Experimental Eye Research 144 (2016) 81–89

Contents lists available at ScienceDirect

Experimental Eye Research

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

Review

The role of autophagy in axonal degeneration of the optic nerve

Jan Christoph Koch [a, **], Paul Lingor [a, b, *]

[a] Department of Neurology, University Medicine Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany
[b] Center for Nanoscale Microscopy and Molecular Physiology of the Brain (CNMPB), Göttingen, Germany

ARTICLE INFO

Article history:
Received 20 March 2015
Received in revised form
6 August 2015
Accepted in revised form 18 August 2015
Available online 24 August 2015

Keywords:
Autophagy
Optic nerve
Axonal degeneration
Retinal ganglion cells
Glaucoma
Optic atrophy

ABSTRACT

Different pathological conditions including glaucoma, optic neuritis, hereditary optic atrophy and traumatic injury lead to a degeneration of retinal ganglion cell axons in the optic nerve. Besides this clinical relevance, several experimental models employ the optic nerve as a model system to examine general mechanisms of axonal degeneration in the central nervous system.

Several experimental studies have demonstrated that an activation of autophagy is a prominent feature of axonal degeneration in the optic nerve independent of the underlying pathological condition. However, the function of autophagy in axonal degeneration remains still unclear. Inhibition of autophagy was found to attenuate axonal degeneration within the first hours after optic nerve lesion. Other studies focusing on survival of retinal ganglion cells at later postlesional time points report contradicting results, where both inhibition and induction of autophagy were beneficial for survival, depending on the model system or examination time. Therefore, a more precise understanding of the role and the kinetics of autophagy in axonal degeneration is mandatory to develop new therapies for diseases of the optic nerve.

Here, we review the literature on the pathophysiological role of autophagy in axonal degeneration in the optic nerve and discuss its implications for future therapeutic approaches in diseases of the eye and the central nervous system involving axonal degeneration.

Contents

1. Introduction

The optic nerve transmits visual information from the retina to the brain. It is formed by the axons of retinal ganglion cells (RGCs), which are the only projecting neurons of the retina. Damage to the optic nerve leads to disabling and often irreversible visual impairment. The optic nerve can be affected by several clinically relevant pathological conditions: In glaucoma, an increased intraocular pressure (IOP) results in damage and eventually mechanical transection of RGC axons at the lamina cribrosa of the optic nerve head, in addition to several intrinsic degenerative mechanisms of the RGC

Abbreviations: AAV, adeno-associated viral vector; ADOA, autosomal dominant optic atrophy; CMA, chaperone-mediated autophagy; CNS, central nervous system; IOP, intraocular pressure; LC3, microtubule-associated protein 1 light chain 3; LHON, Leber's hereditary optic neuropathy; Nmnat, nicotinamide mononucleotide adenylyltransferase; ONH, optic nerve head; OPA1, optic atrophy 1; RGC, retinal ganglion cell; ROCK2, Rho-associated protein kinase 2; TNF, tumor necrosis factor; WD, Wallerian degeneration; WLD^S, slow Wallerian degeneration.

* Corresponding author. Dept. of Neurology, University Medicine Göttingen, Robert-Koch-Str. 40, 37075 Göttingen, Germany.
** Corresponding author.
E-mail addresses: jkoch@med.uni-goettingen.de (J.C. Koch), plingor@gwdg.de (P. Lingor).

http://dx.doi.org/10.1016/j.exer.2015.08.016
0014-4835/

axons (Bellezza et al., 2003; Burgoyne et al., 2004, 2005; Nickells et al., 2012). Inflammatory diseases like optic neuritis involve a pathological autoimmune response against optic nerve tissue, primarily against the surrounding myelin sheaths, but also against RGC axons, resulting in a considerable axonal loss (Costello et al., 2006). Several hereditary optic atrophies like Leber's hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (ADOA) lead to chronic degeneration of RGC axons mainly via impairment of mitochondrial function (Newman and Biousse, 2004). A traumatic or mechanical lesion to the optic nerve can result from severe head trauma or local invading tumor growth (Sarkies, 2004). Besides, a mechanical lesion of the optic nerve serves as an important model system in animals to induce and study axonal degeneration in the central nervous system (CNS) (Koch et al., 2011).

All of these pathological conditions result in a degeneration of RGC axons in the optic nerve, which is almost inevitably followed by the apoptotic cell death of the complete RGC (Rabacchi et al., 1994). The clinical prognosis is closely related to the amount of RGC survival, therefore protection of RGCs and their intact axonal projections to the brain via the optic nerve is the ultimate goal of all therapeutic strategies (Lambiase et al., 2009; Martin and Quigley, 2004). This is especially important, because also those RGCs and glial cells, that are not or only partially affected by the primary damage are at risk to be affected by secondary degeneration (Li et al., 2014). Thus, it is crucial to understand the biochemical processes that underlie RGC degeneration in order to design an effective therapeutic strategy.

The optic nerve is an excellent model system for studying the physiology and pathology of axons in the CNS due to its good surgical accessibility, well-defined anatomy and the possibility to easily manipulate RGCs (Koch et al., 2011). Numerous reports showed that the activation of the autophagy cascade is one of the most prominent features of acute and chronic axonal degeneration in the optic nerve (Deng et al., 2013; Kim et al., 2008; Knoferle et al., 2010; Munemasa and Kitaoka, 2015; Piras et al., 2011; Rodriguez-Muela et al., 2012).

Autophagy is an important physiological cellular process for the degradation of damaged organelles, digestion of misfolded proteins and adaption to unfavorable nutrient conditions (Boya et al., 2013). It can be subdivided into three different classes: macroautophagy, microautophagy and chaperone-mediated autophagy (CMA) (Mizushima and Komatsu, 2011).

The most abundant and best-studied type is macroautophagy, which is characterized by the formation of a double-membrane vesicular structure, called autophagosome, engulfing the cytosolic substrates to be degraded. The specific marker protein of the mature autophagosome is LC3-II (Klionsky et al., 2012). The mature autophagosome eventually fuses with the lysosome to form an autolysosome, in which the contents are finally hydrolytically degraded. Macroautophagy can be analyzed by the quantification of autophagosomes in electron microscopy, LC3-puncta in immunohistochemistry or LC3-II levels in immunoblotting. Notably, the autophagic flux, which corresponds to the activity of the macroautophagic machinery, can only be determined by application of substances that block the late stages of autophagy, e.g. bafilomycin (Klionsky et al., 2012).

One important linker protein that labels substrates for autophagic degradation is the ubiquitin-binding scaffold protein p62, also called sequestosome 1 (SQSTM1) (Lippai and Low, 2014). It interacts with ubiquitinated proteins and protein aggregates and binds to LC3. Thereby the ubiquitinated proteins are specifically targeted to the autophagic machinery and finally degraded in the lysosome. An inhibition of autophagic flux usually leads to an increase of p62 as its degradation is impaired. Therefore determination of p62 levels is often used as an indirect measurement of autophagic flux (Bjorkoy et al., 2009). However, changes in p62 can also arise from altered levels of ubiquitinated proteins independent of autophagy and p62 can have individual effects on neuronal survival (Bjorkoy et al., 2005; Kojima et al., 2014).

Microautophagy occurs via the direct engulfment of portions of the cytoplasm into invaginations of the lysosomal membrane (Li et al., 2012).

In CMA, proteins with a KFERQ amino-acid motif are recognized and transported to the lysosome by the chaperone Hsc-70 and its co-chaperones. After binding to the lysosomal protein LAMP-2A, the substrates are translocated across the lysosomal membrane for degradation (Cuervo et al., 1995).

In neurons, there are usually only very few autophagosomes detectable under physiological conditions (Mizushima et al., 2004). This is, however, most probably due to a very efficient autophagic machinery in neurons, as the inhibition of lysosomal degradation leads to a rapid accumulation of autophagosomes in primary cortical neurons (Boland et al., 2008; Lee et al., 2011), while genetic suppression of autophagy results in marked neurodegeneration in several model systems (Hara et al., 2006; Komatsu et al., 2006; Sigmond et al., 2008). Many studies have demonstrated that the enhancement of autophagy can have positive therapeutic effects, especially in neurodegenerative proteinopathies (Liang et al., 2010; Pickford et al., 2008; Renna et al., 2010). On the other hand, enhanced autophagy was shown to trigger neuronal death under other circumstances such as hypoxic/ischemic brain injury and traumatic nerve lesion, where inhibition of autophagy was beneficial (Ginet et al., 2009; Knoferle et al., 2010; Koike et al., 2008). Therefore, a vulnerable homeostasis of autophagic activity seems to be essential to prevent neuronal pathology.

Under most pathological conditions affecting the optic nerve, including optic nerve transection, glaucoma and retinal ischemia, a marked increase in autophagic markers in the RGC has been described (Deng et al., 2013; Kim et al., 2008; Knoferle et al., 2010; Piras et al., 2011; Rodriguez-Muela et al., 2012) (Table 1). However, it remains unclear, whether this increase plays a protective or detrimental role under these conditions and whether therapeutic approaches should foster or inhibit autophagy. Below we will discuss these questions in more detail.

2. Traumatic lesions of the optic nerve

Traumatic lesions of the optic nerve have been used extensively in animal studies to examine mechanisms of axonal de- and regeneration in general and in ocular diseases in particular. A traumatic lesion to the optic nerve can be induced by pin lesion of single axon bundles, crush lesion or transection of the complete optic nerve. The local transection of RGC axons leads to acute followed by chronic axonal degeneration, which then results in the apoptotic death of the RGCs in a dying-back fashion (Rabacchi et al., 1994; Villegas-Perez et al., 1993). The mechanisms of RGC death after axonal damage are still not completely understood, but several factors including growth factor deprivation and oxidative stress seem to be involved (Isenmann et al., 2003; Tezel, 2006).

Several studies including our own have demonstrated a pivotal role of autophagy and a rapid increase of autophagic activity after injury of RGC axons. Based on the optic nerve crush model in rats we established an in vivo live imaging setup of the optic nerve to monitor early changes within the first hours after lesion (Knoferle et al., 2010). We found that acute axonal degeneration starts within minutes after lesion with alterations of the cytoskeleton that could be visualized by electron microscopy: neurofilaments appear condensated and misaligned while microtubules are partly fragmented already at 30 min after crush. During the next 6 h, the axon