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CELL SCIENCE AT A GLANCE

Transcriptional regulation of mammalian autophagy at a glance

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ABSTRACT

Macroautophagy, hereafter referred to as autophagy, is a catabolic process that results in the lysosomal degradation of cytoplasmic contents ranging from abnormal proteins to damaged cell organelles. It is activated under diverse conditions, including nutrient deprivation and hypoxia. During autophagy, members of the core autophagy-related (ATG) family of proteins mediate membrane rearrangements, which lead to the engulfment and degradation of cytoplasmic cargo. Recently, the nuclear regulation of autophagy, especially by transcription factors and histone modifiers, has gained increased attention. These factors are not only involved in rapid responses to autophagic stimuli, but also regulate the long-term outcome of autophagy. Now there are more than 20 transcription factors that have been shown to be linked to the autophagic process. However, their interplay and timing appear enigmatic as several have been individually shown to act as major regulators of autophagy. This Cell Science at a Glance article and the accompanying poster highlights the main cellular regulators of transcription involved in mammalian autophagy and their target genes.

KEY WORDS: Autophagy, Lysosome, Transcription

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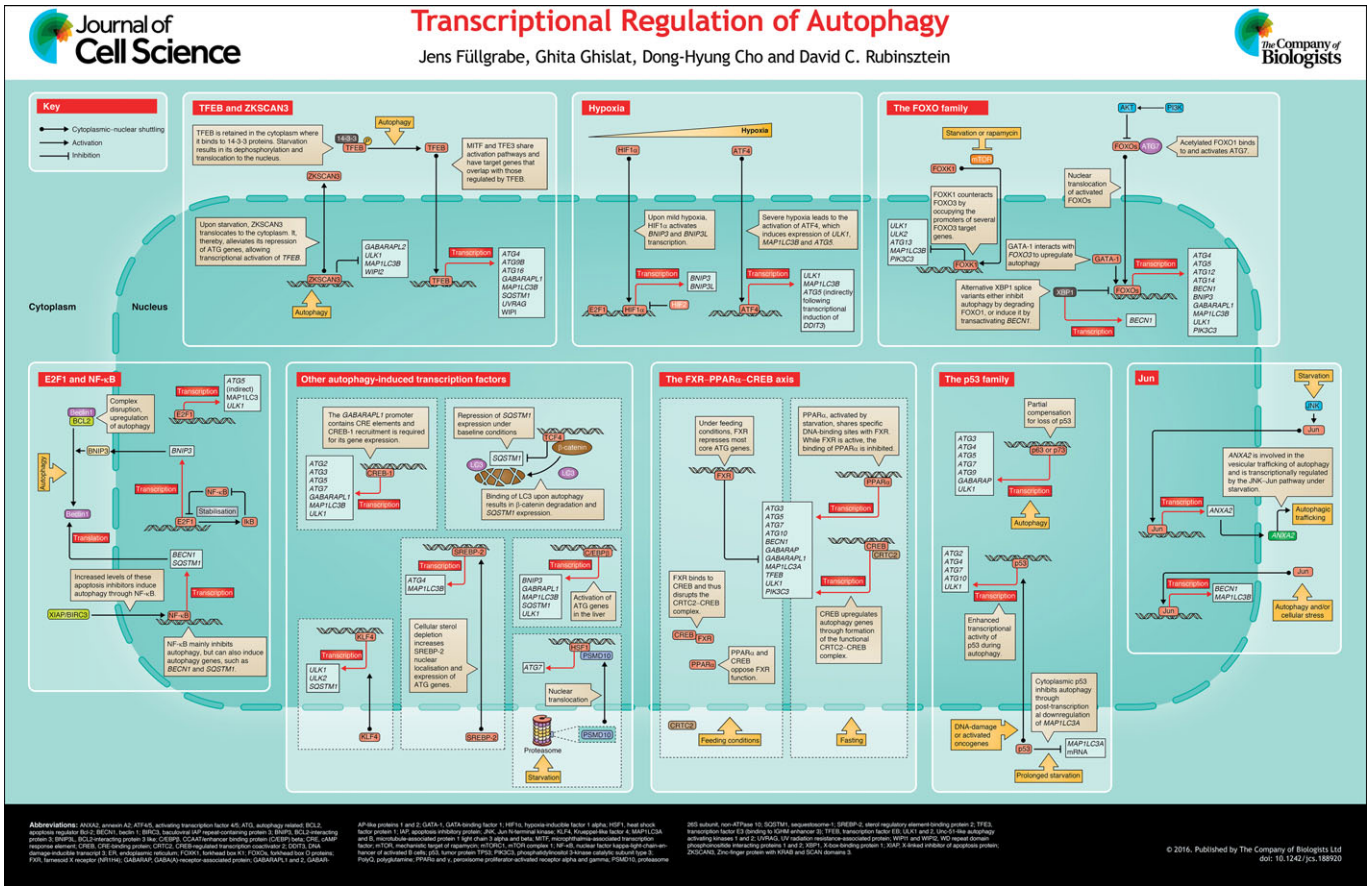
Introduction

Autophagy is a pathway that cells use to degrade cytoplasmic contents, organelles – such as the ER and mitochondria – aggregate-prone proteins and various infectious agents (Levine and Kroemer, 2008). These substrates are engulfed by cup-shaped structures called phagophores that become autophagosomes after their edges extend and fuse. Completed autophagosomes can fuse



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with endosomes to form amphisomes (Ravikumar et al., 2009). Autophagosomes and/or amphisomes are then trafficked to the lysosomes with which they exchange content, enabling degradation of the autophagic contents by the lysosomal hydrolases (Jahreiss et al., 2008). Autophagy is mediated by a set of so-called ATG proteins (Xie and Klionsky, 2007).

The primordial function of autophagy may be as a response to stresses, such as starvation, because autophagic end-products can be released from lysosomes to enable some maintenance of the cellular energy status (Rabinowitz and White, 2010). Indeed, starvation leads to inhibition of mammalian target of rapamycin complex 1 (mTORC1), a negative regulator of autophagy, and activation of Jun N-terminal kinase (JNK; also known as MAPK8), which stimulates autophagy (Wei et al., 2008). Many diseases are associated with autophagy dysregulation, and drugs modulating autophagy have been successful in several animal models of disease, especially neurodegenerative disorders. Neurodegenerative disorders, including Alzheimer's, Huntington's or Parkinson's disease, involve the accumulation of protein aggregates in neurons (Decressac et al., 2013; Tsunemi et al., 2012). Because autophagy acts as a cellular clearance mechanism, its activation appears especially promising in potential treatment of these diseases (Menzies et al., 2015).

The early years of autophagy research focused on the dynamic membrane rearrangements and the post-translational modifications of ATG proteins, neglecting a potential nuclear regulation of autophagy (Füllgrabe et al., 2014). Indeed, the discovery that autophagy can be induced and is functional in enucleated cells lead to the assumption that nuclear events are of minor importance for this process (Tasdemir et al., 2008).

However, already in 1999 it was shown in yeast that induction of autophagy by nitrogen starvation results in the transcriptional upregulation of an autophagy-related gene within minutes (Kirisako et al., 1999). The research on transcriptional regulation of autophagy gained momentum in 2011 after a landmark paper that showed that transcription factor EB (TFEB), the master regulator of lysosomal pathways, regulates a wide range of autophagy-related genes (Settembre et al., 2011).

Here, we aim to summarise the current knowledge about transcriptional regulators of autophagy and highlight their regulatory mechanisms in the accompanying poster.

TFEB and ZKSCAN3 – the master autophagy regulators

Although transcriptional regulators of core mammalian autophagy-related proteins were previously known, the transcriptional regulation by TFEB enables a rapid induction of autophagy-related proteins that are involved in all steps of the process, and its overexpression is sufficient to induce autophagy (Settembre et al., 2011). Under baseline conditions in nutrient-replete medium, TFEB is retained in the cytoplasm following phosphorylation by the mammalian target of rapamycin (mTOR), which leads to its binding to 14-3-3 proteins. However, after autophagy activation in response to different stimuli, such as nutrient depletion (starvation) or rapamycin treatment, mTOR is inhibited, which results in dephosphorylation of TFEB and its rapid translocation to the nucleus (Martina et al., 2012) (see poster). There, TFEB binds directly to the promoters of a multitude of autophagy-related genes, thereby induce the expression of key factors that regulate autophagic flux, including *ATG4*, *ATG9B*, microtubule-associated protein 1 light chain 3B (*MAP1LC3B*), UV radiation resistance associated protein (*UVRAG*) and WD-repeat domain phosphoinositide interacting protein (WIPI). Apart from its direct regulation of core autophagy genes, TFEB is also a master regulator of lysosomal biogenesis. Given that the completion of autophagic flux requires the degradation of cargo by the lysosomal compartment, TFEB has the ability to regulate multiple steps of the autophagic process (Settembre et al., 2011).

The overexpression of *TFEB* alone is sufficient to alleviate disease associated with protein aggregation in rodent models. For instance, overexpression of *TFEB* rescues toxicity of α-synuclein and protects dopaminergic neurons in a rat model of Parkinson's disease that is induced by viral overexpression of α-synuclein (Decressac et al., 2013); it also ameliorates toxicity by enhancing the clearance of misfolded polyglutamine-expanded (polyQ) huntingtin protein (Tsunemi et al., 2012) and the mutant androgen receptor that causes X-linked spinal and bulbar muscular atrophy (Cortes et al., 2014). Gene transfer of *TFEB* alleviates pathology in a mouse model of alpha-1-anti-trypsin deficiency (Pastore et al., 2013). Moreover, activation of autophagy and lysosomal activity by TFEB attenuates the pathological phenotype in mouse models of Pompe disease (Spampanato et al., 2013). Taken together, regulation of autophagy by transcriptional activity of TFEB plays a significant role in various pathological conditions.

The zinc-finger protein with KRAB and SCAN domains 3 (ZKSCAN3) represents the transcriptional counterpart of TFEB, because it represses the transcription of a number of autophagy-related genes, including Unc-51-like autophagy activating kinase 1 (*ULK1*) and *MAP1LC3B* (see poster). Upon autophagy induction, ZKSCAN3 translocates from the nucleus to the cytoplasm, allowing the transcriptional activation of target genes by TFEB. Significantly, *ZKSCAN3* knockdown is sufficient to induce autophagy, whereas its overexpression can inhibit autophagy (Chauhan et al., 2013).

Hence, during concomitant translocation of TFEB from the cytosol to the nucleus and the translocation of ZKSCAN3 from the nucleus to the cytosol during autophagy, a wide range of autophagy-related genes is induced. This specific shuttling of transcription factors during autophagy is common to most transcriptional regulators of autophagy, including members of the forkhead box O (FOXO) family discussed next.

The FOXO family – location matters

Members of the FOXO family of transcription factors (FOXOs) have been linked to diverse physiological functions, including various developmental programs and tissue homeostasis. FOXOs are activated by a multitude of environmental stimuli to coordinate processes, such as glucose homeostasis, angiogenesis or stem cell maintenance. The FOXO family was also one of the first transcriptional regulators to be linked to autophagy (Zhao et al., 2007). Like TFEB, FOXOs are regulated by phosphorylation and, in their activated form, translocate to the nucleus to induce the expression of a number of autophagy-related genes, including *ATG4*, *ATG12*, *BECN1*, *BNIP3*, *MAP1LC3B*, *ULK1*, VPS34 (also known as *PIK3C3* in human) and *GABARAPL1* (Mammucari et al., 2007; Zhao et al., 2007; Sanchez et al., 2012) (see poster). It was shown in muscle and heart that FOXK1 counteracts FOXO3 by occupying the promoters of several FOXO3 target genes (Mammucari et al., 2007; Zhao et al., 2007; Schips et al., 2011). The shuttling of FOXK1 between the nucleus and cytoplasm depends on mTOR and chromosomal maintenance 1 (CRM1), and mTOR-inhibition by amino-acid starvation results in its dissociation from chromatin (Bowman et al., 2014). In addition, the nuclear translocation of FOXO1 has been correlated with transcriptional activation of *ATG5* (Xu et al., 2011), *ATG14* (Xiong et al., 2012) and *PIK3C3* (Liu et al., 2009). In accordance with this concept, the transcriptional activity of FOXO1

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was shown to also enable the autophagic function of beclin 1 (BECN1) (Xu et al., 2011). Beclin 1 associates with and regulates the activity of PIK3C3, a kinase that generates phosphatidylinositol 3-phosphate, which is crucial for autophagosome biogenesis (Russell et al., 2013). Interestingly, GATA-binding factor 1 (GATA-1), the master regulator of hematopoiesis, activates transcription of *MAP1LC3A* and *MAP1LC3B* and its homologs (*GABARAP*, *GABARAPL1*, and *GABARAPL2*), both directly and indirectly, and this has been suggested to rely on direct transcriptional induction of *FOXO3* by GATA-1 (Kang et al., 2012). The transcription factor X-box-binding protein 1 (XBP1) is another crucial regulator of FOXO1 activation and degradation. In addition, spliced XBP1 can directly bind to the promoter region of *BECN1* thus acting as an autophagy activator or inhibitor depending on the splice isoform (Margariti et al., 2013). Unlike TFEB, FOXO1 also acts as an autophagy inducer within the cytosol by directly binding to autophagy-related proteins (Zhao et al., 2010).

In summary, members of the FOXO family can act as autophagy inducers and repressors depending on their cellular localisation. This feature is shared with, arguably the most prominent transcription factor in the human genome, p53.

p53 – deciding between cell death and survival

Although activation of tumor-suppressor protein TP53 (hereafter referred to as p53) has been described to inhibit mTORC1 and thus to activate autophagy, several studies have shown that cytoplasmic p53 is a potent inhibitor of autophagy. The mechanisms for this inhibition are largely unknown (Green and Kroemer, 2009); however, post-transcriptional downregulation of *MAP1LC3A* by p53 has been suggested to be, at least partly, responsible (Scherz-Shouval et al., 2010). The effect of p53 within the nucleus was investigated in a whole-genome study, which showed that the promoters of numerous autophagy-related genes, including *ATG2*, *ATG4*, *ATG7*, *ATG10* and *ULK1*, were bound by p53 (Kenzelmann Broz et al., 2013) (see poster). Diverse inducers of autophagy – such as DNA damage or activated oncogenes – lead to activation of p53, which results in enhanced autophagy, an effect that depends on its role as a transcription factor (Tasdemir et al., 2008). Furthermore, the other members of the p53 tumor suppressor family, p63 and p73, appear to have a similar range of autophagy-related target genes and are able to compensate for the loss of p53 to a certain extent during the induction of autophagy (Kenzelmann Broz et al., 2013). On the one hand, p-ΔNp63α, the phosphorylated version of the N-terminally truncated p63 isoform (ΔNp63α), can bind to the promoters of several autophagy genes, including *ULK1*, *ATG5* and *ATG7*, as well as indirectly regulate autophagy through the transcription of miRNAs (Huang et al., 2012). p73, on the other hand, is inhibited by mTOR and induced by the classic inducer of autophagy rapamycin. Like p53, p73 has been shown to bind the promoters of a range of autophagy-related genes, including *ATG5*, *ATG7* and *GABARAP* (Rosenbluth et al., 2008).

In summary, the p53 family members have overlapping functions in the regulation of several autophagy-related genes upon a diverse set of stimuli. Noteworthy, transcription factor E2F1 – one of the main co-regulators of p53 with regard to life-or-death decisions made by the cell – is also an important transcriptional regulator of autophagy-related genes (Polager and Ginsberg, 2009).

E2F1 and NF-κB – competing for the spotlight

E2F1 activation induces autophagy, whereas reduction in its protein levels inhibits autophagy. E2F1 has a range of autophagy-related target genes, including *ULK1*, *MAP1LC3A* and/or *MAP1LC3A* and *BNIP3*, and was also shown to indirectly regulate the transcription of *ATG5* (Polager et al., 2008) (see poster). BNIP3 acts as a positive regulator of autophagy by disrupting the B-cell lymphoma 2 (BCL2)-mediated inhibition of beclin 1 (Tracy et al., 2007). Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) has been described as a molecular switch for transactivation of *BNIP3* by inhibiting the binding of E2F1 to its promoter (Shaw et al., 2008). Hence, whereas E2F1 induces autophagy by activating the transcription of *BNIP3*, NF-κB inhibits this transactivation. Another connection between these two autophagy-regulatory factors is the stabilisation of IκB, the inhibitor of NF-κB by E2F1 (Polager et al., 2008). By contrast, NF-κB was shown to also induce autophagy-related genes, including *BECN1* and sequestosome-1 (*SQSTM1*) (Copetti et al., 2009; Ling et al., 2012). One should bear in mind that it is not always clear whether the transcriptional activity of a protein is invariably needed for the induction of ATG genes or autophagy as, for instance, E2F1 lacking its transcriptional activity domain can still induce autophagy (Garcia-Garcia et al., 2012). Interestingly, two classic apoptosis inhibitory proteins (IAPs), X-linked inhibitor of apoptosis protein (XIAP) and baculoviral IAP repeat-containing protein 3 (BIRC3), have recently been shown to induce autophagy by upregulating *BECN1* transcription through the activation of NF-κB (Lin et al., 2015).

Thus, transcription of the autophagy activator *BNIP3* is mainly regulated by E2F1 and NF-κB. Moreover, E2F1 is one of several transcription factors known to become activated upon hypoxia, which, in turn, induces autophagy (Yurkova et al., 2008).

Hypoxia and autophagy – well-studied but still enigmatic

A surprisingly large number of studies have investigated transcriptional regulation of ATG genes by using hypoxia to induce autophagy, and the induction of *BNIP3* and *BNIP3L* by hypoxia-inducible factor 1 alpha (HIF1α) has been described in a number of papers (Zhang et al., 2008; Bellot et al., 2009; Pike et al., 2013) (see poster). Interestingly, the degree of hypoxia appears to determine which transcription factors are activating autophagy. In moderate hypoxia, HIF1α activates *BNIP3* transcription, whereas severe hypoxia leads to a response involving activating transcription factor 4 (ATF4) (Pike et al., 2013). ATF4 induces the transcription of *MAP1LC3B* under hypoxia by direct binding to a cyclic AMP response element (CRE)-binding site in the promoter of *MAP1LC3B* (Rzymski et al., 2010). Additionally, *ULK1* is upregulated by ATF4, whereas *ATG5* is indirectly upregulated through the transcriptional induction of DNA damage inducible transcript 3 (*DDIT3*) mediated by ATF4 (Rouschop et al., 2010).

Jun – activated by diverse stresses

The JNK pathway is activated by cytokines and environmental stresses (Raingeaud et al., 1995). Since autophagy is also activated upon cellular stress, a connection between both pathways is not unexpected. Annexin A2 (ANXA2), which is necessary and sufficient for autophagy both under basal conditions and in response to amino-acid starvation, has recently been shown to be involved in the vesicular trafficking of autophagy and to be transcriptionally regulated by the JNK–Jun pathway following amino-acid starvation (Moreau et al., 2015) (see poster). Since ANXA2 overexpression itself induces autophagy, the JNK–Jun–ANXA2 transcriptional program appears – even *in vivo* – to be a key process in the regulation of autophagy in response to starvation (Moreau et al., 2015). Several studies have investigated the direct induction of autophagy genes by Jun, highlighting its role in the

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Table 1. Transcription factors that regulate core autophagy genes in mammmals

Gene	Transcription factor	Reference
Regulation of autophagy induction		
MTOR	ATF5	Sheng et al., 2011
ULK1	ATF4	Pike et al., 2013
	C/EBPb (CEBPB)	Ma et al., 2011
	CREB	Seok et al., 2014
	E2F1	Polager et al., 2008
	FOXO3	Schips et al., 2011
	KLF4	Liao et al., 2015
	p53 (TP53)	Gao et al., 2011; Kenzelmann Broz et al., 2013
	ΔNp63α	Huang et al., 2012
	FOXK1	Bowman et al., 2014
	FXR	Seok et al., 2014
	ZKSCAN3	Chauhan et al., 2013
ULK2	KLF4	Liao et al., 2015
	TFE3	Perera et al., 2015
	p53 (TP53)	Kenzelmann Broz et al., 2013
	FOXK1	Bowman et al., 2014
ATG13	FOXK1	Bowman et al., 2014
Vesicle formation		
BECN1	Jun (JUN)	Li et al., 2009
	FOXO1	Fiorentino et al., 2013
	FOXO3A	Sanchez et al., 2012
	NF-κB	Copetti et al., 2009; Lin et al., 2015
	PPARα	Lee et al., 2014
	XBP1	Margariti et al., 2013
	ΔNp63α	Huang et al., 2012
	FXR	Lee et al., 2014
	STAT-1	McCormick et al., 2012
ATG14	FOXOs	Xiong et al., 2012
PIK3C3	FOXO1	Liu et al., 2009
	FOXO3	Mammucari et al., 2008
	PPARα	Lee et al., 2014
	FOXK1	Bowman et al., 2014
	FXR	Lee et al., 2014
BCL2	MITF and TFE3	Martina et al., 2014
	NF-κB	Tamatani et al., 1999
AMBRA1	FOXK1	Bowman et al., 2014
UVRAG	MITF and TFE3	Martina et al., 2014
	TFEB	Settembre et al., 2011
	p73 (TP73)	Rosenbluth et al., 2008
ATG9A	ΔNp63α	Huang et al., 2012
ATG9B	MITF	Perera et al., 2015
	TFE3	Martina et al., 2014
	TFEB	Settembre et al., 2011
ATG3	CREB	Seok et al., 2014
	TFE3	Perera et al., 2015
	ΔNp63α	Huang et al., 2012
	FXR	Seok et al., 2014
ATG4	GATA-1 and/or FOXO3	Kang et al., 2012
	SREBP-2	Seo et al., 2011
	p53 (TP53), p63 (TP63) and/or p73 (TP73)	Kenzelmann Broz et al., 2013
	ΔNp63α	Huang et al., 2012
ATG5	DDIT3	Rouschop et al., 2010
	CREB	Seok et al., 2014
	E2F1	Polager et al., 2008
	FOXO1	Fiorentino et al., 2013
	ΔNp63α	Huang et al., 2012
	FXR	Seok et al., 2014
	GATA-1	Kang et al., 2012
ATG7	CREB	Seok et al., 2014
	PPARα	Lee et al., 2014
	PSMD10 and HSF1	Luo et al., 2015
	p53 (TP53), p63 (TP63) and/or p73 (TP73)	Kenzelmann Broz et al., 2013

Continued

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Table 1. Continued

Gene	Transcription factor	Reference
	ΔNp63α	Huang et al., 2012
	FXR	Seok et al., 2014
ATG10	MITF	Perera et al., 2015
	SOX2	Cho et al., 2013
	TFE3	Perera et al., 2015
	p53 (TP53), p63 (TP63) and/or p73 (TP73)	Kenzelmann Broz et al., 2013
	ΔNp63α	Huang et al., 2012
	FXR	Seok et al., 2014
ATG12	FOXO1	Liu et al., 2009
	FOXO3	Zhao et al., 2007
	GATA-1 and/or FOXO3	Kang et al., 2012
	FOXK1	Bowman et al., 2014
ATG16	MITF, TFE3 and TFEB	Martina et al., 2014
	FXR	Seok et al., 2014
BNIP3	C/EBPb (CEBP)	Ma et al., 2011
	E2F1	Yurkova et al., 2008; Shaw et al., 2008
	FOXO3	Mammucari et al., 2007
	HIF1	Zhang et al., 2008; Bellot et al., 2009
	PPARα	Lee et al., 2014
	FXR	Lee et al., 2014
	NF-κB	Shaw et al., 2008
	pRB (RB1) and/or E2F	Tracy et al., 2007
MAP1LC3A and/or *MAP1LC3B*	ATF4	Rouschop et al., 2010; Milani et al., 2009
	C/EBPb (CEBP)	Ma et al., 2011
	Jun (JUN)	Jia et al., 2006; Sun et al., 2011
	CREB	Seok et al., 2014
	E2F1	Polager et al., 2008
	FOXO1	Fiorentino et al., 2013
	FOXO3A	Sanchez et al., 2012
	GATA-1 and/or FOXO3	Kang et al., 2012
	MITF and TFE3	Perera et al., 2015
	PPARα	Lee et al., 2014
	SREBP-2	Seo et al., 2011
	TFEB	Settembre et al., 2011
	FOXK1	Bowman et al., 2014
	FXR	Lee et al., 2014
	ZKSCAN3	Chauhan et al., 2013
GABARAP	GATA-1 and/or FOXO3	Kang et al., 2012
	PPARα	Lee et al., 2014
	FXR	Seok et al., 2014
GABARAPL1	C/EBPb (CEBP)	Ma et al., 2011
	CREB	Hervouet et al., 2015
	FOXO1	Liu et al., 2009
	FOXO3A	Sanchez et al., 2012
	GATA-1 and/or FOXO3	Kang et al., 2012
	MITF, TFE3 and TFEB	Martina et al., 2014
	PPARα	Lee et al., 2014
	FXR	Lee et al., 2014
GABARAPL2	GATA-1 and/or FOXO3	Kang et al., 2012
	ZKSCAN3	Chauhan et al., 2013
SQSTM1	C/EBPb (CEBP)	Ma et al., 2011
	KLF4	Riz et al., 2015
	MITF and TFE3	Perera et al., 2015
	NF-κB	Ling et al., 2012
	TFEB	Settembre et al., 2011
	β-catenin and/or TCF	Petherick et al., 2013
ATG2	CREB	Seok et al., 2014
	TFE3	Perera et al., 2015
	p53	Kenzelmann Broz et al., 2013
	FXR	Seok et al., 2014
WIPI1 and *WIPI2*	MITF, TFE3, TFEB	Martina et al., 2014
	PU.1 (SPI1)	Brigger et al., 2014
	TFEB	Settembre et al., 2011
	FXR	Seok et al., 2014
	ZKSCAN3	Chauhan et al., 2013

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regulation of *BECN1* and *MAP1LC3B* transcription (Jia et al., 2006; Li et al., 2009; Sun et al., 2011).

The FXR–PPARα–CREB axis – the new kid on the block

Recently, the farnesoid X receptor (FXR, also known as NR1H4) was highlighted by two publications as the first direct link between nuclear receptors and autophagy (Seok et al., 2014; Lee et al., 2014) (see poster). Whereas both studies agree that an impressive number of core autophagy-related genes are directly repressed by FXR in the liver under feeding conditions (compared to autophagy-inducing fasting conditions), they propose different regulatory mechanisms. On the one hand, according to Seok et al., the fasting transcriptional activator, CRE-binding protein (CREB), upregulates autophagy genes, including *ATG7*, *ULK1* and *TFEB*; these are otherwise repressed by FXR, which disrupts the functional complex between CREB and CREB-regulated transcription coactivator 2 (CRTC2) (Seok et al., 2014). On the other hand, Lee et al. described the opposing roles of FXR and another nutrient-sensing regulator, peroxisome proliferation factor-activated receptor α (PPARα). PPARα is activated by fasting and shares specific DNA binding sites (called DR1 elements) with FXR. When FXR is active, binding of PPARα is inhibited (Lee et al., 2014). Both mechanisms might act in concert, which is highlighted by the fact that, under nutrient starvation, PPARα and CREB complexes occupy different regions of the *MAP1LC3A* and *ATG7* genes.

Interestingly, PPARα activation with its agonist pirinixic acid (Wy-14643) reduces proinflammatory responses by promoting activation of autophagy in a mouse model of acute liver failure (Jiao et al., 2014). Activation of PPARα by gemfibrozil also upregulates the expression of *TFEB*, which, in turn, transcriptionally increases the levels of ATG proteins (Ghosh et al., 2015). PPARγ is also a master regulator of adipocyte differentiation (Jonker et al., 2012). However, the role of PPARγ-mediated transcriptional regulation of autophagy remains controversial. Indeed, Troglitazone, a PPARγ agonist, induces autophagy and cell death in bladder cancer cells (Yan et al., 2014), whereas another PPAR agonist, 15d-prostaglandin J_2, suppresses autophagy in ischemic brain (Xu et al., 2013; Qin et al., 2015).

Even more transcription factors – cell-type- and stimulus-dependent effects on autophagy

An increasing number of transcription factors have been linked to the transcriptional activation of autophagy-related genes involved in all steps of the process. Most of these transcriptional activators specifically shuttle from cytosol to the nucleus upon autophagy induction, which we call functional translocation (Zhang et al., 2015). As a surprising example, proteasome 26S subunit non-ATPase 10 (PSMD10) has recently been reported to translocate to the nucleus upon amino-acid starvation and binds to the transcription factor heat shock factor protein 1 (HSF1) at the *ATG7* promoter to induce its transcription (Luo et al., 2015) (see poster). Noteworthy, autophagic flux and the expression of autophagy-related genes in the liver appear to follow a circadian rhythm. Hence, the transcriptional regulator of circadian rhythm, CCAAT/enhancer binding protein beta (C/EBPβ), which can also be stimulated by amino-acid starvation, activates several ATG genes, including *MAP1LC3A* and/or *MAP1LC3B,* and its homolog *GABARAPL1* (Ma et al., 2011). A recent study highlighted the presence of CREs in the promoter of *MAP1LC3A* and – indeed – CREB1 recruitment to the *GABARAPL1* promoter is required for *GABARAPL1* expression (Hervouet et al., 2015). However, the number of studies on transcription factors that are activated by the diverse inducers of autophagy and that bind to promoters of autophagy-related genes far exceeds the scope of this short Cell Science at a Glance article, and a list of mammalian transcription factors that have been shown to regulate autophagy through the regulation of transcription of autophagy-related genes can be found in Table 1.

Perspectives

The work on TFEB has led to an explosion in research on transcriptional regulators of autophagy. Owing to space limitations, this Cell Science at a Glance article can only act as an up-to-date introduction of this topic and is restricted to the mammalian system (for a more-detailed review see e.g. Pietrocola et al., 2013; Füllgrabe et al., 2014; Zhang et al., 2015). The work on transcription factors, such as TFEB, Jun and FOXO3, has shown us that the altered activity of a single transcription factor can be sufficient to either induce or inhibit autophagy. Considering this, the sheer number of transcription factors that act on key autophagy genes remains surprising. It is possible that transactivation of key autophagy genes by different transcription factors enables the integration of autophagy into different stress responses. Autophagy is induced by a range of environmental stresses and an overlapping set of autophagy genes is likely to be required for sustained autophagy that is independent of the inducer, whereas the transactivation of other ATG genes might be specific to a particular cellular stress type. Strikingly, key autophagy genes, especially *MAP1LC3B* and its homologs, as well as *BECN1* and *ULK1*, have a vast number of transcriptional activators, which indicates a key role for their transcriptional induction upon diverse autophagic stimuli. However, in some cases, it is unclear whether the autophagy responses are driven necessarily by changes within a single target gene (e.g. *MAP1LC3A* and/or *MAP1LC3B*), whose levels are not crucial for autophagy regulation (Mizushima et al., 2004; Maruyama et al., 2014) or are, instead, exerted by a set of targets.

Noteworthy, in the past few years, it has been shown that the nuclear impact on autophagy is not limited to the regulation of transcription factors but also involves epigenetic marks, microRNAs and the specific shuttling of core autophagy proteins between the nucleus and cytosol (reviewed in Füllgrabe et al., 2014). The interplay between these factors during autophagy has only been investigated in a few studies and these highlight a very complex picture of histone modifications, DNA methylation and nuclear or cytosolic shuttling, all of which need to be carefully controlled within the cell to achieve the desired level of autophagic flux. How these factors are interconnected in order to enable different autophagic outcomes remains one of the most intriguing questions in the field. It will also be important to assess cell-type specificity for transcriptional regulators of autophagy responses in future.

Competing interests

The authors declare no competing or financial interests.

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Cell science at a glance

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