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Short communication

Inflammation and autophagy in peripheral nerves of rodent models with metabolic syndrome and type 2 diabetes mellitus

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ABSTRACT

Metabolic syndrome (MetS) and type 2 diabetes mellitus (T2D) are associated with inflammation and the accumulation of macrophages in peripheral nerves, which increases the risk of developing peripheral neuropathy (PN). We have previously investigated that macrophage infiltration in the peripheral nerves of animals with T2D (leptin-deficient *ob/ob* mice, leptin receptor-deficient *db/db*) correlated with PN, whereas this process in animals with MetS (Wistar Ottawa Karlsburg W (*RT1u*) *WOKW* rat) did not lead to neuropathic changes. Additional data presented in this study suggest an association between increased mRNA expression of the anti-inflammatory marker IL-10 and autophagy in the prevention of neuropathy.

Obesity, hypertension, hyperinsulinemia, and impaired glucose tolerance (IGT), diagnosed in patients with the MetS and diabetes are predictors which activate inflammatory processes in adipose tissue (Wellen and Hotamisligil, 2005; Andersen et al., 2016). Chronic inflammation in diabetes simultaneously leads to secondary complications such as peripheral neuropathy, nephropathy and retinopathy. However, clinical studies confirm that IGT and inflammation are already risk factors for the development of peripheral neuropathy (PN), even in the absence of manifest diabetes (Miscio et al., 2005; Gordon Smith and Robinson Singleton, 2006). Thus, patients with MetS develop a peripheral neuropathy phenotype similar to that diagnosed in patients with manifest diabetes, including decreased motor and sensory nerve responses, pain, microvascular dysfunction, damage of the small nerve fibers, accompanied by macrophage infiltration into endo/perineum (Ziegler et al., 2009; Zhou et al., 2011). Similarly, our research group showed extensive autonomic nerve dysfunctions, affecting both parasympathetic and sympathetic nervous systems with damage of thinly myelinated and C unmyelinated fibers already in the obese children without diabetes (Baum et al., 2013).

Notably, the activation of macrophages in the inflammation process could occur bidirectional (Pop-Busui et al., 2016). Whereas the classically activated macrophages (M1) express a specific set of pro-inflammatory mediators, alternatively activated macrophages (M2) exhibit an anti-inflammatory phenotype (Osonoi et al., 2022). The expression of pro-inflammatory mediators like interleukin −1ß and-6 (IL-1β, IL-6), tumor necrosis factor alpha (TNFα) and monocyte chemoattractant protein-1 (MCP-1) of obese individuals is among the biomarker for the diagnosis of PN (Pop-Busui et al., 2016; Sommer et al., 2018) Recently, a successful anti-inflammatory treatment with M2 polarized macrophages in the peripheral nerves have been demonstrated (Huang et al., 2020). Similarly, switching from M1 to M2 with niacin administration in patients with Parkinson's disease or ex vivo

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administration of M2 macrophages in patients with stroke showed a positive therapeutic effect (Chernykh et al., 2016; Wakade et al., 2018). Both, the stimulation and inactivation of inflammation are distinctly regulated by the process of autophagy (Levine et al., 2011). Generally, autophagy performs a neuroprotective function in the neural tissue by clearance of aggregated and toxic proteins (Menzies et al., 2017). Genetic studies in human and mouse nerve cells have shown that basal deficiency or shutdown of autophagy genes like *Atg5*, *Atg7* causes neurodegeneration and cell death (Aman et al., 2021; Sun et al., 2023). The authors postulated that the mechanistic relationship between autophagy deficiency and nerve cell death could be the target for therapeutic interventions. Although up-regulation of autophagy has been observed in post-inflammatory peripheral nerve regeneration (Mohseni, 2011), the alternation of inflammatory pathways associated with autophagic activity is still poorly understood.

These studies complement our previous results by showing a correlation between pro/ anti-inflammatory pathway activation and autophagy in peripheral nerves of animal models with MetS and T2D.

The following animals have been used for experimental studies: *ob/ob* leptin-deficient mice with mild type 2 diabetes (B6.V-Lep *ob/ob*) and ob/+ healthy control mice (B6.V-Lep ob/J), *db/db* leptin receptor-deficient mice with severe type 2 diabetes and *db/+* healthy control mice, Wistar Ottawa Karlsburg W (*RT1u*) *WOKW* rats with metabolic syndrome and healthy *LEW.1 W* control rats. *Ob/ob*, *ob/+* , *db/db* and *db/+* mice were obtained from the Taconic Europe (Ry, Denmark) and *WOKW* and *LEW.1 W* rats from the Department of Laboratory Animal Science of the University of Greifswald (Karlsburg, Germany) and transferred to Leipzig in 2010. All animals were adjusted to the local animal facilities and maintained on a 12 h light/dark cycle with free access to water and were fed with regular food (Global Rodent T.2018. R12; Harlan Teklad) containing 12 % of calories from fat. Animal studies were approved by the local authorities of the state of Saxony, Germany, as recommended by the responsible local animal ethics review board (Approval No: TVV10/11, TVV25/12, TVV63/12, T01/13, TVV65/15, T08/16, Landesdirektion Leipzig, Germany). The characteristics of the metabolic parameters of compared animals have been summarized in **Table 1**.

Sciatic nerve tissue samples were collected immediately after euthanasia by an overdose of isoflurane followed by cervical dislocation, as previously published (Kosacka et al., 2012, 2013, 2019; Paeschke et al., 2019). Total RNA was isolated from sciatic nerves (n = 3 per group) of *db/db*, *db/+* , *ob/ob* and *ob/+* mice, *WOKW* and *LEW.1 W* rats using TRIzol (Life Technologies, Grand Island, NY), and 1 μg RNA was reverse transcribed with standard reagents (Life Technologies, Grand Island, NY). Quantitative real-time PCR (qPCR) were performed using the standard curve method in a fluorescent temperature cycler using the TaqMan assay as previously described (Kosacka et al., 2022). Fluorescence was detected on an ABI PRISM 7000 sequence detector (Applied Biosystems, Darmstadt, Germany). From RT-PCR, 2 μl was amplified in a 26-μl PCR using the Brilliant SYBR Green QPCR Core Reagent kit from Stratagene (La Jolla, CA) according to manufacturer's instructions. The mouse and rat primers probes, Atg5 (Mm01187303_m1, Rn01767063_m1), Atg7 (Mm00512209_m1, Rn01492725_m1), Beclin1 (Mm01265461_m1, Rn00586976_m1), IL-6 (Mm00446190_m1, Rn01410330_m1), IL-10 (Mm01288386_m1, Rn99999012_m1), IL-13 (Mm99999190_m1, Rn00587615_m1), MCP-1 (Mm00443258_m1, Rn00580555_m1), mTOR (Mm00444968_m1, Rn00693900_m1), TNFα (Mm00443258_m1, Rn99999017_m1) and 18sRNA (Hs99999901_s1, endogen reference) were purchased from Life technologies (Darmstadt, Germany). The quantification of the mRNA was carried out using the second derived maximum method of the TaqMan (Applied Biosystems) software.

Our previous studies have shown the significant infiltration of macrophages and T cells in the peripheral nerves of WOKW rats with MetS (Kosacka et al., 2013), ob/ob and db/db mice with mild and severe T2D (Kosacka et al., 2012, 2019; Paeschke et al., 2019), respectively. Whereas, the inflammatory signs in diabetic mice leaded to degeneration of small myelinated A-delta and unmyelinated C nociceptive fibers of skin and of the large myelinated Aα proprioceptive, reduction of nerve conduction velocity (NCV), the WOKW rats do not develop overt neuropathy. The characteristics of neuropathy symptoms of the compared animals are summarised in Table 2.

Unexpectedly, the significant up-regulated autophagy with atg5 and atg7 protein expression, increased LC3-II/LC-I ratio and massive autophagosomes formation, has been determined in sciatic nerves of WOKW rats as compared to health LEW.1 W control animals (Kosacka et al., 2013).

It has been proposed that activation of inflammatory signaling pathway and cytokine production could be stimulated by autophagy (Rocha et al., 2020). The mechanisms of balance expression of pro-inflammatory and anti-inflammatory cytokines in peripheral nerves is still unclear. Here, we investigated whether there is a relationship between the expression of cytokines and markers of autophagy at the mRNA level. We detected significantly higher expression of pro-inflammatory cytokines: IL-6, MCP-1 and TNFα mRNA in sciatic nerves of ob/ob, db/db and WOKW animals as compared with healthy controls, respectively (*Fig. 1* A). However, the mRNA expression of anti-inflammatory cytokine, IL-10, has been significantly and about 4-fold upregulated in sciatic nerves of WOKW rats, exclusively vs. healthy LEW.1 W control animals (*Fig. 1* A). Simultaneously, a significant increase in mRNA expression of autophagy marker Atg7 (2.8-fold) and Beclin-1 (1.8-fold) has been found in peripheral nerves of WOKW rats as compared with control animals (*Fig. 1* B). Similar, but less significant tendency was observed in the Atg7 expression (1-fold) in peripheral nerves of ob/ob mice (mild T2D) vs. healthy ob/+ controls (*Fig. 1* B).

Table 1
Characteristics of study subjects at an age of 3-months (n = 10; mean ± SD).

	ob/+	*ob/ob*	*db/+*	*db/db*	*LEW.1 W*	*WOKW*
Body weight (g)	31.1 ± 1.7	50.5 ± 6.6**	32.1 ± 2.1	45.4 ± 9.3**	503.3 ± 12	673.4 ± 21**
Blood glucose (mmol/l)	5.8 ± 1.4	12.5 ± 0.6***	6.1 ± 0.7	18.5 ± 1.8***	5.8 ± 0.5	6.5 ± 0.9^{NS}
HbA1c (%)	3.9 ± 0.4	6.1 ± 1.5^{I*}	4.2 ± 0.2	8.2 ± 2.0^{I**}	3.7 ± 0.3	3.8 ± 0.2^{NS}
Triglyceride	0.8 ± 0.2	0.6 ± 0.1^{NS}	1.0 ± 0.2	1.6 ± 0.5^{NS}	1.8 ± 0.3	5.4 ± 1.6**
Cholesterol	1.7 ± 0.2	4.5 ± 0.7**	2.4 ± 0.2	4.3 ± 0.9*	1.7 ± 0.2	3.7 ± 0.9*
HDL	1.5 ± 0.1	2.8 ± 0.5*	2.0 ± 0.3	3.5 ± 0.6*	1.3 ± 0.2	3.0 ± 0.8*
LDL	0.2 ± 0.1	1.6 ± 0.2*	0.3 ± 0.1	0.7 ± 0.5^{NS}	0.3 ± 0.1	0.4 ± 0.1^{NS}
Serum insulin (ng/ml)	0.9 ± 0.4	12.9 ± 4.1**	0.9 ± 0.4	1.5 ± 0.6^{NS}	1.3 ± 0.5	9.1 ± 0.6***

Blood glucose concentrations were measured in whole blood taken from the ventral caudal vein using an Opticum Omega glucometer (GlucoMen, Menarini Diagnostics, Berlin, Germany). Serum analyses have been performed in the Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics at Leipzig University.

[I]references: Type 2 Diabetes mellitus HbA1c ≥ 5. Note that the HDL level in *db/db* mice, *ob/ob* mice, and *WOKW* rats is higher than in control animals, which is different from patients with T2D. Values represent means ± SEM; * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, according to the one-way analysis of variance together with Newman-Keuls test; NS, not significant.

Table 2
Nerve conduction studies, macrophages distribution in sciatic nerve and intraepidermal nerve fibers density (n ≥ 5; mean ± SEM).

	ob/+	*ob/ob*	*db/+*	*db/db*	*LEW.1 W*	*WOKW*
mNCV (m/s)	46 ± 0.6	34 ± 2**	47.8 ± 6.7	31 ± 8***	47 ± 6.5	47 ± 10.5^{NS}
s/mix aff. NCV (m/s)	57.8 ± 5	45 ± 4.8*	63.8 ± 15.5	54.7 ± 23^{NS}	68.5 ± 10	58.4 ± 7^{NS}
IENFD (fibers/mm^2)	16 ± 3	7 ± 1***	24 ± 2	18 ± 2***	23 ± 5	21 ± 3^{NS}
Number of macrophages /mm^2	5.0 ± 1^{I}	15 ± 2^{I**}	9.0 ± 1^{II}	17 ± 2^{II**}	5.0 ± 2^{I}	90 ± 9^{I**}
Degree of PN	N/C	moderate	N/C	high	N/C	N/C

IENFD, intraepidermal nerve fiber density (characterized by PGP9.5 immunostaining of hind foot skin samples), mNCV, motor nerve conduction velocity (performed on sciatic nerve), s/mix.aff. NCV, sensory/mixed afferent nerve conduction velocity (performed on sciatic nerve), N/C, no changes, PN, peripheral neuropathy. The number of macrophages in the sciatic nerve was determined by Iba-1^{I} or F4/80^{II} immunostaining. Values represent means ± SEM; * p ≤ 0.05, ** p ≤ 0.01, *** p ≤ 0.001, according to the one-way analysis of variance together with Newman-Keuls test. NS, not significant.
Adapted from (Kosacka et al., (2013), (2019); Paeschke et al., (2019).

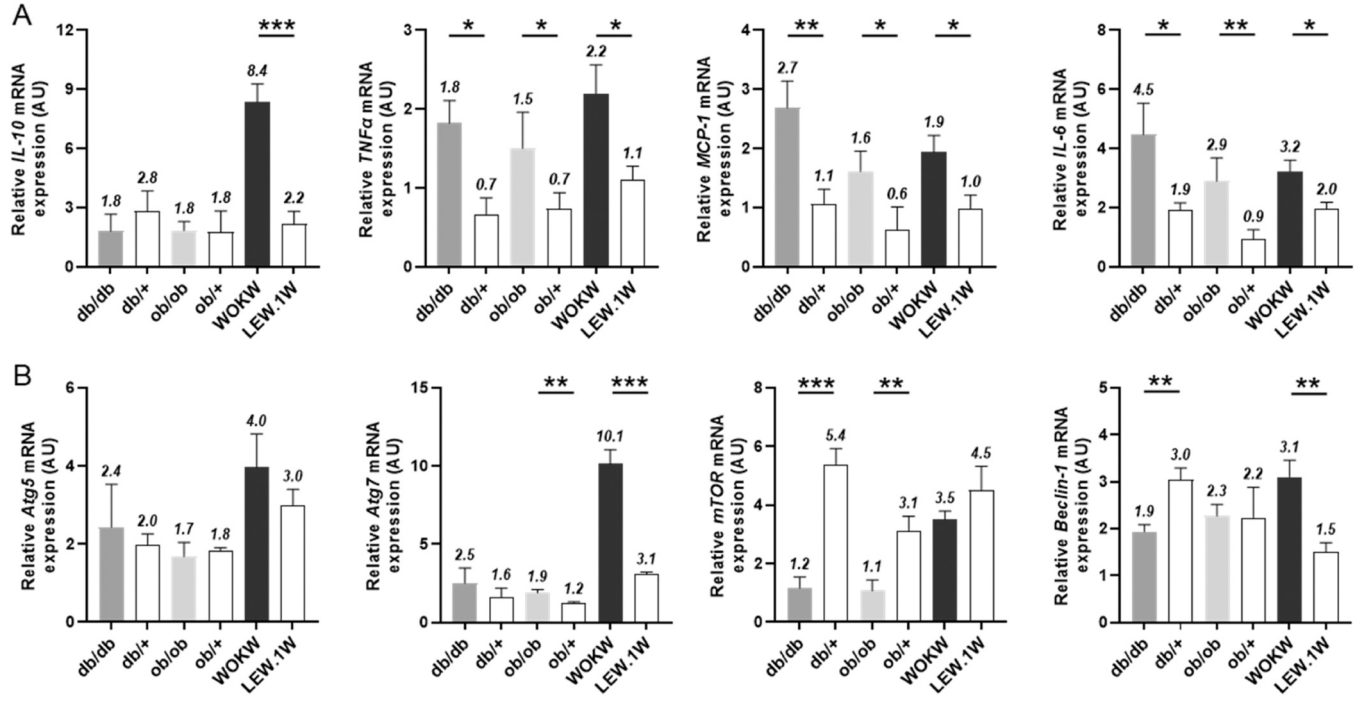

Fig. 1. mRNA expression of pro-inflammatory, anti-inflammatory and autophagy related genes in sciatic nerves of animals with MetS and mild or severe T2D. **A**: TNFα, MCP-1 and IL-6 mRNA expression was increased in sciactic nerves in animals with MetS and T2D vs. healthy controls. Anti-inflammatory IL-10 and autophagy marker Atg7 and Beclin 1 mRNA expression (**B**) was significantly higher in the sciatic nerves of WOKW rats with MetS as compared to other groups. Data from n = 3 per group are represented as mean ± SEM. * p ≤ 0.05, ** p ≤ 0.01, *** p ≤ 0.001, according to the one-way analysis of variance together with the Newman-Keuls test. The individual mean values are presented on the bars.

In addition, the function of inflammatory and autophagy genes in relation to the development of neuropathy in animals with MetS and T2D has been investigated using correlation analysis. A positive correlation between up-regulated expression of autophagy markers (Atg7 and Beclin 1) and anti-inflammatory IL-10 cytokine has been found in sciatic nerves of WOKW rats with MetS without neuropathy. Simultaneously, moderate autophagic activity was shown corresponding to moderate expression of anti-inflammatory cytokines in correlation with mild and severe T2D with neuropathy compared to healthy controls (no changes). These results indicate a neuroprotective function of autophagy in peripheral nerves by regulating the anti-inflammatory signaling pathway (*Fig. 2*). Importantly, the mRNA expression of anti-inflammatory and autophagy marker were significantly higher in the sciatic nerves of WOKW rats and resulted with healthy nerve phenotype as compared to other groups.

Although PN is classified as a multifactorial disease, active inflammation appears to be a determining factor in neurodegeneration. Increased oxidative stress and production of reactive oxygen species (ROS) lead to macrophage recruitment, induction of their pro-inflammatory M1 phenotype, what is accompanied by neuropathic pain (Scholz and Woolf, 2007; Rendra et al., 2019). Thus, the total number of macrophages does not appear to be as important as their phenotype, e.g., anti-inflammatory (M2) and the mechanisms responsible for the switch (M1/M2). Our results suggest that pro- and anti-inflammatory mechanisms occurring in peripheral nerves are dependent on autophagy activity. However, the elevated expression of the pro-inflammatory cytokines *TNFα*, *MCP-1*, and *IL-1* was observed in the sciatic nerve of all animals with MetS (*WOKW* rats) and in those with mild and severe T2D (*ob/ob* and *db/db* mice). Unexpectedly, high expression of the anti-inflammatory cytokine *IL-10* was found to accompany increased autophagy levels only in the nerves of *WOKW* rats, even when compared to healthy controls. In accordance, the unbalanced regulation of pro-/anti-inflammatory cytokines with lack of expression of anti-inflammatory marker, *IL-10* in peripheral nerves of mice with T2D and neuropathy have been confirmed by Yanik and coauthors (Yanik et al., 2020). The exogenously administration of IL-10 significantly reduced the inflammation of peripheral nerves (Yanik et al., 2020). Although it has been proven that the switch from M1 to M2

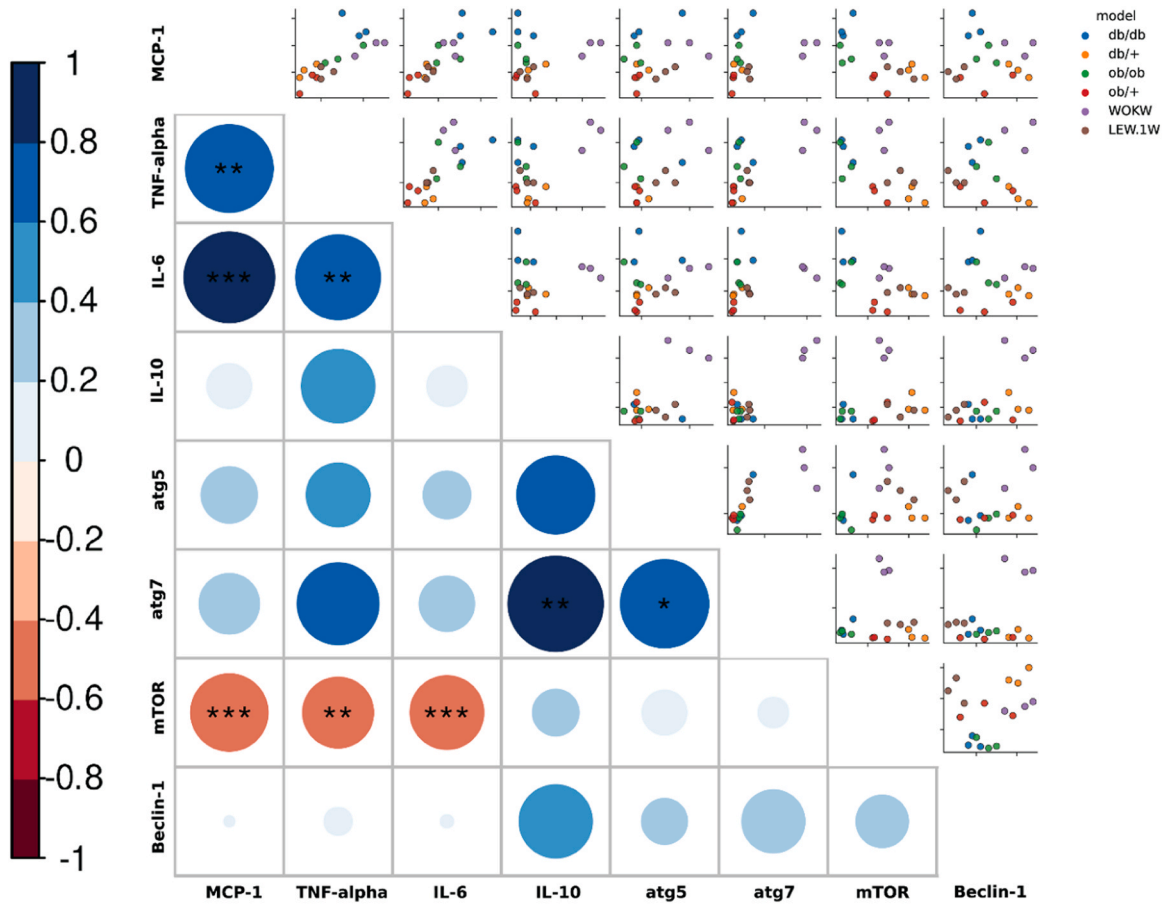

Fig. 2. Correlation analysis of neuronal expression of pro/anti-inflammatory and autophagy markers in MetS without PN (*WOKW* rats) and in mild and severe T2D with PN (*ob/ob*, *db/db* mice). Correlation matrix based on Pearson analysis with positive correlation in blue and negative correlation in red. Areas of the circle are proportional to the correlation coefficient. Significance levels are *0.05, **0.01, and ***0.001, with p-values adjusted for multiple testing using Benjamini and Hochberg (BH); n = 3 per group. Corresponding individual scatter plots colored by animal model.

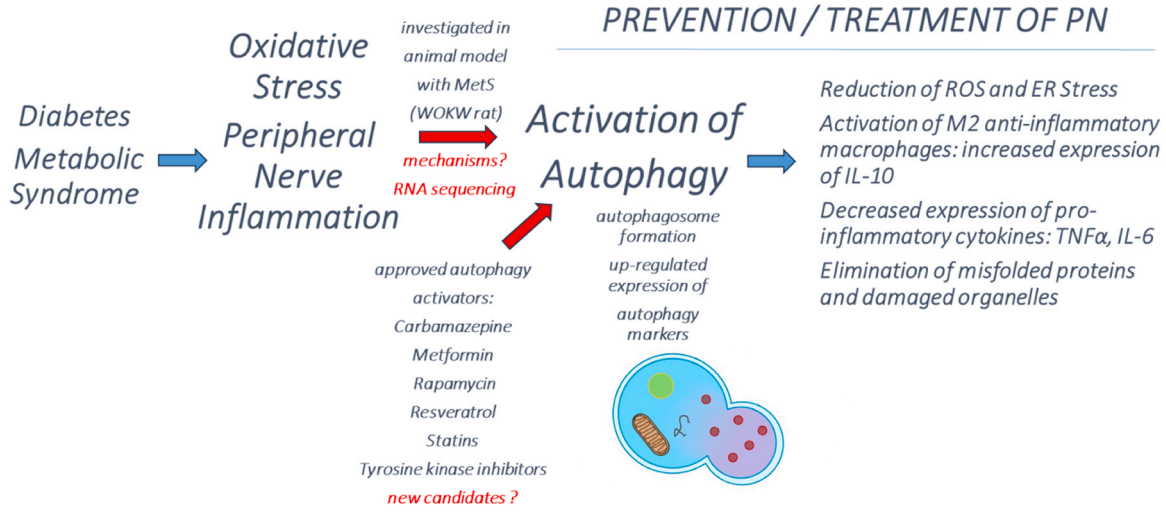

Fig. 3. Schematic illustration of prevention / treatment of diabetic and metabolic complications such as peripheral neuropathy. The mechanism and target disease shown based on our own animal studies and human data, adapted from Levine et al. (Levine et al., 2015). An unknown, alternative mechanism of autophagy activation, beyond inflammation, in the peripheral nerves of animals with metabolic syndrome may prove crucial in therapy. ER, endoplasmic reticulum, IL-10, interleukin-10, IL-6, interleukin-6, ROS, reactive oxygen species, TNFα, tumor necrosis factor alpha.

macrophages in peripheral nerves is promoted by *IL-10*, other cytokines, such as *IL-13*, are also involved in this process, creating a microenvironment conducive to the repair of damaged neural tissue (Ma et al., 2015). Our additional studies on *IL-13* mRNA expression showed minimal nerve exposure to this cytokine in mice and no expression in rats (data not shown). Analysis of *IL-13* mRNA expression in the sciatic nerves of *ob/ob* mice with moderate neuropathy revealed a statistically significant increase in this group, although the increase was a maximum of 2-fold compared to control animals. In the peripheral nerves of *db/db* mice, a severe neuropathy model, there was an increase in *IL-13* expression of approximately 1.5-fold compared to controls, but this change was not statistically significant.

In our previous works, we have investigated the protective role of autophagy in adipose tissue (AT) of patients with MetS vs. T2D patients (Kosacka et al., 2015) and in peripheral nerves of *WOKW* rats with MetS (Kosacka et al., 2013). Here, we have shown that autophagy-dependent regulation of anti-inflammatory cytokine *IL-10* correlated with MetS without neuropathic changes. Conversely, a pro-inflammatory phenotype of peripheral nerve due to moderate or impaired autophagic activity in *ob/ob* and *db/db*, T2D mice with neurodegeneration

Since autophagy can activate an anti-inflammatory response, it is believed that this process may play the important role in the treatment of inflammatory diseases (Levine et al., 2015; Rocha et al., 2020). Currently, autophagy inducers are used in anti-inflammatory therapy, tested for the form of application and for its side effects. The precise mechanism of "self-activation" or compensatory alteration of autophagy gene expression (Fig. 3) in animals with MetS towards tissue protection requires further explanation.

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None

CRediT authorship contribution statement

Nowicki Marcin: Writing – review & editing, Supervision, Data curation. **Palus Katarzyna:** Validation. **Blüher Matthias:** Validation. **Bulc Michal:** Project administration. **Stock Peggy:** Writing – review & editing. **Paeschke Sabine:** Visualization, Methodology. **König Matthias:** Formal analysis. **Klöting Nora:** Resources, Methodology, Funding acquisition. **Ebert Thomas:** Investigation. **Baum Petra:** Writing – review & editing, Visualization, Conceptualization. **Krupka Sontje:** Methodology. **Kosacka Joanna:** Writing – original draft, Supervision, Funding acquisition, Data curation, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationship that could have appeared to influence the work reported in this paper.

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