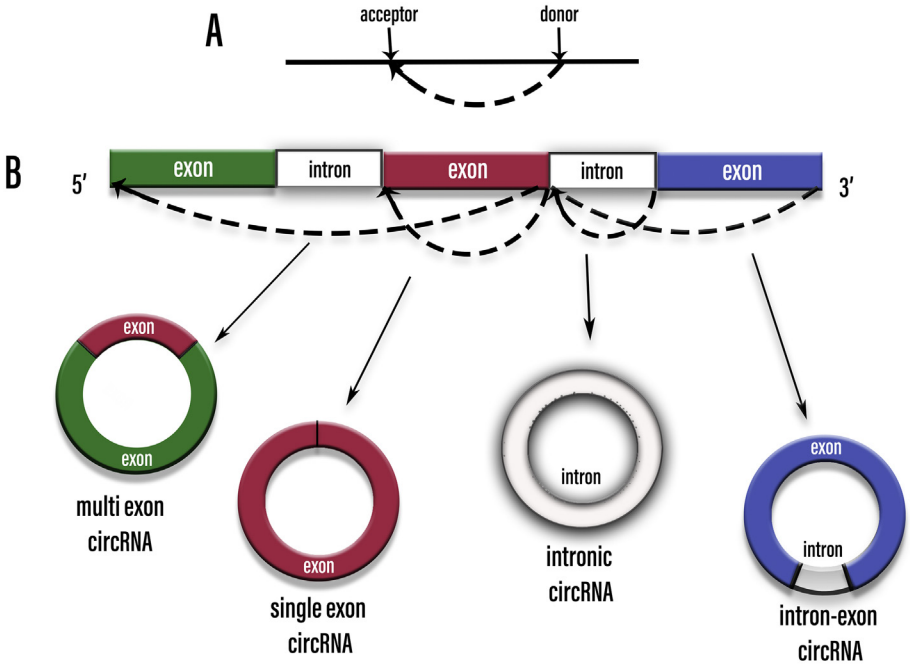

Fig. 1. Backsplicing mechanism of circRNA generation.

diseases, including cancers, neurodegenerative, autoimmune and infectious diseases; suggesting their role in the mechanisms leading to these conditions (Qian et al., 2018). CircRNAs possess several interesting properties. The correlation between cell division rates and abundance of circRNA is particularly intriguing. It has been thoroughly documented that there is a higher accumulation of circular RNAs in low-proliferating cells, such as neurons, than in highly proliferating cells (Bachmayr-Heyda et al., 2015). These results are supported by the observation of high abundance of circular RNAs in the brain versus other organs like the liver or thyroid gland both in mice and humans (Rybak-Wolf et al., 2015). It has been hypothesized that in proliferating cells the number of circular RNAs from the parent cells are divided between the daughter cells, reducing the number of circular RNA (Bachmayr-Heyda, Reiner, 2015).

The enrichment of circRNAs in cytoplasm and their extensive complementarity to linear miRNA counterparts raises the possibility that circRNA might exert their functions by binding to miRNA (Jeck and Sharpless, 2014). miRNA are single stranded, small non-coding RNA molecules that regulate gene expression and protein synthesis and are involved in fundamental biological processes like development, cell differentiation, proliferation and cell death and also in several pathological events like cancer, neurodegeneration and autoimmunity (Bartel, 2004; Esteller, 2011). Nearly one-third of human messenger RNAs might be targeted by miRNAs. miRNA have been intensively studied in the context of biomarker properties for several diseases and nearly one hundred circulating miRNAs have been proven to be able to distinguish diseased individuals from healthy subjects (Zeng et al., 2014).

Given the circRNA correlation with miRNAs, circRNAs have been intensively studied as a miRNA regulators. Indeed circRNA emerged as critical posttranscriptional regulators of gene expression by binding of miRNAs and buffering their repression of mRNA targets (Fig. 2). Since single circular RNA might bind to several miRNAs and have several biding sites for individual miRNA the buffering repression mechanisms have been called a 'sponge' type-of interaction (Hansen et al., 2013a, 2013b; Tay et al., 2014). The first identified miRNA sponge was ciRS-7 (also known as CDR1as) which was generated from the cerebellum degeneration- related protein 1 antisense transcript (CDR1) (Zheng et al., 2017a, 2017b).

ciRS-7 contains > 70 conserved binding sites for miR-7 and hence acts as an effective miR-7 sponge that affects miR-7 target gene activity. In zebrafish, its expression impaired midbrain development in a manner analogous to miR-7 knockdown (Memczak et al., 2013). ciRS-7 is highly abundant in the human brain, and is associated with a brain-specific miRNA (miR-7). Another example of circRNA with a sponge-like activity is Sry transcript. This circRNA has 16 binding sites for miR-138 (Capel et al., 1993). It has been shown that Sry dependent inhibition of this miRNA resulted in severe impairment of miRNA-138 mediated mechanisms in the brain. Furthermore evidence for the circRNAs spongy type of activity that counter balance the miRNA effect came from macrophage polarization studies (Zhang et al., 2017b) as well as other immune functions analyses (Cadena and Hur, 2017; Chen et al., 2017; Yang et al., 2018a). The above results implicate the particularly important role of circRNA sponge mechanisms in the immune processes and immune mediated disorders. In addition, it was shown that circRNA might influence the post-transcriptional regulation via other miRNA-independent, mechanisms. Specifically, circRNA might be responsible for binding and sequestering RBPs (RNA binding proteins), base pair with other that miRNA types of transcripts, and regulate translation or production of proteins (Jeck and Sharpless, 2014).

Another intriguing feature of circRNAs is that in contrast to regular RNAs which are not known to be generally stable due to high abundance of RNA endonuclease (e.g. serum their half-life times are < 15 s), circRNAs are extremely stable inside the cells, with most species exhibiting a half-life time over 48 h. This results from circRNA resistance to RNA degrading enzymes due to the lack of RNA ends (Cocquerelle et al., 1993). The high stability of circRNAs facilitate to extend their interactions with miRNA and to optimize their miRNAs sponge type regulatory activity. The long half-lifes of circRNA make them more attractive candidates for biomarkers of many diseases. From the standpoint of biomarker activity of circRNAs it is significant that these molecules have been found in serum extracellular vesicles including exosomes (Li et al., 2015). Thus, circRNA might be involved in the exosome communication network between cells within the same tissue as well as between different organs. All this data make circRNAs an excellent candidate for biomarker investigations.

4. Circular RNA and brain function

The importance of circRNA in nervous system function was initially pointed out by the dis-covery that expression of circRNAs in the brain are the highest among all organs (Memczak et al., 2015). In rodent and human brains > 10,000 different cirRNAS have been identified (Hanan et al., 2017). This observation strongly suggests that circRNAs might play an important role in brain function and likely in brain diseases (Ashwal-Fluss et al., 2014). circRNAs demonstrated high conservancy

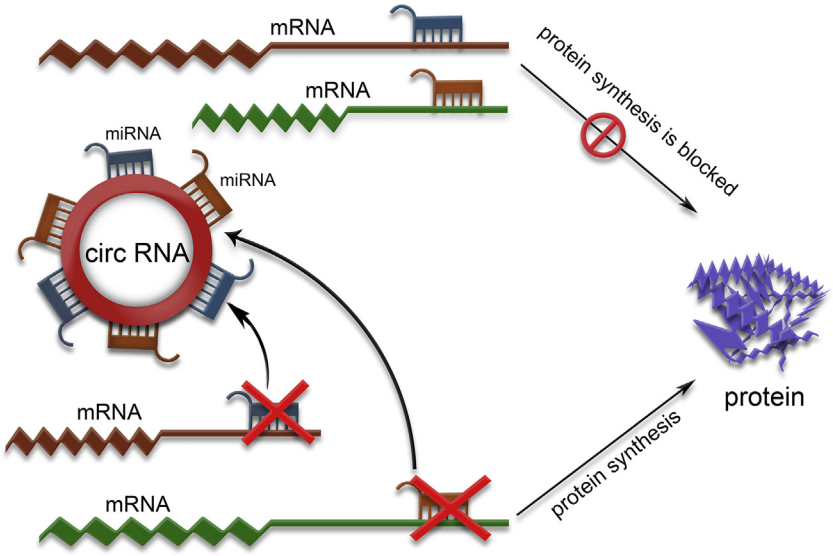

Fig. 2. Mechanism of circRNA inhibition of miRNAs – spongy type of activity.

across the species which might underscore circRNAs specific role in the CNS. It has been documented that expression of circRNAs is specific to different brain regions. In addition, a subset of circRNAs is highly enriched in synapses (Rybak-Wolf et al., 2015) suggesting their involvement in brain plasticity and learnings. Analysis of circRNAs levels during porcine brain development showed different circRNA levels in different anatomic locations with the highest in cortex and in the cerebellum (Veno et al., 2015). In addition an interesting age-dependent neural accumulation of circRNA in flies, mice and human brains were observed (Szabo et al., 2016). The cellular localization of circRNA is frequently different from their linear counterparts suggesting that they may have different roles in neuronal activity. However, the function of most of brain specific circRNA was not discovered to date.

One of the best characterized brain specific circRNA was recently identified CDR1as. CDR1 showed the highest expression in the brain and is accumulated most in excitatory neurons but not in glial cells (Piwecka et al., 2017). CDR1 contains several conserved binding sites for miR-7 and hence acts as an effective sponge that reduce miR-7 target gene activities. CDR1as also serves as a crucial factor engaged in the functioning of neurons and removal of CDR1as locus from mice genome caused problems with the filtering of unnecessary information resulting in sensimotor gating impairment (Piwecka, Glazar, 2017). Thus CDR1as is an excellent example of the brain specific circRNA that influences the CNS function and may contribute to CNS pathological conditions. It was shown later that additional genes, e.g. circTulp4, circElf2, circPhf21a or circMyst4, encode circRNAs within the brain with higher efficiency in comparison to other tissues (Rybak-Wolf, Stottmeister, 2015). More interestingly, many of circRNA-producing genes are exclusively expressed in the brain suggesting that the brain environment promotes circRNA production. These circRNAs have been implicated in neurogenesis, neuronal differentiation, and synaptic function (Rybak-Wolf, Stottmeister, 2015, You et al., 2015). With regard to neuronal differentiation and development it was shown that several circRNAs were upregulated and demonstrated different kinetic and spatial expressions than linear RNA molecules. These circRNAs included CDR1as, circ-RTN4, circTulp4 and circ-cRIMS2 (You, Vlatkovic, 2015). Importantly, many of these circRNAs are the products of genes encoding proteins involved in neuronal development. Another intriguing observation suggests that neuronal activity may change the expression pattern of circRNAs. For example, in response to GABA inhibition, several circRNAs, including circHomer, were found to be upregulated (You, Vlatkovic, 2015). Thus, cirRNA may represent instrumental mechanisms in many basic processes within the CNS.

The role of circRNA in CNS pathologic conditions is still in the early stage of investigation. The CDR1as is considered a potential candidate for a factor contributing to development of several neurological disorders like Parkinson (Kumar et al., 2018) and Alzheimer's disease (Akhter, 2018; Zhao et al., 2016) (Table 1). As described above CDR1as removes miRNA-7 in a spongy type of mechanism and this miRNA was suggested to play a neuro-protective role for dopaminergic neurons. miR-7 can influence α-synuclein translation process and prevents dopaminergic neurons death. In the case of Alzheimer's disease it was shown that CDR1-miRNA7 complex targets the ubiquitin protein ligase A (UBE2A) leading to disturbances in protein degradation (Lukiw et al., 2016a, Lukiw et al., 2016b, Zhao et al., 2016). Another argument supporting the role of circRNAs in neurodegenerative conditions is the observation of accumulation of circRNAs in ageing brains. It was shown in different species from flies to humans that the amount of circRNA increased several times in older brains (Cai et al., 2019; Gruner et al., 2016). There are also numerous reports suggesting the role of circRNAs in pathogenesis of brain tumors (Liu et al., 2019; Yang et al., 2018b; Zhang et al., 2018a). Overall, emerging evidence suggest a role of circRNA in disorders of the CNS.

5. Circular RNA and immunity

CircRNAs have also been found to be involved in immune system activity and their expression has been described in several immune cells (Memczak et al., 2015; Savelyeva et al., 2017). It was discovered that circRNA expression is cell-type specific and alters during differentiation. Furthermore, differentiated cells contain substantially higher levels of circRNA than the corresponding linear RNA. A recent study has found that lymphocytes have particularly higher levels of circRNA expressed (Nicolet et al., 2018, Savelyeva et al., 2017). The number of distinct circRNA however was similar in various cell populations, indicating that the abundance of circRNA, but not the variety of circRNA, was increased in B cells, CD4+ and CD8+ T cells, and in NK cells. These findings suggest that circRNAs were generated during myeloid cell differentiation and did not reflect an accumulation of stable circRNAs from the progenitor cell. It was noted that circRNAs were highly expressed in differentiated myeloid cells but the highest number of circRNAs are detected in the enucleated erythrocytes and platelets. Analysis of the presence of circRNA in ageing myeloid cells show that in contrast to the linear RNA forms circRNA expression was stable or increased. Several circRNAs, e.g. circRNA 100,783, have been found to be involved in chronic CD28-associated CD8(+) T cell ageing. (Wang et al., 2015). More recently the role of circRNAs has also been studied in the functionality of immune cell subsets. It has been shown that circPan3 bound mRNA encoding the cytokine IL-13 receptor subunit IL-13Rα1 and increased its stability, leading to enhanced expression of IL-13Rα1 in stem cells. IL-13 produced by innate lymphoid cells engaged IL-13Rα1 and activated signaling mediated by IL-13–IL-13R, which in turn initiated expression of the transcription factor Foxp1. Thus, these novel findings allow us to link circRNA with the primary regulatory circuit of the immune system. In light of these findings it is of interest that circRNAs have been highlighted in mechanisms of some autoimmune diseases. Specifically, it has been shown in peripheral blood mononuclear cells of patients with rheumatoid arthritis that several

Table 1
The role of circRNA in CNS conditions.

Circular RNA	Disease	References
hsa_circ_0106803	Multiple sclerosis	Cardamone et al., 2017
circ_0005402 and circ_0035560		Iparraguirre et al., 2018
ciRS-7	Parkinson's disease	Hansen et al., 2013a,b
	Alzheimer's disease	Lukiw et al., 2016a,b
	Dysfunction of excitatory synaptic transmission	Piwecka et al., 2017
rno_circ_0006298	Neuropathic pain	Zhou et al., 2017
IQCK, MAP4K3, EFCA1, DTNA, MCTP1	Multiple system atrophy	Chen et al., 2016a
mmu-circRNA-015947	Cerebral ischemia-reperfusion injury	Lin et al., 2016
circHIPK3	Neuroinflammation	Huang et al., 2017
circRar1	Lead poisoning	Nan et al., 2017
circ-FBXW7	Glioma	Yang et al., 2018a,b
has_circRNA_103636	Depression	Cui et al., 2016
hsa_circRNA104597	Schizophrenia	Yao et al., 2019

circRNA have been differentially expressed and targeted relevant miRNA. Many of these circRNAs e.g. has_circ_0038644, were derived from the host genes with similar proimmune activity (Zheng et al., 2017a, 2017b). Similarly, in type 2 diabetes circANKRD36 has been found to be significantly upregulated in peripheral blood immune cells (Fang et al., 2018). In another autoimmune condition, systemic lupus erythematosus, has_circ0045272 was significantly downregulated in T cells (Li et al., 2018).

Particularly interesting are studies on the role of circRNA role in malignant hematopoietic cells development and differentiation. In Burkitt lymphoma (BL) it was discovered that circRNAs, ZDHHC11 and ZDNN11, having multiple binding sites for miR-150, have been significantly upregulated. It is hypothesized that abovementioned circRNAs in normal cells might inhibit proliferation by binding miR-150 and causing proto-oncogene MYC-repression. Adversely, in BL the circRNA ZDHHC11 and ZDNN11B upregulation increases proliferation and may be linked with BL pathogenesis (Dzikiewicz-Krawczyk et al., 2017). The above listed data demonstrates the specific role of circRNAs in B cell biology and neoplastic transformation of immune cells.

Several recent studies implicated circRNAs in antiviral immune response. Initially, the mechanism of this antiviral activity was linked with circRNAs spongy type of miRNA neutralization. It was found that in chickens resistant to avian leukosis virus infection twelve circRNAs had been upregulated and all of them targeted miRNAs implicated in modulation of B cell function (Zhang et al., 2017a). Similarly in grass carp virus infection a total of 41 differentially expressed circRNAs have been identified (He et al., 2017). All the circRNAs had binding sites for miRNAs performing important functions in immune homeostasis. The above results indicated that the protection from viral infection can be provided by already accepted mechanisms mediated by circRNAs interacting with miRNAs and subsequently enhancing translation of antiviral proteins. However, more recently Chen et al. (Chen et al., 2017) reported on antiviral activities of circRNAs which were independent of miRNAs. They found that circRNAs activates RIG-I (retinoid acid-inducible gene-I), one of the key factors in the host antiviral defense mechanisms. Interestingly, they found that RIG-I was activated by circRNAs using self-splicing introns instead of more typical endogenous exon splicing. The recognition of self versus non-self circRNA is marked with a different pattern of RNA-binding proteins (RBP). The mechanism by which RBP protects self circRNA from RIG-I activation remains unknown. Another anti-viral mechanism of circRNAs is associated with enhancement of LPS-dependent mechanisms by circRasGEF1B (Ng et al., 2016). Consequently circRasGEF1B stabilizes ICAM-1 mRNA, the critical factor controlling the recruitment of leukocytes to inflamed tissue. Moreover, it has been recently revealed that the process of circRNAs regulation of innate immune dsRNA receptor PKR is misregulated in patients with autoimmune diseases (Chu-Xiao et al., 2019).

Despite the fact that circRNA can influence immune response to viral infections, the immune system can also impact generation of circRNAs. Under normal conditions two immune factors, NF90 and NF110, bind to circRNAs and stabilize circRNA structures (Li et al., 2017a). During viral infection both factor are released from circRNAs and are transfered from the nucleus to the cytoplasm. The released NF90 and NF110 binds to viral mRNAa and inhibit proliferation of the virus. This process leads to decreased presence of circRNAs in the nucleus.

On the other hand, viral circRNAs might behave opposite to the host cell circRNAs and demonstrate pro-viral activity. Viruses are known to use their cellular miRNAs for silencing of the genes involved in protection of viral infection. Viral circRNAs may neutralize host cell miRNAs and thus enhance production of pro-viral proteins. Viruses can also use for the same purpose the host cell circRNAs. They can also deliver miRNAs directly neutralizing the translation of anti-viral proteins. An important counter mechanism of the host cell is the production of circRNAs directly targeting viral miRNAs. A large number of host circRNAs are predicted to contain binding sites for viral miRNAs (Ghosal et al., 2014). Of particular interest for MS is the finding that circRNA, hsa_circ_002048 express 36 binding sites for EBV encoded miRNA-BART20-5p (Ghosal, Das, 2014). EBV has been implicated in the pathogenesis of MS. It should also be remembered that RBPs having a wide spectrum of interaction with circRNAs can also trigger anti-viral immune response dependent on circRNA-miRNAs-viral protective protein network. Although growing evidence support the role of circRNA in several immune mechanisms further studies on their function in adaptive and innate immunity are needed.

6. Multiple sclerosis and miRNA

In the last few years, compelling evidence implicated the role of miRNA in epigenetics of MS. It was shown that epigenetic mechanisms influence inflammatory genes expression as well as myelination factors (Kucukali et al., 2015). It has been documented that dysregulation of many miRNA plays a role in the pathogenesis of multiple sclerosis. With regard to miRNA involvement in immune mechanisms of MS it was found that miR-326 highly correlated with disease severity in patients with MS and mice with EAE. In vivo silencing of miR-326 resulted in fewer Th17 cells and mild EAE, and its overexpression lead to more Th17 cells and severe EAE (Du et al., 2009). It was also found that miR-155 promoted T cell-dependent tissue inflammation in EAE (O'Connell et al., 2010). Subsequently it was reported that brain-specific miR-124 is expressed in microglia but not in peripheral monocytes or macrophages. During EAE, miR-124 was downregulated in activated microglia. Peripheral administration of miR-124 in EAE caused systemic deactivation of macrophages, reduced activation of myelin-specific T cells and suppressed the disease. Conversely, knockdown of miR-124 in microglia and macrophages resulted in activation of these cells in vitro and in vivo (Ponomarev et al., 2011). The results of our own group discovered the critical role of miRNA-301a in Th17 development in EAE mice (Mycko et al., 2012). miR-301a inhibition in T cells led to inhibition of Th17 in vitro and in vivo development via the modulation of the STAT3 activation pathway. Furthermore we have also identified miR-155-3p as encephalitogenic T helper cell specific miRNA regulating EAE via heat shock protein 40 expression (Cichalewska et al., 2015; Mycko et al., 2015).

A number of miRNAs were analyzed in CSF, serum, plasma, whole blood, PBMCs and brain lesions of MS patients (Keller et al., 2014; Ma et al., 2014). Several miRNAs revealed to be either up- or down-regulated in MS patients vs. controls and differently expressed in different stages and types of the disease. Gandhi et al. revealed that miR-92a-1* and miR-145 differentiate RRMs patients from SPMS and HC and let-7 family differentiates SPMS from HCs and RRMS from SPMS (Gandhi et al., 2013) Also the link between miRNAs and progression of disease disability was found. Siegel et al. (Siegel et al., 2012) analyzed 900 miRNAs in HC and MS patients and identified a specific serum miRNA expression pattern of MS which included six up-regulated miRNAs (miR-614, miR-572, miR648, miR-1826, miR-422a, miR-22) and one down-regulated (miR-1979). Fenoglio et al. (Fenoglio et al., 2013) investigated PPMS group vs HC revealing the decrease of miR-223 and miR-15b levels with diagnostic accuracy to discriminate between those two groups. In another study (Sondergaard et al., 2013) it was found that miRNA-145, miR-660 and miR-939 levels showed significant increases in the plasma of MS patients in remission (Sondergaard, Hesse, 2013). In addition, levels of miRNAs may change in response to MS treatment e.g. fingolimod decreases plasma miR-150 levels whereas natalizumab increases it (Bergman et al., 2016).

Overall all data has demonstrated the different miRNA expression profiles between MS and controls. However an attempt to identify a clinically usefully miRNA biomarker in MS have so far been futile due to lack of a robust signal in MS and a low reproducibility of results between different studies. Therefore an analysis of circRNA, a newer layer of miRNA regulation, might reveal a more robust biomarker of MS.

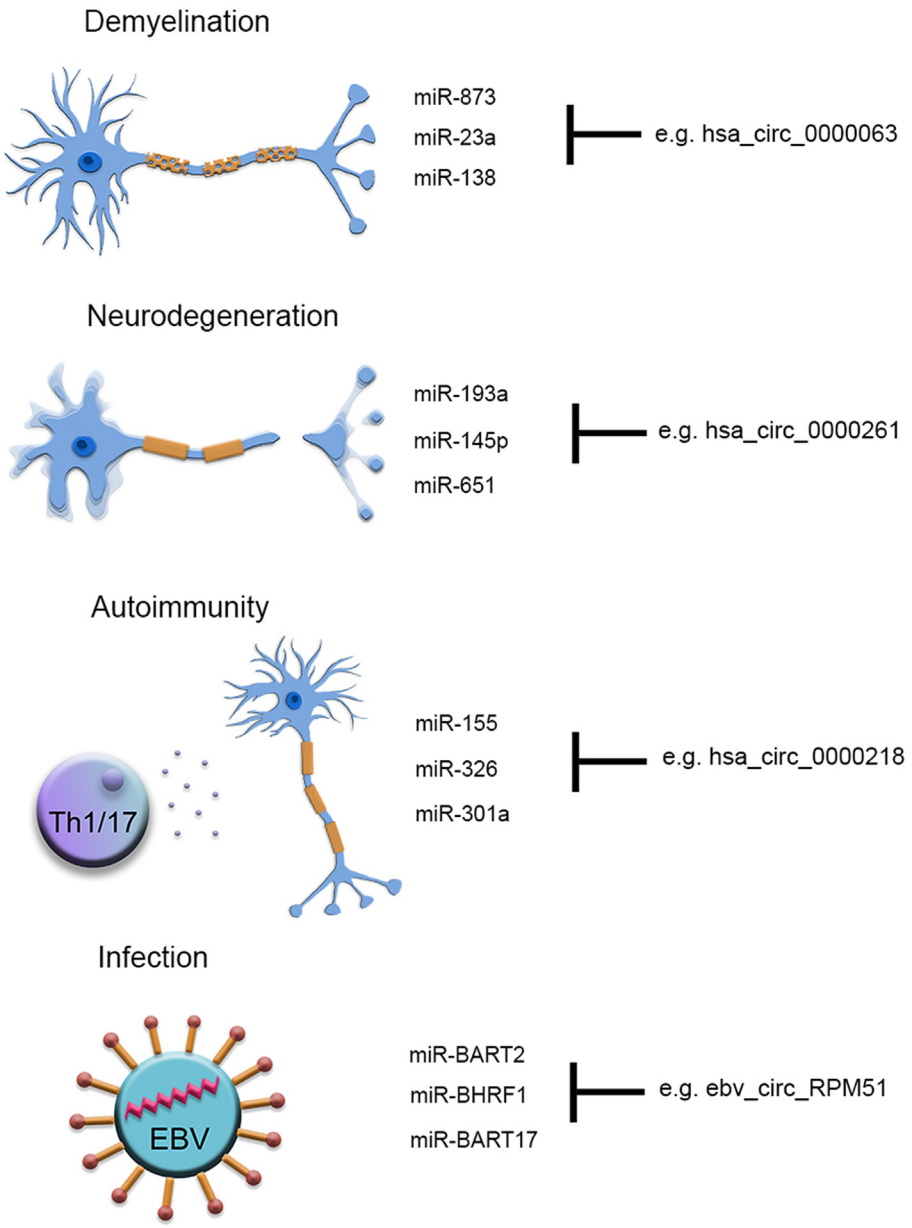

Fig. 3. Schematic presentation on the role of circRNA in the miRNA controlled process in MS and EAE. circRNA sequences have been selected from data base search Interactome.

7. Circular RNA and MS

Although the accumulating data demonstrates key roles of circRNA in the CNS as well as their role in the immune cell function, the role of these RNA in pathogenesis of MS is still largely unknown and only few reports have addressed this topic. The first published investigation in this field was Cardamone et al. (Cardamone et al., 2017) which discovered circRNAs role in dysregulation of alternative splicing of GSDMB (Gasdermin B) gene involved in apoptosis. The same group has found in MS patients upregulation of the lncRNA MALAT1 gene leading to backsplicing of circRNAs and splicing abnormalities of MS-associated genes (IL7R, SP140) (Cardamone et al., 2019). IL7R was found in several genetic association studies in MS (Gregory et al., 2007; Lundmark et al., 2007; Tavakolpour, 2016; Traboulsee et al., 2014). Another recent research conducted by Iparraguirre et al. (Iparraguirre et al., 2018) demonstrated dysregulated profiles of circRNAs in peripheral blood mononuclear cells of MS patients. Detailed analysis showed that circ_0005402 and circ_0035560, both located in chromosome 15 inside the ANXA2 gene, are down-regulated in MS. The same trend was observed shortly after disease diagnosis in clinically isolated syndrome patients. Paraboschi et al. reported (Paraboschi et al., 2018) bioinformatic analysis of circRNA enrichments derived from non-coding elements in MS associated genome and suggested their possible involvement in the susceptibility to the disease. They found in regions harboring MS-associated SNPs a total of 482 circRNAs vs. a mean of 194 ± 65 in the random sets. By evaluating RNA sequencing data of two cell lines, SH-SY5Y and Jurkat cells, they identified 18, including two novel circRNAs, derived from MS-associated genes. Our group discovered that circRNA are differentially expressed in immune cells of RRMS versus controls. The analysis of the protein coding transcripts affected by these circRNA elucidated a pathway directly linked with STAT3, a critical transcription factor determining the polarization of the immune response toward Th17 and development of inflammatory demyelination (Zurawska et al., 2018). All of the data suggests that circRNAs might contribute to MS pathogenesis (Fig. 3).

Apart from the role of circRNA as a novel contributor to the

molecular pathways of immune dysregulation in MS, circRNAs may show great promise as novel biomarkers of this disease. This conclusion depends on known circRNA resistance to RNAse activity due to covalent closed cyclic structure (Jeck and Sharpless, 2014). High abundance of circRNAs in the CNS supports this assumption. Thus, it is anticipated that further studies on circRNA will facilitate the delineation of new diagnostic and prognostic biomarkers in MS.

8. Conclusions

A wealth of information is accumulating that clearly indicates increasingly important but also the very complex impact of circRNAs on the functioning of the human immune and nervous systems. The discovery of circRNA has led to the demonstration of a previously unknown phenomenon of their specific control mechanism over other non-coding RNAs, especially over miRNAs. miRNAs have been shown to correlate with immune cell polarization and induction of several immune effector functions. The abundant expression of circRNA in the brain and their involvement in CNS specific processes underscore their potential role in MS. Several lines of evidence implicated circRNAs as having specific and selective roles in the pathogenesis of this disease. circRNAs could play a distinctive role in both adaptive and innate immune responses in MS. Our preliminary results of the circRNA profiling in the MS patients indeed demonstrated profound and very specific changes of these transcripts in peripheral blood cells. In addition, bioinformatics analyses suggests a putative role of the circRNA in promoting the immune processes leading to MS. Together, emerging recent data clearly supports the notion of circRNAs involvement in the mechanisms of MS.

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