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EDITORIAL

Autophagy mechanisms and roles: recent advances and implications

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Autophagy is the main catabolic process by which cells recycle cytoplasmic components and superfluous or damaged organelles to preserve metabolic homeostasis under normal conditions and promote survival under stress. As a tightly regulated and dynamic process, autophagy has critical roles in development and cell differentiation, immune function, organismal health and lifespan. Accumulating findings suggest that defective or dysregulated autophagy accelerates ageing and increases susceptibility to diseases, such as neurodegenerative disorders and cancer, among others. This virtual issue of the *FEBS Journal* on Autophagy includes a collection of articles that present recent advances on the regulation of autophagy and provide a view of its complex roles in physiological and pathological contexts.

The issue begins with a Viewpoint by Stolz and Grumati on selective degradation of endoplasmic reticulum (ER) by autophagy, the so-called ER-phagy. The authors give an overview of the process that is crucial for ER turnover, with consequent effects on ER homeostasis. A historical view and a summary of the main ER-phagy receptors both the intra- and the transmembrane ones are provided, and open questions in this emerging field are highlighted [1].

A recent review by Palamiuc *et al*. summarizes our current knowledge on the role of a tiny group of phospholipids, the phosphoinositides, in the autophagy process and its regulation. Moreover, some advanced biochemical and imaging techniques that allow the identification of subcellular localization of phosphoinositides are presented. Finally, examples of pathologies associated with deficiencies in certain kinases and phosphatases involved in phosphoinositide metabolism are also discussed [2].

A study by Sikder *et al*. identified the transcriptional positive coactivator 4 (PC4), which is a non-histone chromatin-associated protein, as a new negative regulator of autophagy upon stress such as exposure to gamma irradiation. The authors showed that PC4 knockdown increases autophagy in embryonic kidney cell lines and enhances cell survival upon exposure to gamma irradiation through epigenetic changes. Moreover, ChiP and quantitative PCR data suggest that depletion of PC4 induces the transcriptional upregulation of autophagy genes. On the other hand, genetic or pharmacological inhibition of autophagy abrogates the beneficial effects of PC4 deficiency on survival rendering cells sensitive to gamma irradiation. Collectively, these findings support the notion that autophagy mediates radiation resistance upon PC4 depletion [3].

In a recent review that was part of *The FEBS Journal*'s Special Issue on the Extracellular matrix in health and disease, Roedig *et al*. discuss emerging observations that suggest a dual role for the small leucine-rich proteoglycan, biglycan. Indeed, biglycan appears to act as a molecular switch that propagates Toll-like receptor signalling either towards inflammation by interacting with CD14 co-receptor or autophagy by binding to CD44 co-receptor. In this latter case, biglycan promotes the resolution of inflammatory responses. Thus, biglycan can be regarded as a double-edged sword with obvious implications in inflammatory diseases [4].

The State-of-the-Art review by Sánchez-Martín *et al.* describes current evidence suggesting a role for the selective autophagy receptor p62/SQST1 in the activation of Nrf2, mTORC (mechanistic target of rapamycin) and NF-kB signalling pathways. As such, p62 acts as an intracellular hub for integrating signals related to antioxidant and detoxifying response, nutrient sensing and inflammation, respectively. Special emphasis is placed on the molecular mechanisms by which p62 modulates the aforementioned signal transduction cascades whose perturbation by both up- and downregulation of p62 can promote tumorigenesis. Taken together, these findings indicate that p62 influences a wide range of biological processes by acting as a regulator of cell signalling pathways and mediating the autophagic clearance of some of its binding partners [5].

Another State-of-the-Art review by Humphreys *et al.* focuses on the multifunctional protein FLIP (Fas-associated death domain-like IL-1β-converting enzyme-inhibitory protein) and its relevance to cancer. The authors summarize the involvement of FLIP in various cellular processes that influence cell death and survival signalling cascades such as apoptosis, necroptosis and autophagy. Moreover, the article highlights emerging findings, which support a key role for FLIP in promoting the survival of immunosuppressive tumour-promoting immune cells [6].

In their State-of-the-Art review, Mowers *et al.* elaborate on the complex role of autophagy in cancer. The authors discuss the contribution of autophagy to tumour cell migration and invasion, tumour stem cell maintenance and drug resistance. Moreover, they describe how autophagy in non-tumour cells of the dynamic environment in which tumour cells reside and interact, the so-called tumour microenvironment, can promote tumour cell growth and metastasis [7].

A research article by Rahman *et al.* provides mechanistic insight into how mTORC (mechanistic target of rapamycin) modulates autophagy by interfering with lipid/membrane biogenesis. In this article, the Nem/Spo7–Pah1/lipin axis has been shown to be required for autophagy induction and survival during periods of nutrient scarcity when TORC1 is inactivated. Indeed, loss of Pah1 or Nem1/Spo7, at least partially, impairs autophagy. Moreover, nucleophagy (both the piecemeal micronucleophagy and macronucleophagy) is also affected in yeast cells carrying mutations in these genes. Whether this mechanism is evolutionarily conserved is not yet known [8].

Giguère *et al.* describe the role of mTOR in gene regulation in their State-of-the-Art review. The authors discuss recent findings regarding the function of mTOR as a *bona fide* transcription factor/cofactor, with emphasis given on mammalian cells. Beyond its well-established roles in cell growth and proliferation, metabolism and ageing, the TOR kinase has emerged as a crucial regulator of gene expression. It exerts this latter function by acting either indirectly to modulate the epigenome or activity of transcription factors outside the nucleus or directly by operating in the nucleus where it participates in the transcription of specific gene networks. Notably, nuclear mTORC1 phosphorylates and activates the acetyltransferase p300, thereby inhibiting autophagy and promoting lipogenesis through transcription activation [9].

Focusing on the cellular and physiological underpinnings of neurodegeneration, a brief review by Surmeier taken from the Special Issue on Neurodegeneration highlights the key traits that render dopaminergic neurons in the substantia nigra pars compacta more vulnerable to degeneration compared to other neural cell types in patients with Parkinson's disease. The long, highly branched axon and their distinctive physiology with regard to low intrinsic calcium buffering and slow cytosolic calcium oscillations are among the features that predispose dopaminergic neurons to degeneration. Moreover, impaired mitochondrial function leading to enhanced mitophagy and lysosomal dysfunction that impairs turnover of misfolded proteins such as α-synuclein fibrils is considered to have a critical role in mediating dopaminergic neuron loss [10].

This collection of articles on autophagy ends with a review (also from the Special Issue on Neurodegeneration) by Gegg and Schapira, which describes the role of the lysosomal enzyme glucocerebrosidase (GCase) in PD pathogenesis. The authors summarize the cellular and molecular mechanisms by which mutant forms of the enzyme influence disease onset and progression. In this regard, accumulating findings indicate that decreased GCase activity leads to autophagy dysfunction with important consequences for α-synuclein metabolism. Other studies provide evidence that links GCase deficiency with the activation of the ER unfolded protein response (UPR^{ER}). Moreover, several studies have implicated mitochondrial dysfunction in PD pathogenesis. Consistently, cellular and animal models harbouring mutations in the *GBA* gene that encodes GCase display impaired mitochondrial function and neuroinflammation [11].

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