Neurochemistry International 107 (2017) 66–77

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/nci

The role of SUMOylation in cerebral hypoxia and ischemia

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ARTICLE INFO

Article history:
Received 10 November 2016
Received in revised form
9 March 2017
Accepted 15 March 2017
Available online 18 March 2017

Keywords:
Small ubiquitine-like modifier
SUMO
Neuroprotection
Brain
Stroke
Metabolic stress response

ABSTRACT

The process of protein modification by adding or detaching small ubiquitin-like modifiers (SUMO) proteins, called SUMOylation, contributes to the regulation of numerous processes in eukaryotic cells. SUMOylation also represents a key response and adaption mechanism to different forms of metabolic stress. The central nervous system (CNS) and neurons in particular are highly susceptible to hypoxic-ischemic stress due to the lack of significant oxygen and energy reserves. SUMOylation is observed in many molecular responses to metabolic stress in the brain, and is therefore supposed to represent an endogenous neuroprotective mechanism. However, the detailed roles of SUMOylation during CNS hypoxia-ischemia are not well understood so far. Moreover, SUMOylation is subjected to complex regulatory mechanisms and might exert protective, but also detrimental processes during hypoxic-ischemic stress.

This review provides a comprehensive overview on SUMOylation processes under physiological and pathological conditions in the CNS. A particular spotlight is set on clinically relevant hypoxic-ischemic conditions such as stroke by focusing on peri- and postischemic SUMOylation in neurons and astrocytes. The review describes relevant SUMOylation targets in these cells to discuss confirmed and supposed downstream mechanisms potentially contributing to neuroprotection, but also to sometimes detrimental processes. The review further provides unique insights into the time course of SUMO responses during cerebral ischemia in different cerebral cell populations. This includes neurons, astrocytes, but also phagocytes that become activated (microglia) and/or migrate (macrophages/monocytes) to the ischemic CNS. Based on this compact knowledge, the review finally suggests potential directions for future basic and translational research.

Contents

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http://dx.doi.org/10.1016/j.neuint.2017.03.011

1. Introduction

Posttranslational modifications are a fast and efficient cellular mechanism to react on pathophysiological stimuli. Next to well described processes such as phosphorylation and ubiquitination, dynamic protein modification by adding or detaching of 11 kDa small ubiquitin-like modifiers (SUMO) proteins represents a key regulatory and response mechanism in eukaryotic cells (Dorval and Fraser, 2007). SUMO proteins covalently bind to lysine residues on target proteins via a multi-step enzymatic cascade. This process is called SUMOylation and requires a SUMO-activating enzyme E1, a SUMO-specific conjugating enzyme E2 (Ubc9), and a SUMO ligase E3 (Geiss-Friedlander and Melchior, 2007). Four subtypes (SUMO-1 to SUMO-4) have been identified in human cells. SUMO-1 (15% of expressed isoforms) exhibits a 47% homology to SUMO-2 and 3 (70% and 15% of expressed isoforms, respectively). SUMO-2 and -3 show a 95% homology, and are therefore often referred to as SUMO2/3. SUMO-2 and -3 appear to act very similar if not redundantly. SUMO -1, −2 and −3 are expressed ubiquitously and can be detected in the vertebrate brain. SUMO-4, which is less well investigated, is mainly expressed in kidney and liver, but not in the brain (Bohren et al., 2004; Hay, 2005).

SUMOylation is a reversible process and de-conjugation is mediated by SUMO-specific proteases (SENPs). The balance between Ubc9-mediated conjugation and SENP mediated de-conjugation changes the functional properties of the target proteins. For example, SUMOylation of target proteins can affect their intracellular localization, activity and stability as well as interaction with other proteins (Deyrieux et al., 2007; Geiss-Friedlander and Melchior, 2007; Johnson, 2004; Loriol et al., 2012; Xu et al., 2008). Both SUMO-1 and SUMO-2/3 use the same conjugation mechanism. A large pool of non-conjugated SUMO-2/3 proteins is usually available in the cell, and SUMO-2/3 proteins are conjugated to different target proteins during and after cellular stress (Saitoh and Hinchey, 2000). In contrast, SUMO-1 is rarely detected unbound (Meulmeester and Melchior, 2008).

An increasing body of evidence underlines the key regulatory roles exerted by SUMOylation in numerous metabolic processes in the central nervous system (CNS) (Dorval and Fraser, 2007; Martin et al., 2007b). However, its role during hypoxic-ischemic stress is less well known and only partly understood, as are the spatial temporal profiles of SUMOylation in hypoxic-ischemic stress. This review summarizes the current state of knowledge on physiological and pathophysiological functions of SUMOylation in the CNS, and highlights its effects on the cellular counter-balance of hypoxic-ischemic injury.

2. Physiological functions of SUMOylation

Several hundred SUMO substrates have been identified so far. Many SUMO substrates were identified in the nucleus, but others are detected in the cytoplasm, mitochondria and the cell membrane (Tempé et al., 2008). The majority of SUMO targets are transcription factors, co-activators, or -suppressors. SUMOylation has also been described to play a role in chromatin modeling, DNA repair, telomere maintenance, as well as intracellular transport and signaling (Flotho and Melchior, 2013; Hay, 2005). SUMO further participates in the regulation of the cell cycle and mitochondrial activity (Andreou and Tavernarakis, 2009; Harder et al., 2004). Eukaryotic cells require SUMO activity for maintaining physiological functions and survival, but not all isoforms are equally required for this. For example, SUMO-2 can compensate for a lack of SUMO-1 in mice (Evdokimov et al., 2008; Zhang et al., 2008) and even for a lack of SUMO-3 if expressed in sufficient quantities (Wang et al., 2014b). In turn, SUMO-$2^{-/-}$ animals do not survive embryonic day E10.5 (Wang et al., 2014b).

Dynamic SUMOylation also plays a central role in neural cell differentiation and synaptogenesis in the CNS (Shalizi et al., 2006). For instance, SUMO exerts a direct influence on axonal mRNA transport and protein synthesis, thereby influencing axonal regeneration including growth cone orientation, and synaptic plasticity (van Niekerk et al., 2007). Moreover, numerous iono- and metabotropic membrane receptors, potassium channels and glucose transporters (GLUT) can be SUMOylated, indicating a profound regulatory influence of SUMOylation on ion flow/distribution, resting potentials and neuronal excitability (Loriol et al., 2012; Martin et al., 2007b; Scheschonka et al., 2007; Wilkinson et al., 2010). Moreover, SUMOylation can regulate transmitter release (Feligioni et al., 2009) and synaptic transmission. Table 1 summarizes processes and proteins subjected to SUMO regulation in the CNS.

3. Pathophysiological functions of SUMOylation

Due to the abundance of SUMO-regulated processes, functional SUMOylation deficits are associated with severe diseases and congenital malformation (Alkuraya et al., 2006; Bettermann et al., 2012). Since SUMO regulates growth, differentiation, ageing and apoptosis on a cellular level, it is not surprising that deficits in SUMO functionality can contribute to tumorigenesis (Deyrieux et al., 2007; Gill, 2005; Ihara et al., 2007). Indeed, tumor suppressor gene p53 and oncogenic transcription factors *c*-Jun and *c*-Fos present important SUMO substrates, but the exact role of their SUMOylation is still discussed controversially (Bettermann et al., 2012).

SUMOylated proteins have been identified within pathological protein aggregates in the brain while disease-specific proteins in neurodegenerative diseases are often SUMOylation targets (Table 2). SUMO has been identified as a key regulator of numerous disease-relevant protein specifications such as localization, function, degradation, misprocessing, solubility, and aggregation (Dorval and Fraser, 2007). Metabolic stress clearly impacts

SUMOylation, with oxidative stress exerting a particularly profound influence. Even the presence of minor amounts of hydrogen peroxide (H_2O_2; <1 mM) can induce the almost complete loss of SUMO conjugates (Bossis and Melchior, 2006a; 2006b). Inhibition of SUMOylation under oxidative stress conditions can facilitate normalization of the cellular redox state by inducing expression of several anti-oxidative proteins via *c*-Fos and *c*-Jun. The sensitivity of SUMOylation for oxidation-borne inactivation is believed to be of physiological relevance for redox signaling processes such as endogenous H_2O_2 production in phagocytes (Bossis and Melchior, 2006a).

4. SUMOylation under hypoxic-ischemic conditions in the central nervous system

Metabolic stress as induced by hypoxia or hypothermia increases SUMOylation in the brain (Lee et al., 2009a; Yang et al., 2008a,b, 2009; Cimarosti et al., 2008) under physiological and pathophysiological conditions. For instance, a massive increase of SUMO-1- and SUMO-2/3-based SUMOylation is observed in hibernating ground squirrels (Lee et al., 2007). The reduced cerebral blood flow and consecutively reduced oxygen and glucose levels in the hibernating brain can be considered as a natural and mild model of cerebral hypoperfusion, and structural brain damage does not occur in the presence of SUMOylation.

An increased nuclear accumulation of SUMO-2/3 in cortical neurons was detected after hypothermia in the rat brain (Wang et al., 2012). Moreover, SUMO-1 overexpression in cultured rodent primary cortical neurons increases cell survival under oxygen glucose deprivation (OGD) while RNAi-mediated inhibition of SUMO-1 and SUMO-2/3 expression increases cell loss (Lee et al., 2009a; Datwyler et al., 2011). In turn, an increase in global SUMO-conjugation was reported as a main mechanism of hypothermia-mediated SHSY5Y cell and rodent cortical neuron protection during OGD in vitro. Subsequent in vivo studies confirmed these results. Hypothermic treatment of mice before and after permanent middle cerebral artery occlusion (pMCAO) elevated cerebral SUMO-conjugation levels, what was accompanied by a decrease of ischemic lesion size (Lee et al., 2014b). Transgenic Ubc9 mice overexpress the E2 SUMO conjugating enzyme and thereby display elevated basal levels of global SUMOylation even in the steady state. These mice exhibit significantly smaller lesion volumes without hypothermia which, however, could not be further decreased by hypothermic treatment (Lee et al., 2014b). These data strongly suggest that SUMOylation is indeed a major mechanism of hypothermia-induced neuroprotection. The idea that global SUMO conjugation is an important component of ischemic tolerance was further supported by a recent study using neuron-specific SUMO 1–3 knock down (SUMO-KD) mice. SUMO-KD mice exhibited significantly worse functional outcomes after transient forebrain ischemia. Moreover, post-ischemic gene expression was widely affected in SUMO-KD mice showing an overall reduced expression (Zhang et al., 2017).

The SUMO response to ischemic stimuli is rapid. Only 10 min of transient forebrain ischemia in mice lead to a measurable increase of SUMO-2/3 conjugation in cortical and hippocampal neurons whereas unbound SUMO-2/3 is decreased. A strong activation of SUMO-1 and SUMO-2/3 in the infarct border zone was observed already 6 and 24 h following reperfusion in a rat model of transient focal cerebral ischemia. Next to activation in the directly affected striatum, SUMO-2/3 was also increased in the hippocampus, not directly affected by ischemia in this model (Cimarosti et al., 2008). Increase of SUMO-2/3-based, but not SUMO-1-based SUMOylation has also been described after transient ischemia in the spinal cord (Wang et al., 2013). Taken together, these data suggest a protective role of SUMOylation under different hypoxic-ischemic conditions in neurons and in different brain areas (Datwyler et al., 2011). Fig. 1 illustrates typical spatial and temporal patterns of SUMO expression after cerebral ischemia induced by pMCAO. Images were obtained in own, unpublished experiments.

5. Roles and functions of SUMOylation in neurons

Although an increasing body of evidence suggests an important role of SUMOylation as an endogenous neuroprotective mechanism, potential underlying mechanisms require more detailed discussion. A plethora of transcription factors, transporter proteins, ion channels and receptors respond to or even counteract hypoxic-ischemic stress. Many of those are modulated by SUMOylation. There is a massive SUMO activation after hypoxic-ischemic injury (Fig. 1) and numerous regulators and pathways that play a significant role in the response to brain ischemia are SUMOylation targets. However, this does not provide direct evidence that SUMOylation is indeed a part of the response to hypoxic-ischemic injury in the brain although SUMOylation plays a role in the ischemic stress response via these factors in other organs. It is nevertheless appealing to consider these potential mechanism concepts in order to inform future research addressing novel targets for neuroprotective interventions.

5.1. SUMOylation of transcription factors during hypoxia-ischemia

SUMOylation activates or represses many transcription factors (Lyst and Stancheva, 2007). One prominent example of a hypoxic signaling cascade mediator is the hypoxia-inducible factor (HIF)-1, which serves as a transcription factor and participates in the adaption to low oxygen concentration. HIF-1 contains an oxygen-regulated α-subunit as well as a constitutively expressed β-subunit. It helps to regulate glucose metabolism and genes enrolled in angiogenesis (Núñez-O'Mara and Berra, 2013). HIF-1α, HIF-1β and HIF-2α are substrates of SUMO-1 and SUMO-2/3, but activity and stability of the resulting constructs are discussed controversially (Silveirinha et al., 2013). Hypoxia induces HIF-1α SUMOylation, which promotes HIF-1α degradation. The SUMO protease SENP-1 deconjugates SUMOylated HIF-1α and allows HIF-1α to escape degradation and thereby promotes hypoxia-induced transcription of HIF-1α-dependent genes in fibroblasts (Cheng et al., 2007). A deficit of the SUMO protease SENP-1 impairs the protective HIF-1 signaling cascade and aggravates post-ischemic reperfusion damage in myocardial cells (Gu et al., 2014). HIF-1 is activated after focal cerebral ischemia in the adult rat brain (Sharp et al., 2001). This suggests HIF-1 as a potent mediator of neuroprotection, with its function crucially depending on SUMOylation. However, any functional studies to address this hypothesis are yet lacking.

The transcription of heat shock proteins is controlled by SUMO via heat shock factor protein 1 (HSF-1) regulation. This is of potential relevance for cerebral ischemia since HIF-1 can protect ischemic myocardial tissue, and is activated by oxygen and glucose deprivation (OGD) in astrocytes (Bergeron et al., 1996). Heat shock stimulates SUMO-2/3, but not SUMO-1 conjugation, and SUMO-1 cannot compensate the function of SUMO-2/3 under these conditions. This underlines the assumption that SUMO-2/3 is more prevalent and important than SUMO-1 during hypoxic-ischemic stress (Golebiowski et al., 2009; Saitoh and Hinchey, 2000). On the other hand, the nuclear factor erythroid 2-related factor (Nrf)-2, a transcription factor which is essential for the response to hypoxic-ischemic stress (Patel and Chu, 2011) by controlling the expression of glutathione and super-oxide dismutase, is a substrate of both SUMO-1 and SUMO-2/3 (Malloy et al., 2013). Moreover, a recent report has shown that NQO1, a key enzyme downstream of Nrf-2,

Table 1
SUMO-regulated CNS proteins.

SUMO-regulated target protein	Function	References
axin: activation of *c*-Jun NH(2)-terminal kinase (JNK) signaling	regulation of phosphorylation	Rui et al., 2002
cannabinoid receptor 1	synaptic transmission	Gowran et al., 2009
CASK (peripheral plasma membrane protein)	synaptic transmembrane protein anchoring, ion channel trafficking, dendritic spine morphology	Chao et al., 2008
caspase 7	apoptosis	Hayashi et al., 2006
caspase 8	apoptosis	Besnault-Mascard et al., 2005
coilin (survival of motor neuron (SMN) protein in Cajal bodies)	pre-mRNA processing	Navascues et al., 2008
dynamin-related protein 1 (DRP-1)	mitochondrial fission during mitosis	Figueroa-Romero et al., 2009; Zunino et al., 2009
focal adhesion kinase (linking cytoskeleton to extracellular matrix)	regulation of phosphorylation	Mitra et al., 2005
glial excitatory amino acid transporter 2 (EAAT-2)	modulation of glutamate transport	Foran et al., 2014
glucose transporter GLUT-1 and GLUT-4	glucose transport	Giorgino et al., 2000; Liu et al., 2007
glycogen synthase kinase 3β (GSK 3β)	regulation of phosphorylation	Eun Jeoung et al., 2008
kainate receptor subunit GluK2	synaptic transmission	Martin et al., 2007a
K2P1	potassium channel modulation	Plant et al., 2012; Rajan et al., 2005
Kv1.5	potassium channel modulation	Benson et al., 2007
Kv2.1	potassium channel modulation	Dai et al., 2009; Plant et al., 2011
metabotropic glutamate receptor 8 (mGluR8)	synaptic transmission	Dütting et al., 2011
mRNA binding protein La	axonal mRNA transport	van Niekerk et al., 2007
myocyte enhancer factor 2 A (MEF-2A)	postsynaptic differentiation	Shalizi et al., 2007; Shalizi et al., 2006
protein tyrosine phosphatase 1B (PTB1B)	regulation of phosphorylation, hypothalamic regulation of food intake and body weight	Dadke et al., 2007

Table 2
SUMOylation in neurodegenerative diseases.

Neurodegenerative disease	SUMO substrate	Reference
Alzheimer's disease	tau	Dorval and Fraser, 2006
	amyloid precursor protein	Zhang and Sarge, 2008; Li et al., 2003
Amyotrophic lateral sclerosis	super oxide dismutase 1	Fei et al., 2006
	glial excitatory amino acid transporter 2 (EAAT-2)	Foran et al., 2011
Huntington's disease	huntingtin	Steffan et al., 2004
Parkinson's disease	tau, α-synuclein	Dorval and Fraser, 2006
	DJ-1 (PARK7)	Shinbo et al., 2006; Zhong et al., 2006
Spinocerebellar ataxia	ataxin-1	Riley et al., 2005; Ryu et al., 2010

was remarkably increased in rodent brain tissue after MCAO. Blocking of Nrf-2 by decoy double-stranded oligonucleotides (ODN) counteracts the effect of neuroprotective drugs after MCAO (Li et al., 2017). SUMOylation may therefore also be enrolled in the regulation of the ischemic stress response via Nrf-2.

5.2. SUMO and NFkB signaling: regulation of neuroinflammation

Nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) is an important regulator of the immune response. NFκB is expressed in neurons and becomes activated during ischemia. Under normoxic conditions, NFκB is silenced by the inhibitory factor IκB. IκB itself is phosphorylated and conjugated by ubiquitin, leading to its degradation and consecutive NFκB activation. A SUMO-1-conjugation stabilizes IκB and inhibits excessive NFκB activation, but SUMO-2/3 conjugation fosters dissociation of NFκB from IκB, leading to its activation. This is associated by a stronger inflammatory response and neuronal apoptosis in the hypoxic-ischemic brain (Schneider et al., 1999). However, more recent investigations surprisingly also revealed a neuroprotective activity of NFκB reducing lesion volume after stroke (Li et al., 2008). These contrary results require clarification and may point at a so far unknown, additional regulator of NFκB under hypoxic-ischemic conditions, what could partially explain the antagonistic functions of SUMO subtypes.

5.3. SUMO and oxidative stress: a Janus-faced mechanism

SUMO proteases can be reversibly and irreversibly modified under conditions of oxidative stress. The balance between SUMOylation and de-SUMOylation can be shifted towards the latter to stabilize oxidative homeostasis (Xu et al., 2008). This is of relevance since de-SUMOylation of transcription factors *c*-Fos and *c*-Jun enhances their activity and thereby the expression of anti-oxidative proteins under oxidative stress (Bossis et al., 2005; Müller et al., 2000). Further, the *c*-Jun N-terminal kinase (JNK) and downstream signaling pathways play a key role in the induction of apoptosis under oxidative stress. Since JNK signaling is strongly activated after cerebral ischemia, its blockage protects neurons in infarct border zones and the hippocampus from reperfusion damage (Zhang and Chen, 2008). Ataxin-1 is a potent JNK pathway activator. Successful inhibition of the JNK signaling pathway reduces the oxidant-mediated SUMOylation and aggregation of ataxin-1, providing a considerable negative feedback loop being of importance for instance in spinocerebellar ataxia (Ryu et al., 2010). Moreover, JNK itself is a SUMO-1 substrate. Hence, increased

SUMOylation by SUMO-1 contributes to pro-apoptotic mechanisms under oxidative stress. On the other hand, SUMOylation of target proteins can also exert protective mechanisms under oxidative stress. For instance, strong expression of SUMO-1 dampens production of reactive oxygen species (ROS) by reducing p38, and SUMO-1-based SUMOylation of NADPH-oxidase 2 indirectly reduces intracellular production of ROS (Kim et al., 2011; Silveirinha et al., 2013). This dynamic regulation is considered to be key molecular switch in the regulation of the cellular response to oxidative stress. The fine balance between SUMOylation and de-SUMOylation are complex and not well understood yet (Feligioni and Nisticò, 2013), while the relevance of the discussed pathways remain to be confirmed for cerebral ischemia-hypoxia.

5.4. SUMOylation and mitochondrial functionality

Apoptosis and autophagy take place in the ischemic penumbra due to oxygen and glucose deprivation (Rami and Kögel, 2008; Wen et al., 2008). Many proteins enrolled in this processes as well as a number of DNA repair proteins are SUMO substrates (Cajee et al., 2012). Mitophagy (mitochondrial autophagy) fosters ischemic damage because mitochondrial degradation leads to an increased release of ROS and subsequent cellular damage (Pamenter et al., 2012). Mitochondria further play a pivotal role in the cellular response to ischemic stressors as they can increase their number by division and proliferation, increasing the cell's capacity to produce ATP. Mitochondria are also important for synapse maintenance and activity (Li et al., 2004). A central regulator protein of mitochondrial division is dynamin-related protein (DRP)-1, which mediates membrane cutting during mitochondrial fission (Smirnova et al., 2001). DRP-1 is a SUMO substrate. SENP-5-regulated de-SUMOylation leads to oligomerization of DRP-1 helping to control the fission process, what is particularly relevant for cell mitosis under physiological conditions (Zunino et al., 2009). However, SENP-5 inactivity leads to increased production of ROS, underpinning the important role of the SENP-5-SUMO-axis for the mitochondria-based compensation of oxidative stress. Whether or not these processes are also of relevance for the cellular response to hypoxia-ischemia in the CNS remains to be investigated. However, another and to some extent contrary process has been described as a neuroprotective mechanism under metabolic stress. The SUMO-2/3-specific protease SENP-3 is degraded during OGD, what extends SUMOylation of DRP-1. This in turn suppresses the DRP-1-mediated release of cytochrome C and caspase-mediated apoptotic cell death. The dynamic regulation of DRP-1 via the SENP-3-SUMO-2/3-axis therefore represents an adaptive pathway to extreme cellular stress in neurons (Guo et al., 2013).

5.5. SUMOylation of ion channels, receptors and membrane proteins

Next to its nuclear activities, SUMO contributes to the extranuclear modulation of transporter proteins, ion channels and receptors. It therefore plays a role for the homeostasis of neuronal metabolism, but also for the regulation of excitability and transmitter release in the steady state. For instance, the de-SUMOylation of voltage-gated Kv1.5 potassium channels induces a selective hyperpolarizing shift in voltage-dependency, thereby leading to a functional inactivation of these channels (Benson et al., 2007). This inactivation is an energy-saving process under hypoxic-ischemic conditions and dramatically increases ischemic tolerance in neurons. Hence, the SUMO-mediated inactivation of voltage-gated potassium channels is considered as a relevant neuroprotective mechanism (Stapels et al., 2010). Voltage-dependent Kv2.1 potassium channels initiate apoptotic signaling cascades in cortical neurons. (Pal et al., 2003). Conjugation of Kv2.1 channels by SUMO-1 and SUMO-2/3 modulates channel opening and voltage-gating (Plant et al., 2011). The resulting reduction of excitability is an efficient neuroprotective mechanism in neurons experiencing hypoxic-ischemic stress (Silveirinha et al., 2013).

The role of SUMOylation on sodium membrane traffic under hypoxic-ischemic conditions is a double-edged sword. The sodium/

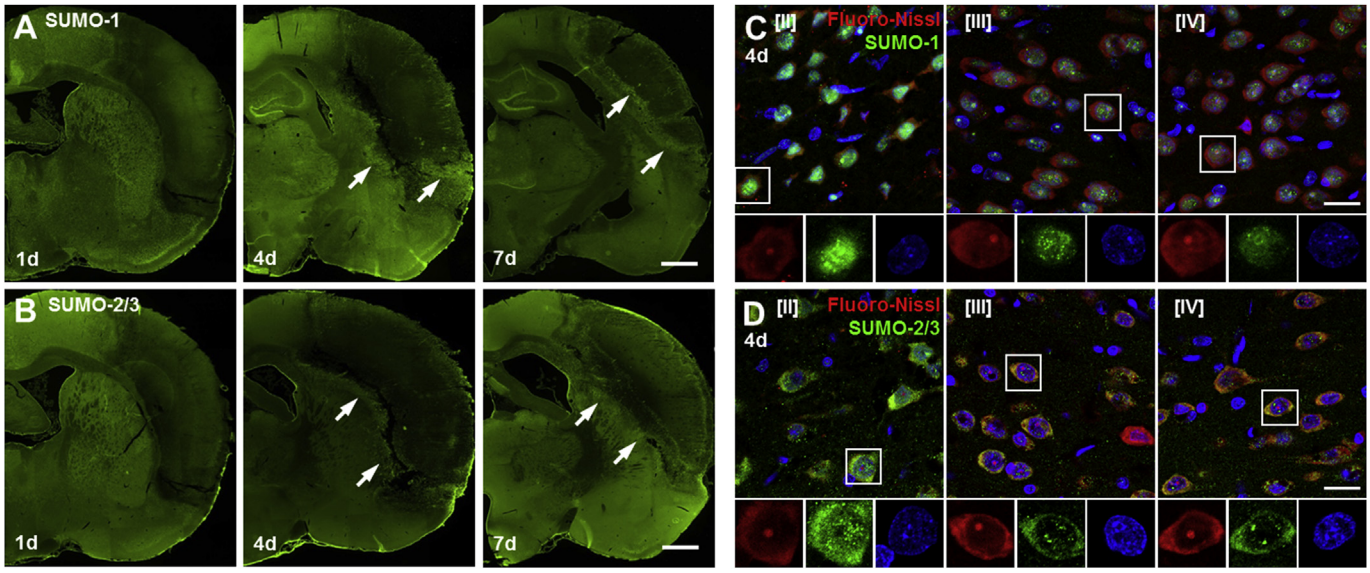

Fig. 1. Temporal and spatial SUMO expression profiles in neurons. **(A)** and **(B)** Coronal sections of the ipsilateral hemisphere of the rat brain. Expression of SUMO-1 (A) and SUMO-2/3 (B) 1, 4 and 7 days after permanent middle cerebral artery occlusion (pMCAO) in the rat. The infarct is clearly seen in the parietal cortex. Arrows point at locations with relatively high SUMO expression. **(C)** and **(D)** Expression of SUMO-1 (C) and SUMO-2/3 (D) in Fluoro-Nissl-positive neurons 4 days after pMCAO. SUMO expression is highest in areas close to the ischemic lesion. Nuclei in (C) and (D) were counterstained with DAPI (blue), and [II] to [IV] correspond to locations as given in Fig. 3A. Regions marked by a square are displayed separately beneath in a higher magnification. Scale bars: 1 mm (A, B), 20 μm (C, D). All images obtained from own, unpublished experiments. The brain specimens were derived from rats subjected to permanent middle cerebral artery occlusion as described elsewhere (Riegelsberger et al., 2011; Wagner et al., 2011). Supplementary material describing methodological details is available with this publication.

calcium exchanger NCX3 plays a relevant neuroprotective role in cerebral ischemia. Knockdown of NCX3 exacerbates ischemic damage induced by pMCAO and transient (t)MCAO (Pignataro et al., 2004; Molinaro et al., 2008). On the one hand, SUMO-1 directly interacts with NCX3. SUMO-1 conjugation pattern significantly increase in response to ischemia in the cortex, and silencing of SUMO-1 significantly increases the ischemic damage induced by tMCAO in the rodent brain (Cuomo et al., 2016). On the other hand, it was recently shown that SUMOylation of NaV1.2, an α-subunit of voltage-gated sodium (Na_v) channel that is widely distributed in the brain, underlies the immediate increase in voltage-gated sodium inward current (I_{Na}) in cultured cortical neurons under hypoxic-ischemic conditions (Plant et al., 2016). Sodium influx is well known to be a key trigger of neuronal damage under hypoxic-ischemic conditions, what illustrates that SUMOylation under these circumstances can exert both, protective and detrimental effects. Hence SUMOylation may be a complex therapeutic target to address in an attempt to optimize SUMOylation-mediated neuroprotection.

Kainate receptors contribute to ischemic cell damage. Neuroprotection can be exerted by the knockdown of the GluK2 kainate receptor subunit under OGD (Pei et al., 2006). SUMOylation reduces GluK2-induced excitation by subunit internalization at the postsynaptic membrane and thus contributes to neuroprotection. Indeed, global cerebral ischemia causes a massive increase in SUMOylation of GluK2, followed by endocytosis of kainate receptors (Zhu et al., 2012). SUMOylation does not only reduce the AMPA- and kainate receptor subunits GluR2/3 and GluR6/7 in the ischemically affected cortex and striatum, but also reduces GluR2/3 in the hippocampus after stroke (Cimarosti et al., 2008). SUMOylation has therefore a profound impairing effect on glutamate-mediated signaling, helping to counterbalance ischemic excitotoxicity in the brain. However, the internalization of AMPA-and kainate receptor subunits also activates JNK signaling, which has been described as an important contributor to ischemic neurotoxicity and apoptosis (Zhu et al., 2012).

SUMOylation further exerts neuroprotective effects by modulation of other receptor types. Metabotropic glutamate receptors modulate synaptic transmission and are believed to mediate neuroprotective effects (Caraci et al., 2012). The group-III glutamate receptor mGluR8b is a SUMO-1 substrate and its SUMOylation is likely an element of the self-protective response to hypoxic-ischemic damage in neurons (Dütting et al., 2011). SUMOylation of the cannabinoid receptor CB-1 is involved in the regulation of p53, which in turn is important for apoptosis under metabolic stress. Of note, CB-1 is a constitutive SUMO substrate and its de-SUMOylation is mediated by agonistic activation (Gowran et al., 2009). This leads to p53 activation, steeply increasing neuronal cell death during ischemia (Yonekura et al., 2006).

Interestingly, opposing effects were observed for the SUMOylation of glycogen synthase kinase 3β (GSK-3β). SUMO modulates subcellular localization, stability and kinase activity of GSK-3β, making affected cells more susceptible to apoptotic stimuli. In turn, inactivation of GSK-3β enhances neuroprotection after stroke, decreasing ischemic infarct size. GSK-3β inactivation also reduces the inflammatory response to cerebral ischemia (Collino et al., 2008; Zhou et al., 2011). On the other hand, GSK-3β phosphorylates the estrogen receptor β (ER-β), maximizing its SUMOylation (Picard et al., 2012). This enhances ER-β stability, what finally mitigates ischemic damage and blood-brain barrier disintegration. This is another good example for the rather complex mechanisms that might potentially be exerted by SUMOylation under hypoxic-ischemic stress in the CNS exerting both beneficial and detrimental effects.

5.6. SUMOylation and posttranslational modifications in the ischemic stress response

The complexity of SUMOylation effects is further exemplified by its interplay with posttranslational modifications. This is of particular relevance for the cellular response to hypoxic-ischemic stressors. Structural and functional similarities of SUMO and ubiquitin can lead to competitive and interdependent conjugations at the same sites of joint substrates. This may even result in sequential modifications of target proteins in the same signaling pathway and thereby exerting antagonistic or synergistic effects (Praefcke et al., 2012). Activation profiles of SUMO and ubiquitin following ischemia are similar. In contrast to SUMO-1, SUMO-2/3 and ubiquitin accumulate in insoluble protein aggregates following ischemia (Hochrainer et al., 2015). Both, ubiquitin and SUMO-3 bind to lysine residues of numerous joint substrates. Experiments with SUMO-transgenic mice indicate that the interplay between SUMO and ubiquitin is activated following cerebral ischemia, which has neuroprotective effects and reduces reperfusion injury. There is also a SUMOylation-dependent ubiquitin conjugation of target proteins, which can be dramatically increased following cerebral ischemia, and can be blocked by silencing SUMO-2/3 expression (Yang et al., 2014). SUMOylation itself contributes to the repair of DNA double helices and SUMOylation of DNA repair proteins is directly triggered by DNA damage. Poly-SUMOylated proteins are substrates of the SUMO-targeted ubiquitin ligases, which interlink SUMOylation and ubiquitin conjugation, and play a pivotal role in genome stability (Prudden et al., 2007). The NFκB inhibitory factor iκBα is an important substrate of competitive conjugation by SUMO proteinases, ubiquitin and phosphorylation. The phosphorylation-dependent ubiquitin conjugation mediates iκBα degradation. This is counter-acted by SUMOylation, which enhances the molecule's stability. This in turn inhibits activation of NFκB, what can increase neuroinflammation and causes detrimental effects during neuronal ischemia (Desterro et al., 1998; Emmanouil et al., 2011; Schneider et al., 1999).

In summary, SUMOylation is a pleiotropic regulator exerting complex effects in response to hypoxic-ischemic injury in the brain which are further complicated by a puzzling interplay with other factors and pathways. SUMOylation can have both beneficial and deleterious consequences, but fosters neuronal survival in the hypoxic ischemic brain. A detailed investigation of the underlying mechanisms and pathways is required to identify new molecular targets for future drug discovery in order to fully exploit the neuroprotective potential of SUMOylation. Fig. 2A summarizes relevant activities of SUMOylation in the post-ischemic neuron.

6. SUMO signaling and astrocytic functions

SUMOylation under hypoxic-ischemic conditions has been described for astrocytes in the brain, but the impact of SUMOylation on glial function is less well known. Our studies have shown that reactive astrocytes exhibit strong SUMO-1 and SUMO-2/3 immunoreactivity in the infarct border zone following permanent middle cerebral artery occlusion pMCAO in the rat (Fig. 3). An increase of nuclear SUMO-1 was observed 2 days after pMCAO, whereas an increase in SUMO-2/3 was seen after 3 days. A delayed upregulation of SUMO-2/3 as compared to SUMO-1 was already described for hippocampal neurons (Cimarosti et al., 2012). SUMO-1/2/3 immunoreactivity decreased at day 7 following pMCAO. The distinct activation patterns of SUMO in astrocytes following stroke points at important functions of SUMOylation also for the astroglial response to hypoxic-ischemic stress.

One study confirmed the presence of SUMO-1 in astrocytes (Akar and Feinstein, 2009). Overexpression of SUMO-1 inhibits β-

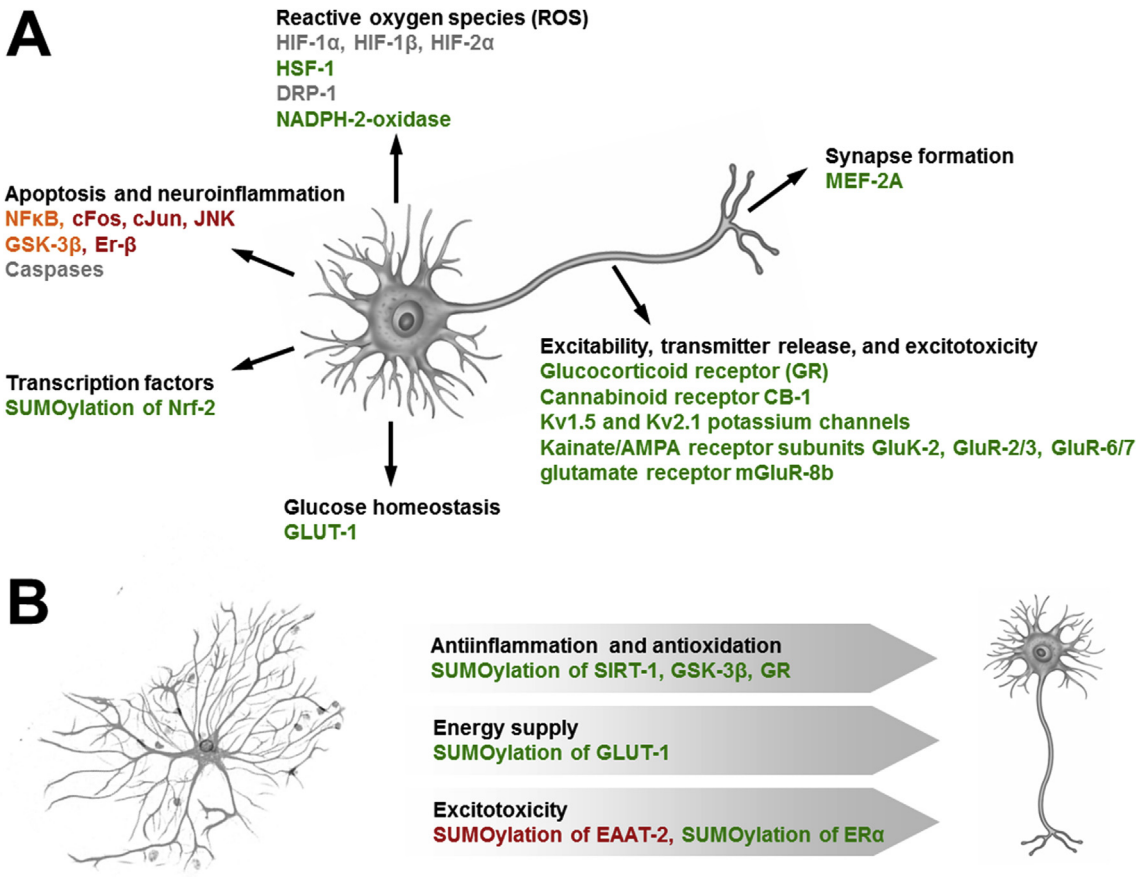

Fig. 2. Effects of SUMOylation under hypoxia-ischemia in neurons and astrocytes. **(A)** summarizes known potential SUMOylation targets in neurons being of relevance for post-ischemic neuroprotection. **(B)** provides an overview on relevant SUMOylation targets in astrocytes. Protective effects of SUMOylation on neurons and/or other neural cell populations are given in green, while red font indicates SUMOylation effects aggravating hypoxic-ischemic cell damage or targets which exert protective functions after deSUMOylation. Orange font indicates targets that can exert both, protective and detrimental effects after SUMOylation. Mechanisms still discussed controversially in literature regarding impact and overall relevance are given in grey font. **Abbreviations:** cFOS, cJUN: proto-oncogenes and elements of activator protein 1; DRP-1: dynamin-related protein 1; EAAT-2: excitatory amino acid transporter 2, a glutamate transporter; ER-β: estrogen receptor β; GLUT-1: glucose transporter 1; GR: glucocorticoid receptor; GSK-3β: glycogen synthase kinase 3β; HIF: hypoxia-inducible factor; HSF-1: heat shock factor protein 1; JNK: *c*-Jun N-terminal kinase; MEF-2A: myocyte-specific enhancer factor 2A; NFκB: nuclear factor kappa-light-chain-enhancer of activated B cells; Nrf-2: nuclear factor erythroid 2–related factor 2; SIRT-1: Sirtuin 1.

amyloid-mediated activation of astrocytes (Hoppe et al., 2013) and reduces expression of the astrocytic, pro-inflammatory NO-synthase (Akar and Feinstein, 2009). The early expression of SUMO-1 in astrocytes might therefore represent an anti-inflammatory response. The NAD-dependent deacetylase Sirtuin (SIRT)-1 attenuates apoptosis, oxidative stress and inflammation in both astrocytes and neurons, for example by downregulating of p53 and NFκB. This significantly contributes to protective effects under hypoxic-ischemic stress (Cheng et al., 2014). SIRT-1 is a SUMO-1 substrate and its SUMOylation is responsible for cardioprotective effects and is upregulated during myocardial ischemic preconditioning (Stastna and Van Eyk, 2015). Hence, the SUMOylated SIRT-1 is also thought to be responsible for protective mechanisms in the ischemic CNS.

The excitatory amino acid transporter 2 (EAAT-2), a glutamate transporter, is predominantly expressed by astrocytes. EAAT-2 is responsible for more than 90% of the glutamate uptake from the synaptic cleft (Yamada et al., 2006). Hence, astrocytic EAAT-2 is an important element of neuroprotection during ischemia. EEAT2 as a whole molecule, but also its CTE fragment (resulting from cleavage by caspase-3) are SUMO substrates. Of note, SUMOylation counteracts neuroprotective effects of EAAT-2. The SUMOylated fragment accumulates in astrocytic nuclei, which leads to a loss of astrocytes and subsequently of motoneurons, for example during the course of amyotrophic lateral sclerosis (Foran et al., 2011). The functional EAAT-2 protein is mainly located on the lipid rafts of astrocytic protrusions (Melone et al., 2011). SUMOylated EAAT-2 is translocated from the plasma membrane to the cytoplasm. This decreases astrocytic glutamate uptake capacities what ultimately aggravates neuronal excitotoxicity. The astrocytic estrogen receptor α (ERα) is supposed to enhance glutamate uptake during ischemia. Since SUMOylated ERα has a higher stability, SUMOylation may increase astrocytic glutamate uptake activities (Picard et al., 2012). Expression of ERα is regulated by GSK-3β, which exerts proinflammatory effects as reviewed above. Increasing ERα stability by SUMOylation rather than ERα expression may therefore be an important astrocytic mechanism contributing to neuroprotection.

Ischemic stress causes activation of the glucocorticoid receptor (GR), being associated with cellular damage during hypoxia-ischemia (Balkaya et al., 2011). The receptor is also expressed on astrocytes. JNK-mediated phosphorylation activates SUMOylation of the GR what in turn reduces its activity, exerting protective effects (Davies et al., 2008; Yang et al., 2014). Glycogen is an important alternative energy source in astrocytes. Astrocytes can process glycogen to glucose and transport it to neurons (Brown and Ransom, 2007). This is mediated by glucose transporters, particularly GLUT-1. Insertion and stability of GLUT-1 in the plasma membrane is regulated by the SUMO-E2 ligase UBc9, and SUMO-

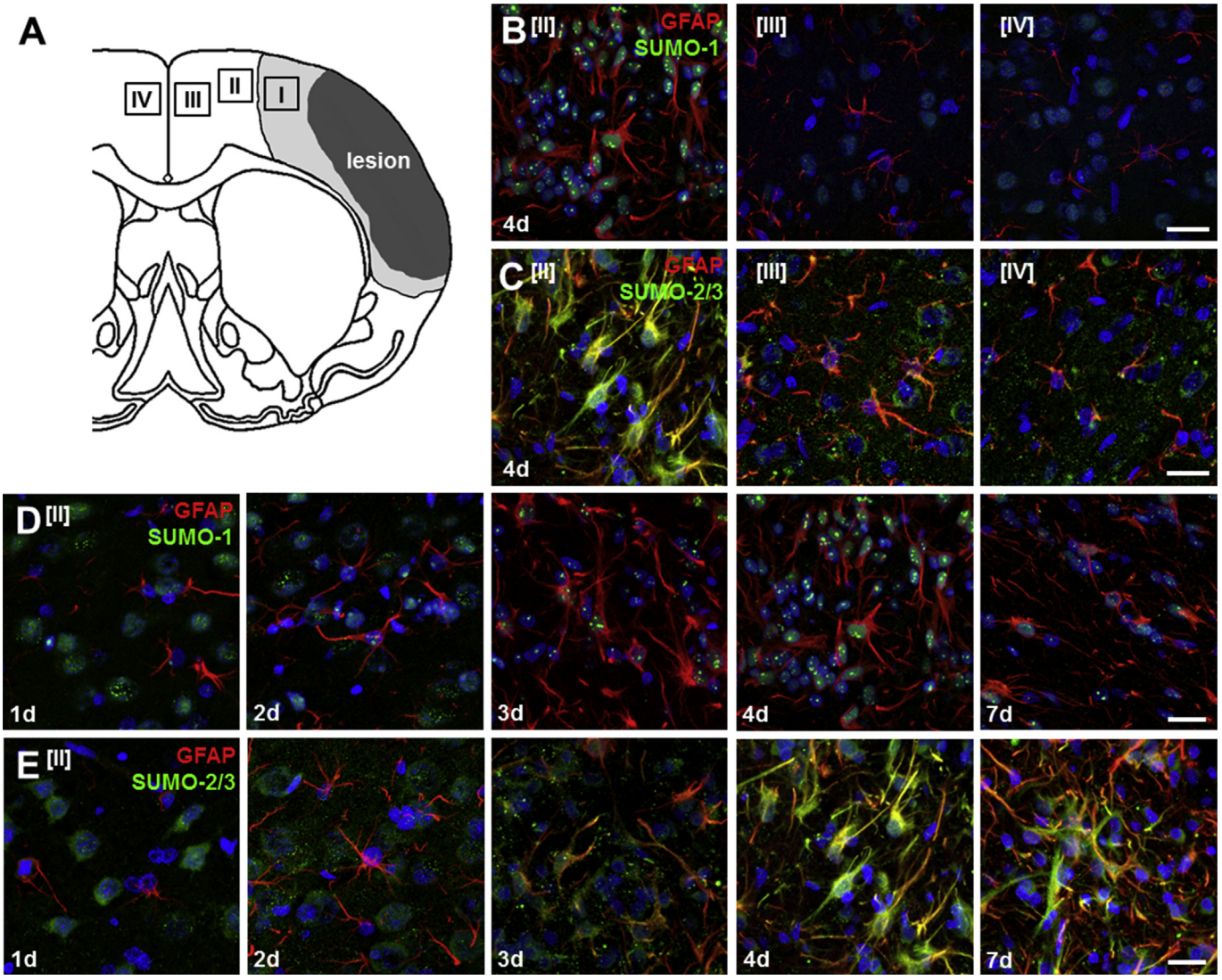

Fig. 3. Temporal and spatial SUMO expression profiles in astrocytes. **(A)** Schematic drawing of rodent brain with ischemic lesion and regions of interest, [I]: inner lesion border zone, [II]: outer lesion border zone, [III]: ipsilateral and [IV]: contralateral, unaffected brain tissue. **(B)** and **(C)** Expression of SUMO-1 (B) and SUMO-2/3 (B) in astrocytes of the outer lesion border [II], in unaffected ipsilateral [III], and unaffected contralateral brain tissue [IV], all 4 days after permanent middle cerebral artery occlusion (pMCAO). SUMO is predominantly expressed in areas close to the ischemic lesion in the rat brain. **(D)** and **(E)** Temporal expression profile of SUMO-1 and SUMO-2/3 in the outer lesion border zone. Astrocytic SUMO expression seems to peak around day 4. In contrast to SUMO-1, SUMO-2/3 expression is still strong at day 7 following pMCAO. Please note double-positive (SUMO-2/3$^+$ and GFAP$^+$) astrocytes in (C) and (E). Nuclei in (B) to (E) were counterstained with DAPI (blue). Scale bars: 20 μm. All images obtained from own, unpublished experiments. The brain specimens were derived from rats subjectedto permanent middle cerebral artery occlusion as described elsewhere (Riegelsberger et al., 2011; Wagner et al., 2011).

mediated GLUT-1 expression may therefore help to at least transiently maintain energy neuronal supply via astrocytic "feeding" during ischemia (Silveirinha et al., 2013). SUMO also supports astrocytic dampening of inflammatory reactions. SUMOylation of the Liver X receptor on astrocytes inhibits STAT-1 induced expression of IFN-γ, TNF-α, and IL-6 what strongly mitigates neuroinflammation (Lee et al., 2009b). An overview of astrocytic function being subject to SUMO regulation is given in Fig. 2B.

7. Post-ischemic SUMO expression in microglia and phagocytes

Ionized calcium binding adaptor molecule 1 (IBA-1) is a marker of phagocytes, particularly for microglia and macrophages. Increased SUMO expression is also observed in IBA-1-positive phagocytes in the infarct border zone, which has been revealed by studies from our lab. These cells are typically microglia or invaded monocytes/macrophages, and also show the characteristic delay in SUMO-2/3 activation (Fig. 4).

So far, however, only scattered knowledge is available regarding the role of SUMOylation in phagocytes after hypoxic-ischemic injury. Kv1.5 potassium channels, which were already discussed with the neuronal SUMO expression, also control microglial proliferation and the production of nitric oxide (Pannasch et al., 2006). It may be speculated that the SUMO-mediated inactivation of voltage-gated potassium channels as seen in neurons (Benson et al., 2007) also plays a role for microglial function, but further research is required to unravel its impact in more detail. In turn, endogenous production of H_2O_2 in phagocytes during the inflammatory reaction (oxidative burst) induces reversible inhibition of cytoplasmatic SUMOylation and may even induce de-SUMOylation in certain proteins or globally, depending on the H_2O_2 donor and amount (Bossis and Melchior, 2006a). This indicates that SUMO functions are strongly suppressed in these cells, but more detailed knowledge

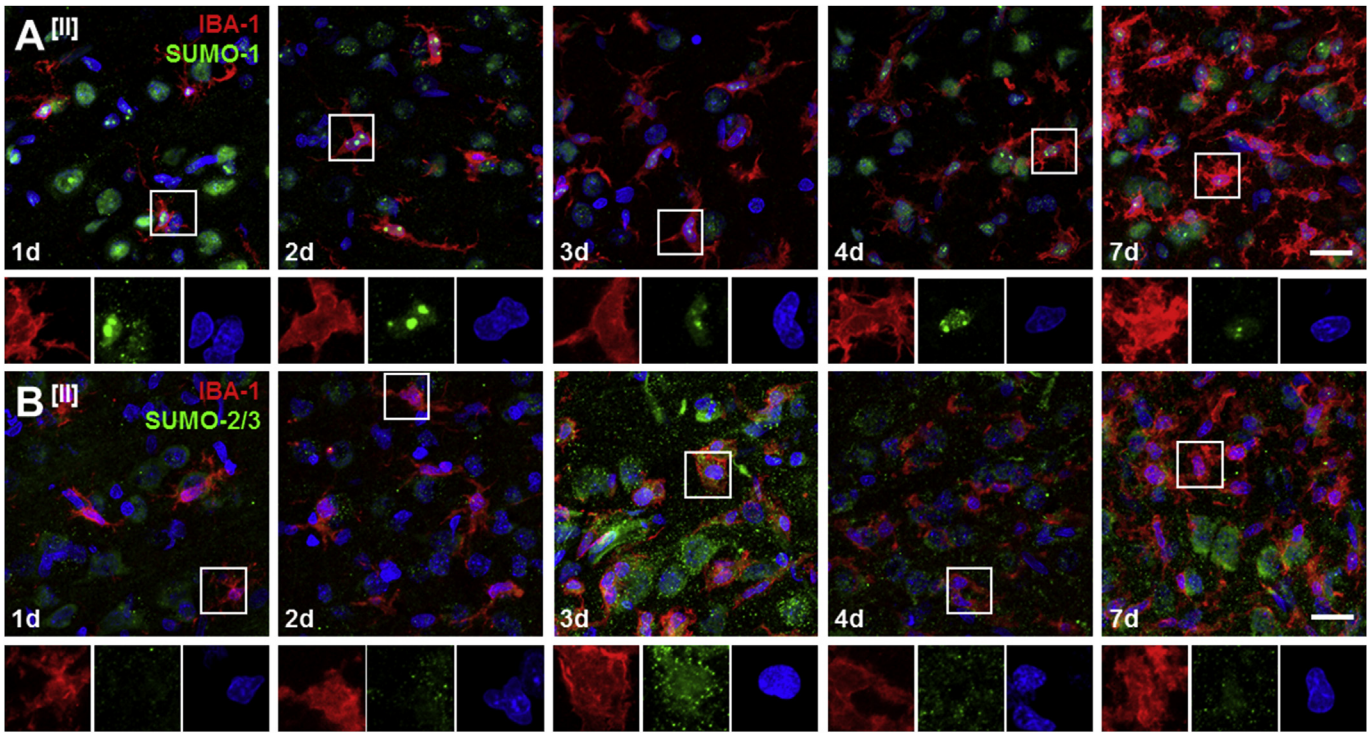

Fig. 4. Temporal SUMO expression profile in IBA-1-positive phagocytes. **(A)** SUMO-positive cells appearing immunonegative for IBA-1 are found 1 day after experimental ischemic stroke in the outer infarct border [II] in the rat. Next, SUMO-1 increases in parallel with the number of IBA-1-positive immune cells until day 7. **(B)** SUMO-2/3 expression is markedly delayed and peaks around day 3. SUMO 2/3 expression does not further increase at day 7, even though the number of IBA-1 cells is increasing. Region [II] corresponds to location given in Fig. 3A. Nuclei were counterstained with DAPI (blue). Regions marked by a square are displayed separately beneath in a higher magnification. Scale bars: 20 μm. All images obtained from own, unpublished experiments. The brain specimens were derived from rats subjected to permanent middle cerebral artery occlusion as described elsewhere (Riegelsberger et al., 2011; Wagner et al., 2011). Supplementary material describing methodological details is available with this publication.

is currently missing.

8. SUMOylation and post-stroke recovery

Neurofunctional deficits are a predominant consequence of hypoxic-ischemic brain injury. Brain plasticity allows the reorganization of the lesioned brain and can help to partially regain initially lost function. It is well known that SUMOylation is involved in synaptic function and plasticity on numerous levels (Schorova and Martin, 2016; Luo et al., 2013). Thereby, SUMOylation can significantly influence the establishment and maintenance of complex neuronal networks. This is exemplified in learning processes, in which SUMOylation is required for long-term potentiation (Lee et al., 2014a). In turn, SUMO-KD mice should have severe impairments in memory formation (Wang et al., 2014a).

There is some indication that the influence of SUMOylation on neural circuit build-up and maintenance is not restricted to cognitive functions. Synapse formation is regulated by the interplay between SUMOylation and acetylation, which is believed to be of importance for the functional regeneration of post-ischemic neuronal networks. The myocyte-specific enhancer factor 2 A (MEF-2A) is a transcription factor being strongly expressed in the brain. It exerts effects on neuronal differentiation and viability (Heidenreich and Linseman, 2004). SUMOylation and phosphorylation of MEF-2A also affects differentiation of the postsynapse and fosters synaptogenesis by suppressing MEF-2A activity. In turn, calcium influx induces dephosphorylation of MEF-2A by calcineurin, leading to de-SUMOylation and acetylation of a lysine residue finally inhibiting synaptic differentiation (Shalizi et al., 2006), what may hinder post-ischemic plasticity.

SUMOylation may hence be enrolled in plasticity-based recovery of sensor and motor functions following hypoxic-ischemic injury. It may therefore be speculated that the overall worse functional outcome in SUMO-KD mice after cerebral ischemia as discussed above (Zhang et al., 2017) may not only be due to lacking endogenous neuroprotection, but to some extent also to impaired post-ischemic brain plasticity, but existing data does not yet allow to confirm this idea. Unraveling the role of SUMOylation for post-stroke recovery requires long-term in vivo experiments, ideally featuring SUMO-KD after ischemic lesion induction to discriminate between SUMOylation influence on acute lesion development and long-term functional recuperation.

9. Conclusions and future research directions

Numerous studies support the idea that SUMOylation plays an important role in the cellular response to hypoxic-ischemic injury. Since most of the effects can contribute to neuronal survival, the assumption that SUMOylation can act as an endogenous neuroprotective mechanism is an intriguing concept. However, future research will have to fill two significant knowledge gaps. Firstly, the increasing body of indirect evidence suggesting that SUMOylation plays a role in the hypoxic-ischemic stress response in the brain needs to be ultimately confirmed by studies designed to provide direct evidence. Secondly, a number of SUMOylation effects are detrimental under conditions of hypoxic-ischemic stress, whereas the central role of others is still not completely elucidated. This situation is based on the fact that SUMOylation is not exclusively a protective response mechanism. It rather fulfills various decisive regulatory roles and helpful functions for intracellular metabolic processes in the steady state, both of which can nevertheless become detrimental in a pathophysiological environment. Hence, a

more detailed investigation of these processes is required for a deeper understanding of the overall ambiguous role of SUMOylation in the hypoxic-ischemic brain. Such understanding will be decisive in future attempts to exploit SUMOylation for mediating neuroprotective effects. Protective and detrimental SUMOylation effects likely take place in one cell and affect many pathways simultaneously, what for instance makes the conception of a drug-based intervention particularly challenging.

Importantly, this future research includes exploration of SUMOylation effects in cell types others than neurons that are affected or contribute to the peri- and postischemic environment. Astrocytes represent an important research subject due to their supportive function for the neuronal compartment. However, revealing the effects of SUMOylation in post-ischemic oligodendrocytes, microglia, and invading immune cells will also be pivotal in this context. It will finally be decisive to understand which clinical situations require and which interventional tools allow the targeted manipulation of the post-ischemic SUMOylation response in order to optimize its neuroprotective impact not only acutely, but also in the long run.

Acknowledgements and funding

The authors want to thank Dr. Christoph Harms for the helpful scientific discussions helping to significantly improve this manuscript. The authors further thank Dr. Alexander Deten for helpful discussions of experimental procedures and the topic itself. Only intramural funds were be used to support own experimental work presented in this review.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.neuint.2017.03.011.

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