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TNFα and microRNA-15b expression changes in experimental model of subarachnoid haemorrhage

Změny v expresi TNFα a microRNA-15b u experimentálního modelu subarachnoidálního krvácení

Abstract

Aim: The aim of the study was to investigate expression changes of pro-inflammatory and pro-apoptotic cytokine tumor necrosis factor alpha (TNFα) and microRNAs (miRNAs) involved in its regulation in early pathophysiological changes after subarachnoid haemorrhage (SAH). *Materials and methods:* MiRNAs (miR-125b, miR-146a, miR-346, miR-155, miR-15b) and mRNA (TNFα) expression were determined by quantitative real-time polymerase chain reaction in brain tissue samples. A total of 88 animals were divided to Sham (control surgery without induction of SAH), Mild SAH, Severe SAH groups in following time-points: 2, 4, 6 and 8 h (n = 7 per group); including 4 animals used as an absolute control. *Results:* We have found a statistically significant difference in TNFα expression between Sham and Severe SAH groups at all the time-points ($p < 0.05$), between Sham and Mild SAH groups 4 h after induction of SAH ($p < 0.05$) and between Mild and Severe SAH groups at 2 and 6 h time-points ($p < 0.05$). Furthermore, a significant difference in miR-15b expression between Sham and Severe SAH groups was observed 8 h after SAH ($p < 0.05$). All the other microRNAs have not been significantly changed. *Conclusions:* SAH was associated with an early increase in TNFα and miR-15b expression especially in Severe SAH group. Despite complex cross-regulation between cytokines and miRNA, any information about the activation of inflammation/apoptotic mechanisms within a few hours after SAH may improve our knowledge of SAH pathophysiology. Furthermore, it can lead to therapeutic improvement using a combination of both pro-apoptotic markers TNFα and miR-15b.

Souhrn

Cíl: Cílem studie bylo prozkoumat změny v expresi pro-zánětlivého a pro-apoptotického cytokinu tumor nekrotizující faktor alfa (TNFα) a mikroRNA (miRNA), které se podílejí na jeho regulaci v časném období po subarachnoidálním krvácení (SAK). *Soubor a metodika:* Exprese miRNA (miR-125b, miR-146a, miR-346, miR-155, miR-15b) a mRNA (TNFα) byly stanoveny pomocí kvantitativní polymerázové řetězové reakce v reálném čase z mozkové tkáně experimentálních zvířat. Celkem 88 zvířat bylo rozděleno do skupin Sham (kontrolní operace bez indukce SAK), Lehké SAK, Těžké SAK, do časových intervalů 2, 4, 6 a 8 h (n = 7 ve skupině); 4 zvířata byla použita jako absolutní kontrola. *Výsledky:* Byly nalezeny statisticky významné rozdíly v expresi TNFα mezi skupinami Sham a Těžké SAK ve všech zkoumaných časových intervalech ($p < 0,05$), dále mezi skupinami Sham a Lehké SAK 4 h po indukci SAK ($p < 0,05$) a mezi skupinami Lehké SAK a Těžké SAK ve 2 a 6h časovém intervalu ($p < 0,05$). Dále byl pozorován významný rozdíl v expresi miRNA-15b mezi skupinami Sham a Těžké SAK 8 h po začátku SAK ($p < 0,05$). U dalších analyzovaných miRNA jsme v expresi nepozorovali žádné statisticky významné změny. *Závěr:* SAK bylo asociováno s časným nárůstem exprese TNFα a miR-15b, zejména u skupiny Těžké SAK. Navzdory komplexitě vzájemné regulace mezi cytokiny a mikroRNA, může informace o časné aktivaci zánětlivých/apoptotických mechanismů několik hodin po SAK přispět k lepšímu poznání patofyziologie SAK. Pochopení mechanismů vzájemné regulace proapoptotických markerů TNFα a miR-15b může přispět ke zlepšení terapie této závažné patologie.

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Klíčová slova

subarachnoidální krvácení – časné poškození mozku – zánět – apoptóza – mikroRNA – perforační model

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Introduction

Aneurysmal subarachnoid haemorrhage (SAH), with an annual incidence of around 10 per 100,000 and case fatality rate of up to 50%, remains a severe condition which affects mainly patients of productive age [1]. Despite advances in surgical treatment and critical care in the last decades, the morbidity and mortality rate of patients suffering from SAH is still high. SAH is therefore a subject of intensive research in both clinical and experimental conditions.

Haemorrhage into the subarachnoid space initiates several pathological processes contributing to early brain injury (EBI), which occurs in the first 72 h following SAH. These include transient cerebral global ischaemia, oxidative stress or inflammation which may result in neuronal or endothelial cell death [2,3]. The mechanisms of the EBI and the brain's response to this injury are very complex and still not clear. Nevertheless, inflammation and apoptosis are among the most commonly proposed mechanisms which may contribute to EBI development [4–6]. One of the key mediators of inflammation is tumor necrosis factor alpha (TNFα) – a pleiotropic pro-inflammatory cytokine. Increased production of TNFα was measured in the brain after injury and its level rises in cerebrospinal fluid (CSF) and blood after stroke in humans [7]. TNFα has been proposed to play a crucial role in neuroinflammatory response after SAH, participating in SAH-related oxidative damage and is involved in cerebral vasospasm development [8]. Moreover, out of many pro-inflammatory cytokines, TNFα is the most potent inducer of apoptosis, representing a link between inflammation and cell death. TNFα mediates apoptotic cell death as well as cell proliferation and differentiation in a number of cell types [9–12].

On the molecular level, pathological changes induced by SAH are probably tightly orchestrated processes in which regulatory molecules named microRNA (miRNA), may play a pivotal role. MiRNAs are small non-coding RNAs able to mediate post-transcriptional regulation of genes. They are known to participate in fundamental cellular processes such as cellular metabolism [13], cell-cycle regulation, including apoptosis [14] or immune response [15]. Several studies have indicated that specific miRNAs are involved in the regulation of inflammation and apoptosis after SAH and are clinically associated with the severity of brain injury [16–18]. However, no details are known about the early dynamics of miRNAs after SAH and about its association with the early dynamics of pro-inflammatory cytokines. Temporal changes in the abundance of specific miRNAs after haemorrhage may provide a novel insight into their role in brain injury and the brain's response. Although several miRNAs were referred to be promising circulating biomarkers and potential diagnostic markers of acute stroke, the miRNAs are not yet used for diagnostic purposes in clinical practice [19].

The aim of the present study was to investigate the expression of pro-inflammatory and pro-apoptotic cytokine TNFα and several miRNAs involved in its regulation in brain tissue up to 8 h after induction of bleeding in an experimental model of SAH. We selected five miRNAs associated with TNFα (miR-15b, miR-125b, miR-146, miR-155, miR-346) which are involved in inflammation and/or apoptosis. From those, miR-125b and miR-155 were evaluated as strong pro-inflammatory regulators of macrophage activation [20]. Moreover, miR-125b was described to inhibit glial cell proliferation, promotes cell apoptosis (via p53) and neuronal differentiation [21–23]. Similarly, miR-146 was described to be involved in cell proliferation, apoptosis and inflammatory response [24–26]. MiR-346 was determined as a negative regulator of inflammation with the ability to suppress cell proliferation [27,28], whereas miR-15b has been identified as a probably essential player in apoptosis by targeting anti-apoptotic genes in different cellular systems [29–32].

Material and methods

Animal experiments

All the experiments were performed in compliance with the Principles of Laboratory Animal Care (NIH Publication no. 86–23, revised 1985). The experimental protocol was approved by the Ethics Committee of the Masaryk University (Brno, Czech Republic). A total number of 88 adult male Sprague Dawley rats (260–300 g) was used for the purpose of this study. Animals were randomly assigned to Sham, SAH groups and divided into one of the following time-point groups: 2, 4, 6 or 8 h (n = 7 per group). Another four animals were used as an absolute control group. All animals were anesthetised using Isoflurane (AbbVie Ltd., Maidenhead, UK), intubated and kept on mechanical ventilation during surgery. SAH was induced by sharpened 4-0 nylon suture through the left internal carotid artery as described previously in Sham animals, the suture was inserted into the artery without perforation. Animals were sacrificed at scheduled time-points, a picture of the basal part of the brain was taken for SAH grade evaluation [33]. Then the samples of the brain, representing the area adjacent to haematoma, were collected (see below). According to SAH grade the animals were assigned to mild/moderate SAH group (SAH grade 6–12; below labelled as Mild SAH) and Severe SAH group (SAH grade 13–18), while animals with SAH grade < 6 were excluded for insufficient SAH, as usual [33,34].

Samples

Brain samples were collected from the basal part of the left hemisphere (the area adjacent to haematoma, which is directly affected by haematoma) and frozen in RNA later at –80 °C. Tissue samples were collected at four different time-points after surgery 2, 4, 6 and 8 h). Isolation of total RNA from brain samples was performed with Tripure reagent (Qiagen GmbH, Hilden, Germany). Single-stranded cDNA was synthesized from 1,000 ng of total RNA using Transcriptor First Strand cDNA Synthesis Kit (Roche s.r.o., Praha, Czech Republic) MiRNA (from 300 ng of total RNA) was transcribed using TaqMan miRNA reverse transcription kit (Applied Biosystems Inc, Foster City, CA, USA). The probes for miRNA (rno-miR-125b-5p, assay ID: 000449; rno-miR-146a-5p, assay ID: 000468; rno-miR-346, assay ID: 001333; rno-miR-155-5p, assay ID: 002571; rno-miR--15b-5p, assay ID: 000390) and mRNA (TNFα, assay ID: Rn01525859_g1) were selected from the TaqMan gene expression assays (Life Technologies, Carlsbad, CA, USA). Expression was evaluated by quantitative real-time polymerase chain reaction at the LightCycler®480 II System (Roche s.r.o., Prague, Czech Republic). The amplified DNA was analysed by the comparative Ct method. Only genes where Ct were lower than 35 were considered significantly expressed. All samples were measured in triplicates. After normalisation with the reference miRNA (U6, assay ID: 001973) and mRNA (HPRT1, assay ID: Rn01527840_m1), the expression levels were presented as a relative fold change compared with the mean value of the absolute control group.

Statistical analyses

The data met criteria of log-normal distribution, the data were logarithmically

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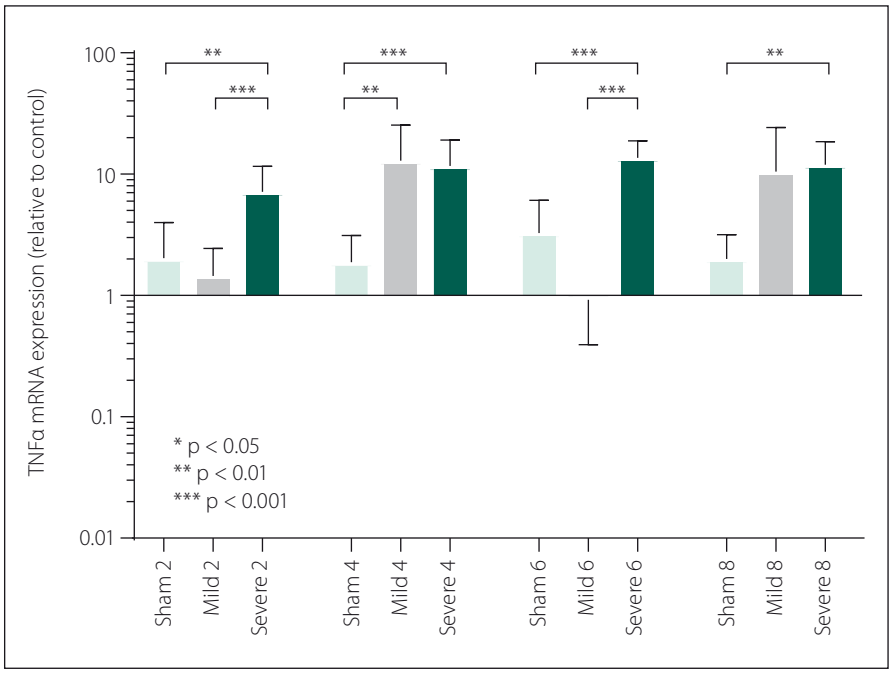

Fig. 1. TNFα expression in area adjacent to haematoma. The data are plotted as a geometric mean and geometric standard deviation factor.

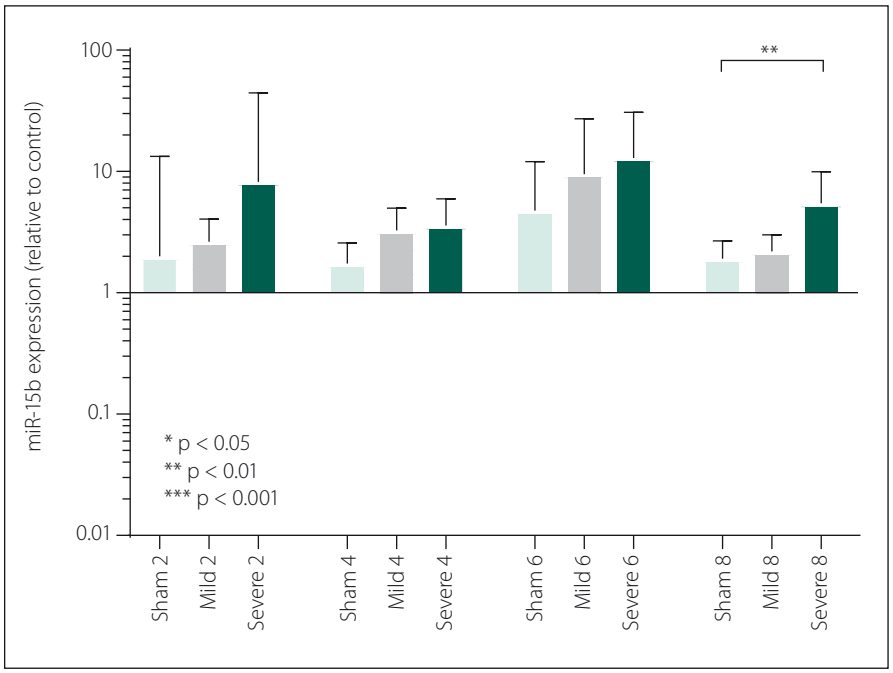

Fig. 2. miR-15b expression in area adjacent to haematoma. The data are plotted as a geometric mean and geometric standard deviation factor.

transformed and the statistical analyses were performed on transformed data. Ordinary one-way ANOVA followed by Bonferroni's multiple comparison test was used to evaluate the data. A p value of <0.05 was considered as statistically significant. Statistical analyses were performed using GraphPad Prism version 7.03 for Windows (GraphPad Software, La Jolla, California, USA). Data are presented as a geometric mean and geometric standard deviation factor of the fold change normalised to the absolute control group.

Results

The expression of TNFα and miR-125b, miR-146a, miR-346, miR-155, miR-15b was quantitatively determined in a total number of 88 animals. The four animals were used as an absolute control and the rest of the 84 animals were divided in Sham, Mild SAH, Severe SAH groups and the following time-points: 2, 4, 6 and 8 h (n = 7 per group). Expression of the above-mentioned markers was evaluated in the area of the brain adjacent to haematoma, which is directly affected by bleeding.

Figure 1 shows TNFα mRNA expression 2, 4, 6 and 8 h after induction of SAH. There is a statistically significant difference between Sham and Severe SAH groups at all the time-points ($p < 0.05$). The difference between Sham and Mild SAH groups is statistically significant 4 h after induction of SAH ($p < 0.05$). The difference between Mild and Severe SAH groups is statistically significant at 2 and 6 h time-points ($p < 0.05$). Fig. 2 shows miR-15b expression 2, 4, 6 and 8 h after induction of SAH. Significant difference between Sham and Severe SAH groups was observed 8 h after SAH ($p < 0.05$). Fig. 3 shows miR-125b expression 2, 4, 6 and 8 h after induction of SAH. No significant difference was observed between the groups at any time-point (p = NS). Fig. 4 shows miR-146a expression 2, 4, 6 and 8 h after induction of SAH. No significant difference was observed between the groups at any time-point (p = NS). Fig. 5 shows miR-155 expression 2, 4, 6 and 8 h after induction of SAH. No significant difference was observed between the groups at any time-point (p = NS). Fig. 6 shows miR-346 expression 2, 4, 6 and 8 h after induction of SAH. No significant difference was observed between the groups at any time-point (p = NS).

Discussion

Early inflammatory response, with the fundamental role of cytokine network, represents a hallmark in the pathology of SAH [35]. Within minutes of a haemorrhage, a large number of proinflammatory cytokines (TNFα, IL-1b, IL-6, IL-8) are released into subarachnoid space. The levels of pro-inflammatory cytokines have been described to be globally elevated (brain tissue, circulation, CSF) after SAH in many studies [35,36]. Pro-inflammatory cytokines have a cytotoxic effect and significantly contribute to SAH associated EBI [12]. TNFα is considered as a major mediator of apoptosis [37] which is able to induce apoptosis directly in various cells, including endothelial cells [11] and neurons [38,39].

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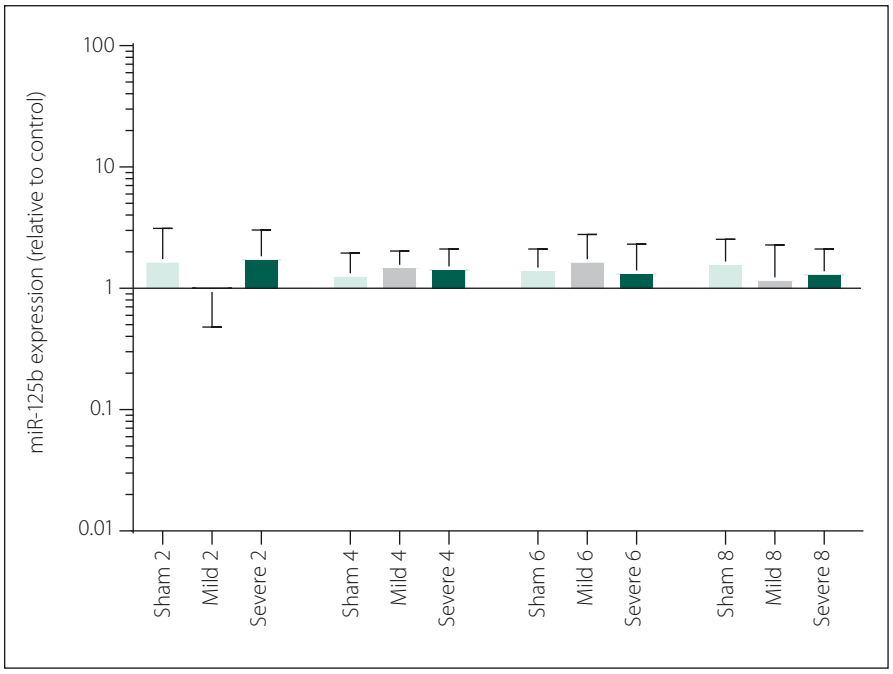

Fig. 3. miR-125b expression in area adjacent to haematoma. The data are plotted as a geometric mean and geometric standard deviation factor.

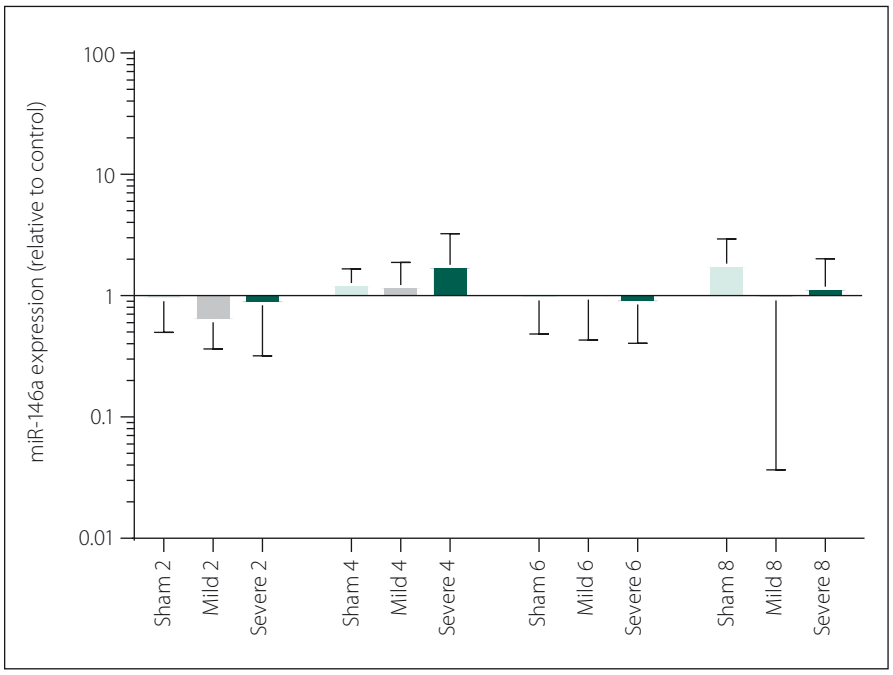

Fig. 4. miR-146a expression in area adjacent to haematoma. The data are plotted as a geometric mean and geometric standard deviation factor.

Apoptosis has been described in different intracranial pathologies such as Alzheimer's disease, Parkinson's disease [40], cerebral ischaemia [41] or SAH [42].

In our study, an activation of early inflammatory response in the brain after experimentally induced SAH was evaluated on the level of crucial pro-inflammatory and pro-apoptotic cytokine TNFα. We have described a significant difference in TNFα mRNA expression between Severe SAH groups and Sham at all the time-points (2, 4, 6 and 8 h). However, the difference between Sham and Mild SAH groups was significant only 4 h after SAH induction. Finally, the difference between Mild and Severe SAH groups was statistically significant at 2 and 6-h time-points. These data suggest that activation of the immune system is strong in Severe SAH, while the immune response in Mild SAH may be variable. TNFα has a broad spectrum of biological activities and probably contributes to the exacerbation of neuronal damage following SAH. Previous studies have shown that TNFα is involved in BBB permeability disruption, in thrombogenic and vascular changes leading to neuronal damage and angiogenesis [43–46]. Furthermore, TNFα participates in the processes of cell death, both necrosis and apoptosis [37,47].

Apoptosis and inflammation are tightly regulated processes at the level of gene expression. Profiling studies in humans have shown that miRNAs participate in different post-stroke pathologies and their levels are changed globally after SAH in CSF and circulation [16,18]. MiRNAs can represent tissue-specific molecular profiles that further define significant pathological features and individual miRNA may have a specific protective or pathogenic role. As master regulators of gene expression, miRNAs participate in apoptosis via targeting both pro- and anti-apoptotic genes and death receptors. Those cell-surface receptors belong to the TNF superfamily and mediate TNF-induced apoptosis [48].

In the perspective of a more comprehensive understanding of the molecular mechanisms activated after SAH, we selected 5 miRNAs involved in TNFα regulation (miR-15b, miR-125b, miR-146a, miR-346, miR-155). We have found significant difference of miR-15b expression between Severe SAH and SHAM in 8-h time-point. Our data are in consensus with other stroke models. Shi et al. reported differential expression of miR-15b at both 24 and 72 h following middle cerebral artery occlusion (MCAO) compared to sham-operated controls [31]. Liu et al. detected increasing expression of miR-15b in embolic stroke model in rats through all time points (0–168 h after MCAO) [49]. The study focused on the effect of ischaemic preconditioning (PC) on cerebral "miRNAsome", miR-15b showed increased expression at three time-points (6, 24 and 72 h) in the cerebral cortex of the rats subjected to PC by a 10-min transient MCAO [50]. MiR-15b exhibited robust up-regulation in ischaemic brain tissue representing thus a major contributor to neural damage following cerebral ischaemia. It was previously reported that

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miR-15b was involved in apoptosis via targeting the mRNA of the anti-apoptotic gene Bcl-2 in cancer cells [29,51]. Under ischaemic conditions, Bcl-2 protein level is suppressed and negatively correlated with miR-15b level [31]. Experimental suppression of miR-15b, exerting its anti--apoptotic effects due to Sevoflurane, has been described to contribute to its ischaemic neuroprotection [31]. Thus, targeting of miR-15b expression represents a novel neuroprotective strategy against ischaemic injury. It has also been reported that miR-15b acts as an upstream regulator of a mitochondrial signalling pathway and its inhibition can protect against cardiac ischaemic injury [30,32,52]. It has been described that miR-15b can regulate TNF--mediated apoptosis in hepatic cells via a Bcl-2 pathway [53]. Bcl-2 is a key anti--apoptotic protein, which protects cells from apoptosis in the TNF-dependent death receptors signalling pathway. An et al. suggested hypothesis, that miR-15b can reduce TNFα at different levels (transcriptional and translational) via Bcl-2. Hence, decreased TNFα production following anti-miR15b treatment may contribute to reduced damage to cells [53].

Our results suggest that miR-15b together with TNFα may play important roles in the severity of brain damage in EBI after SAH. A combination of suppression of both pro--apoptotic TNFα and miR-15b may bring better results in therapeutic strategies for the treatment of SAH. While the EBI in terms of inflammatory response and cell death may be clearly characterised, regulatory mechanism of this response is very complex and hard to define. In our study, pro--apoptotic miR-15b was the only evaluated miRNA, which was influenced by SAH, suggesting that signalling pathways related to apoptosis could be triggered early after SAH [3,42].

Expression of other selected miRNAs was not overly affected by SAH, although these particular miRNAs were described to participate in the regulation of pro--inflammatory cytokine expression. MiRNAs and cytokine activities are strongly interconnected. Recent reports point to cross-regulation between cytokine and miRNA pathways [54,55]. It means, that not only miRNAs regulate cytokine expression, but also vice versa cytokines can modulate both miRNAs expression and secretion [56,57]. This most probably indicates the complexity of miRNAs-cytokine interactions and functions which are pleiotropic and influenced by many hardly defined factors. Moreover, several studies indicate that the selective manipulations with inflammatory response after stroke may be problematic due to the complexity of the signalling network [58,59]. We are, however, aware that we cannot make any conclusion to such a hypothesis based on our data and further study revealing the function of miR-15b in association with TNFα and description of their detailed dynamics is needed.

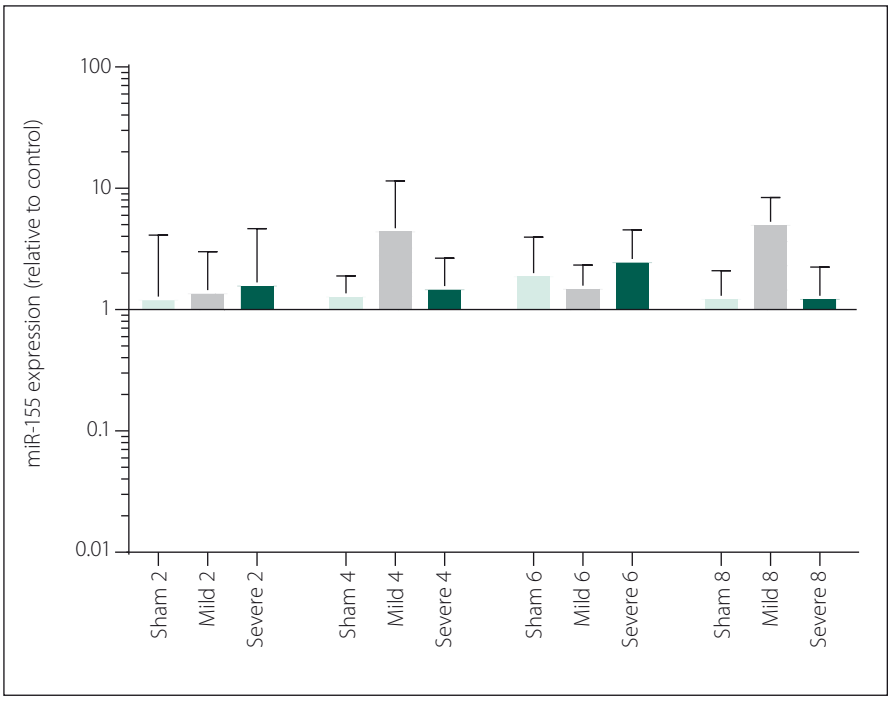

Fig. 5. miR-155 expression in area adjacent to haematoma. The data are plotted as a geometric mean and geometric standard deviation factor.

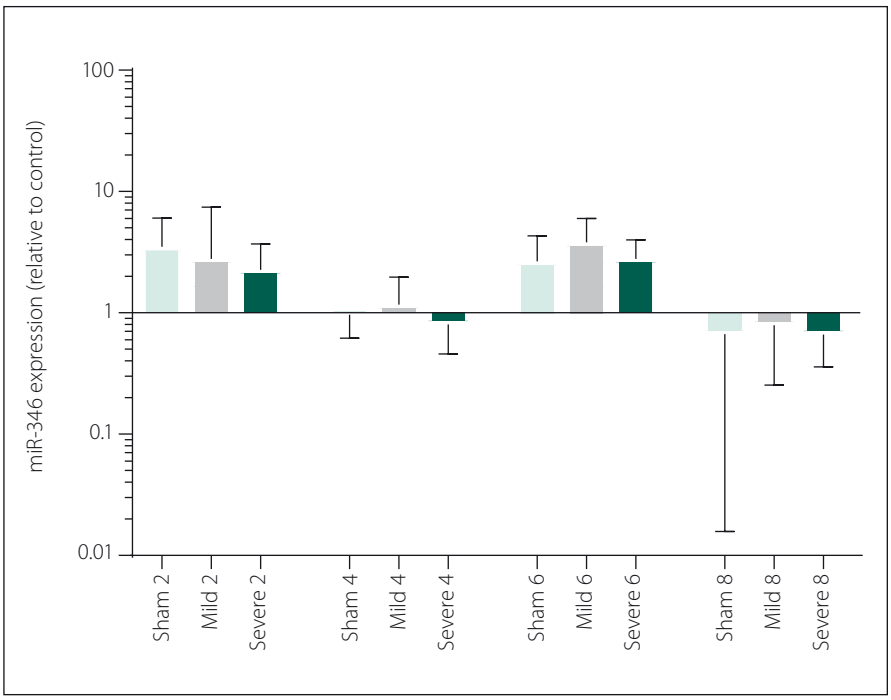

Fig. 6. miR-346 expression in area adjacent to haematoma. The data are plotted as a geometric mean and geometric standard deviation factor.

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Limitations

In this study, we were focused on early dynamics of TNFα and associated miRNAs. We have evaluated selected parameters in a very short period of time following SAH and we have not studied the consequences of activation increased levels of TNFα and this has to be considered as a limitation. However, selected time-points represent the local immune response in brain mediated mainly by microglia and astrocytes, while later time-points (24 h or later) are associated with the second step of inflammatory response – inflammation mediated leukocytes from the periphery. Another limitation is the small number of evaluated miRNAs. Selected miRNAs are crucial for the regulation of TNFα expression, but we are aware that a larger panel of miRNAs could bring us much better information about TNFα regulations. Finally, we have not evaluated any inflammatory parameter other than TNFα. We were focused on this particular cytokine, because TNFα is one of the most important contributors to acute inflammatory response.

Conclusion

Subarachnoid haemorrhage is associated with an early increase in TNFα expression, which is sharp in severe and more variable in mild cases. MiRNAs involved in the regulation of TNFα expression has not been generally affected by SAH, except miR-15b which was increased in Severe SAH groups. Cytokine expression regulations are very complex and more comprehensive study is needed for better information about regulations/deregulations of inflammatory response and apoptosis. Nevertheless, identification of miRNAs involved in the regulation of the mechanisms activated after a SAH and their potential targets may improve our knowledge of SAH pathophysiology and lead to identification of new therapeutic targets in order to minimise neurological impairment and enhance the functional recovery of the patients.

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