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 by diverse conditions, including nutrient deprivation and hypoxia. During autophagy, core autophagy-related (ATG) 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 and the accompanying poster highlights the main cellular regulators of transcription involved in mammalian autophagy and their target genes.

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 with endosomes to form amphisomes (Ravikumar et al., 2009). Autophagosomes/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, as 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 c-Jun N-terminal kinase (JNK), 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). As autophagy acts as a cellular clearance mechanism, its activation appears especially promising in these diseases (Menzies et al., 2015).

The early years of autophagy research focused on the dynamic membrane rearrangements and the posttranslational 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, it was already shown in 1999 in yeast that autophagy induction 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 summarize the current knowledge about transcriptional regulators of autophagy and highlight their regulatory mechanisms in the accompanying poster.

TFEB and ZKSCAN3 – the master autophagy regulators

While 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 was sufficient to induce autophagy (Settembre et al., 2011). During baseline conditions in nutrient-replete medium, TFEB is retained in

the cytoplasm through phosphorylation by the mammalian target of rapamycin (mTOR), which leads to its binding to 14-3-3 proteins. However, after autophagy activation by different stimuli, such as nutrient depletion (starvation) or rapamycin treatment, mTOR is inhibited, which results in TFEB becoming dephosphorylated and rapidly translocating to the nucleus (Martina et al., 2012) (see poster). There, TFEB binds directly to the promoters of a multitude of autophagy-related genes, which induce the expression of key factors that regulate autophagic flux, including *ATG4*, *ATG9*, 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 was 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.

Zinc-finger protein with KRAB and SCAN domains 3 (ZKSCAN3) represents the transcriptional counterpart of TFEB, as 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, while its overexpression can inhibit autophagy (Chauhan et al., 2013).

Hence, by the 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 are induced. This specific shuttling of transcription factors during autophagy is common to most transcriptional regulators of autophagy, including the forkhead box O (FOXO) family discussed next.

The FOXO family - location matters

The FOXO family of transcription factors has 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 like 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, the FOXOs are regulated by phosphorylation and in their activated form, they translocate to the nucleus to induce the expression of a number of autophagy-related genes, including *ATG4*, *ATG12*, *BECN1*, BCL2/Adenovirus E1B 19kDa interacting protein 3 (*BNIP3*), *MAP1LC3B*, *ULK1*, vacuolar protein sorting 34 (*VPS34*) and GABA(A) receptor-associated protein like 1 (*GABARAPL1*) (Mammucari et al., 2007; Zhao et al., 2007; Sanchez et al., 2012) (see poster). Forkhead box K1 (FOXK1) counteracts FOXO3 by occupying an overlapping set of autophagy gene promoters in muscle and heart (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 the activation of the transcription of *ATG5* (Xu et al., 2011), *ATG14* (Xiong et al., 2012) and *VPS34* (Liu et al., 2009). In accordance with this concept, the transcriptional activity of FOXO1 was shown to also enable the autophagic function of Beclin 1 (Xu et al., 2011). (Beclin 1 associates with and regulates the activity of VPS34, a kinase that generates phosphatidylinositol 3-phosphate, which is critical for autophagosome biogenesis (Russell et al., 2013)). Interestingly, GATA-binding factor 1 (GATA-1), the master regulator of hematopoiesis, activates transcription of *MAP1LC3A/B* 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 critical regulator for the activation and degradation of FOXO1. Additionally, XBP1 can directly bind to the promoter region of BECN1, thus acting as an autophagy activator or inhibitor depending on its splice variant (Margariti et al., 2013). Unlike TFEB, FOXO1 also acts as an autophagy inducer in the cytosol by direct 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 localization. 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 p53 has been described to inhibit mTORC1 and thus 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 a posttranscriptional downregulation of MAP1LC3A by p53 has been suggested to be at least partly responsible (Scherz-Shouval et al., 2010). The effect of p53 in the nucleus was investigated in a whole-genome study (Kenzelmann Broz *et al*.), which showed that the promoters of numerous autophagy-related genes, including *ATG2, ATG4, ATG7, ATG10* and *ULK1* (Kenzelmann Broz et al., 2013), were bound by p53 (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 member of the p53 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). For example, p-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 classical inducer of autophagy rapamycin. As with 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 regulating a number of autophagy-related genes upon a diverse set of stimuli. Noteworthy, 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 levels inhibits autophagy. E2F1 has a range of autophagy-related target genes, including *ULK1*, *MAP1LC3* 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 (BCL-2)-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, while E2F1 induces autophagy by activating the transcription of *BNIP3*, NF-κB inhibits this transactivation. Another connection between these two autophagy-regulatory factors is the stabilization of the inhibitor of NF-κB, IκB, by E2F1 (Polager et al., 2008). Conversely, NF-κB was shown to also induce autophagy-related genes, including *BECN1* and sequestosome-1 (*SQSTM1*) (Copetti et al., 2009 and Ling et al., 2012). One should bear in mind that

it is not always clear if the transcriptional activity of a protein is always needed for induction of ATG genes or autophagy, as, for instance, E2F that lacks transcriptional activity can still induce autophagy (Garcia-Garcia et al., 2012). Interestingly, two classical 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 NF-κB activation (Lin et al., 2015).

Thus, the transcription of the autophagy activator BNIP3 is mainly regulated by E2F1 and NF-κB. Moreover, E2F1 is one of a range of 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 using hypoxia to induce autophagy, and the induction of *BNIP3* and *BNIP3L* by hypoxia-inducible factor 1α (HIF1α) has been described by a number of papers (Zhang et al., 2008; Bellot 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 binding site in the promoter of *MAP1LC3B* (Rzymski et al., 2010). Additionally, *ULK1* is upregulated by ATF4 and *ATG5* indirectly through ATF4-dependent transcriptional induction of DNA damage inducible transcript 3 *(DDIT3)* (Rouschop et al., 2010).

c-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 thus not unexpected. Annexin A2, which is necessary and sufficient for autophagy both in basal conditions and amino-acid starvation, was recently shown to be involved in the vesicular trafficking of autophagy and to be transcriptionally regulated by the JNK-c-Jun pathway under amino-acid starvation (Moreau et al., 2015) (see poster). Since Annexin A2 overexpression induces autophagy by itself, the JNK-c-Jun-Annexin A2 transcriptional program appears to be a key process that regulates autophagy in response to starvation, even *in vivo* (Moreau et al 2015). Several studies have investigated the direct induction of autophagy genes by c-Jun, highlighting its role in the 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) 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). While both studies agree that an impressive number of core autophagy-related genes are directly repressed by FXR in the liver under fed conditions (compared to autophagy-inducing fasting conditions), they propose different regulatory mechanisms. According to Seok *et al.,* the fasting transcriptional activator, cAMP response element-binding protein (CREB), upregulates autophagy genes, including *ATG7, ULK1* and *TFEB*, which are otherwise repressed by FXR through the disruption of 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 between 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) with FXR. When FXR is active, the 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 Wy-14643 reduces proinflammatory responses by promoting activation of autophagy in an acute liver failure mouse model (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., 2014).

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 share a functional translocation from the cytosol to the nucleus upon autophagy induction (Zhang et al. 2015). As a surprising example, proteasome 26S subunit non-ATPase 10 **(**PSMD10) was recently reported to translocate to the nucleus upon amino-acid starvation and bind 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 (C/EBP), beta (C/EBPβ), which can also be stimulated by amino-acid starvation, activates several *ATG* genes, including *MAP1LC3B* and its homolog *GABARAPL1* (Ma et al.,

2011). A recent study highlighted the presence of cAMP response elements (CREs) in the promoter of the *MAP1LC3* homolog *GABARAPL1,* and, indeed, CREB-1 recruitment to the *GABARAPL1* promoter was 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 bind to promoters of autophagy-related genes far exceeds the scope of this short review and a list of mammalian transcription factors, which 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. Due to space limitations, this review can only act as an up-to-date introduction into 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 factors, such as TFEB, c-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 regulation of autophagy by different stress responses. Autophagy is induced by a range of environmental stresses and it is likely that there is an overlapping set of autophagy genes that is required for sustained autophagy independent of the inducer while the transactivation of other ATG genes may be specific to particular cellular stress types. Strikingly, key autophagy genes, especially *MAP1LC3* and its homologs, as well as *BECN1* and *ULK1*, have a vast number of transcriptional activators, indicating a key role for their transcriptional induction upon diverse autophagic stimuli. However, in some cases, it is unclear if the autophagy responses are driven necessarily by changes in a single target gene (e.g. *MAP1LC3A/B*), whose levels are not critical 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 was 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., 2013). The interplay between these factors during autophagy has only been investigated in a few studies, but these highlight a very complex picture of histone modifications, DNA methylation and nuclear/cytosolic shuttling, which all need to be carefully controlled in a cell to achieve the desired level of autophagic flux. How these factors are interconnected 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.

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Table 1. Transcription factors regulating mammalian core autophagy genes

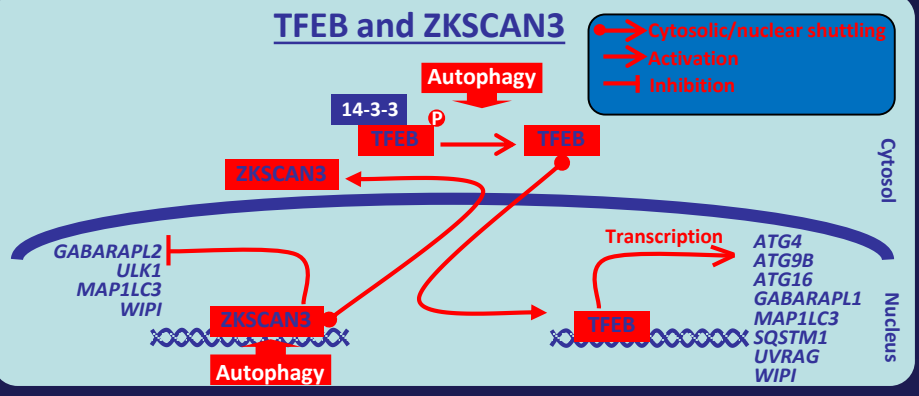
Gene	Transcription Factor	Reference
Regulation of autophagy induction		
MTOR	ATF5	Sheng Z. et al., 2011
ULK1	ATF4	Pike L.R. et al., 2013
	C/EBPb	Ma D. et al., 2011
	CREB	Seok S. et al., 2014
	E2F1	Polager S. et al., 2008
	FOXO3	Schips T.G. et al., 2011
	KLF4	Liao X. et al., 2015
	p53	Gao W. et al., 2011, Kenzelmann Broz D. et al., 2013
	ΔNp63α	Huang Y. et al., 2012
	FOXK1	Bowman C.J. et al., 2014
	FXR	Seok S. et al., 2014
	ZKSCAN3	Chauhan S. et al., 2013
ULK2	KLF4	Liao X. et al., 2015
	TFE3	Perera R.M. et al., 2015
	p53	Kenzelmann Broz D. et al., 2013
	FOXK1	Bowman C.J. et al., 2014
ATG13	FOXK1	Bowman C.J. et al., 2014
Vesicle nucleation		
BECN1	c-Jun	Li D.D. et al., 2009
	FOXO1	Fiorentino L. et al., 2013
	FOXO3A	Sanchez A.M. et al., 2012
	NF-κB	Copetti T. et al., 2009, Lin F. et al., 2015
	PPARα	Lee J.M. et al., 2014
	XBP1	Margariti A. et al., 2013
	ΔNp63α	Huang Y. et al., 2012
	FXR	Lee J.M. et al., 2014
	STAT-1	McCormick J. et al., 2012
ATG14	FOXOs	Xiong X. et al., 2012
VPS34	FOXO1	Liu H.Y. et al., 2009
	FOXO3	Mammucari C. et al., 2008
	PPARα	Lee J.M. et al., 2014
	FOXK1	Bowman C.J. et al., 2014
	FXR	Lee J.M. et al., 2014
BCL2	MITF and TFE3	Martina J.A. et al., 2014
	NF-κB	Tamatani M. et al., 1999
AMBRA1	FOXK1	Bowman C.J. et al., 2014
UVRAG	MITF and TFE3	Martina J.A. et al., 2014
	TFEB	Settembre C. et al., 2012
	p73	Rosenbluth J.M. et al., 2009
ATG9A	ΔNp63α	Huang Y. et al., 2012
ATG9B	MITF	Perera R.M. et al., 2015

	TFE3	Martina J.A. et al., 2014
	TFEB	Settembre C. et al., 2011
Vesicle elongation		
ATG3	CREB	Seok S. et al., 2014
	TFE3	Perera R.M. et al., 2015
	ΔNp63α	Huang Y. et al., 2012
	FXR	Seok S. et al., 2014
ATG4	GATA-1/FOXO3	Kang Y.A. et al., 2012
	SREBP-2	Seo Y.K. et al., 2011
	p53/p63/p73	Kenzelmann Broz D. et al., 2013
	ΔNp63α	Huang Y. et al., 2012
ATG5	DDIT3	Rouschop K.M. et al., 2010
	CREB	Seok S. et al., 2014
	E2F1	Polager S. et al., 2008
	FOXO1	Fiorentino L. et al., 2013
	ΔNp63α	Huang Y. et al., 2012
	FXR	Seok S. et al., 2014
	GATA-1	Kang Y.A. et al., 2012
ATG7	CREB	Seok S. et al., 2014
	PPARα	Lee J.M. et al., 2014
	PSMD10/HSF1	Luo T. et al., 2015
	p53/p63/p73	Kenzelmann Broz D. et al., 2013
	ΔNp63α	Huang Y. et al., 2012
	FXR	Seok S. et al., 2014
ATG10	MITF	Perera R.M. et al., 2015
	SOX2	Cho Y.Y. et al., 2013
	TFE3	Perera R.M. et al., 2015
	p53/p63/p73	Kenzelmann Broz D. et al., 2013
	ΔNp63α	Huang Y. et al., 2012
	FXR	Seok S. et al., 2014
ATG12	FOXO1	Liu H.Y. et al., 2009
	FOXO3	Zhao J. et al., 2007
	GATA-1/FOXO3	Kang Y.A. et al., 2012
	FOXK1	Bowman C.J. et al., 2014
ATG16	MITF, TFE3 and TFEB	Martina J.A. et al., 2014
	FXR	Seok S. et al., 2014
BNIP3	C/EBPb	Ma D. et al., 2011
	E2F1	Yurkova N. et al., 2008 and Shaw J. et al., 2008
	FOXO3	Mammucari C. et al., 2007
	HIF1	Zhang H. et al., 2008 and Bellot G. et al., 2009
	PPARα	Lee J.M. et al., 2014
	FXR	Lee J.M. et al., 2014
	NF-κB	Shaw J. et al., 2008
	pRB/E2F	Tracy K. et al., 2007
MAP1LC3A/B	ATF4	Rouschop K.M. et al., 2010 and Milani M. et al., 2009
	C/EBPb	Ma D. et al., 2011

	c-Jun	Jia G. et al., 2006 and Sun T. et al., 2011
	CREB	Seok S. et al., 2014
	E2F1	Polager S. et al., 2008
	FOXO1	Fiorentino L. et al., 2013
	FOXO3A	Sanchez A.M. et al., 2012
	GATA-1/FOXO3	Kang Y.A. et al., 2012
	MITF and TFE3	Perera R.M. et al., 2015
	PPARα	Lee J.M. et al., 2014
	SREBP-2	Seo Y.K. et al., 2011
	TFEB	Settembre C. et al., 2011
	FOXK1	Bowman C.J. et al., 2014
	FXR	Lee J.M. et al., 2014
	ZKSCAN3	Chauhan S. et al., 2013
GABARAP	GATA-1/FOXO3	Kang Y.A. et al., 2012
	PPARα	Lee J.M. et al., 2014
	FXR	Seok S. et al., 2014
GABAPAL1	C/EBPb	Ma D. et al., 2011
	CREB	Hervouet E. et al., 2015
	FOXO1	Liu H.Y. et al., 2009
	FOXO3A	Sanchez A.M. et al., 2012
	GATA-1/FOXO3	Kang Y.A. et al., 2012
	MITF, TFE3 and TFEB	Martina J.A. et al., 2014
	PPARα	Lee J.M. et al., 2014
	FXR	Lee J.M. et al., 2014
GATE-16	GATA-1/FOXO3	Kang Y.A. et al., 2012
	ZKSCAN3	Chauhan S. et al., 2013
SQSTM1	C/EBPb	Ma D. et al., 2011
	KLF4	Riz I. et al., 2015
	MITF and TFE3	Perera R.M. et al., 2015
	NF-κB	Ling J. et al., 2012
	TFEB	Settembre C. et al., 2011
	β-catenin/TCF	Petherick K.J .et al., 2013
Retrieval		
ATG2	CREB	Seok S. et al., 2014
	TFE3	Perera R.M. et al., 2015
	p53	Kenzelmann Broz D. et al., 2013
	FXR	Seok S. et al., 2014
WIPI	MITF, TFE3 and TFEB	Martina J.A. et al., 2014
	PU.1	Brigger D. et al., 2014
	TFEB	Settembre C. et al., 2011
	FXR	Seok S. et al., 2014
	ZKSCAN3	Chauhan S. et al., 2013

Transcriptional regulation of autophagy

TFEB and ZKSCAN3

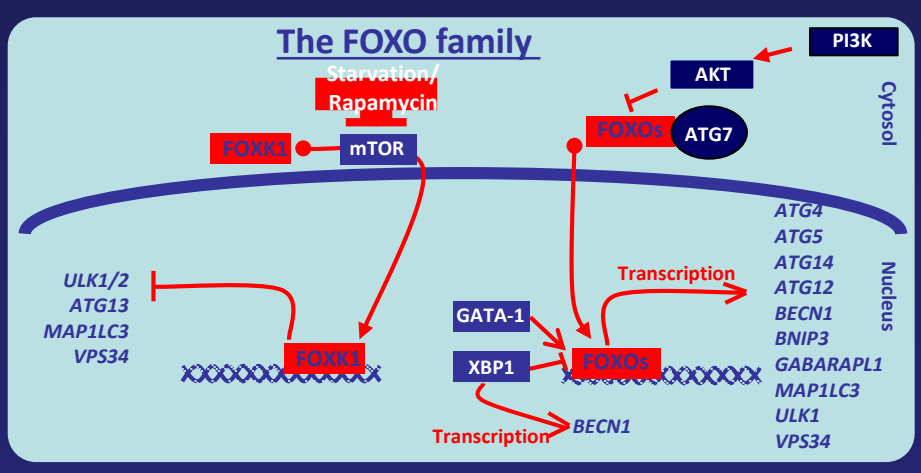


•TFEB is retained in the cytoplasm where it binds to 14-3-3 proteins. Starvation results in its dephosphorylation and translocation to the nucleus.

• MITF/TFE3 share activation pathways and have overlapping target genes to TFEB.

•ZKSCAN3, is a repressor of the transcription of ATG genes. Upon starvation, ZKSCAN3 translocates from the nucleus to the cytoplasm allowing the transcriptional activation of target genes by TFEB.

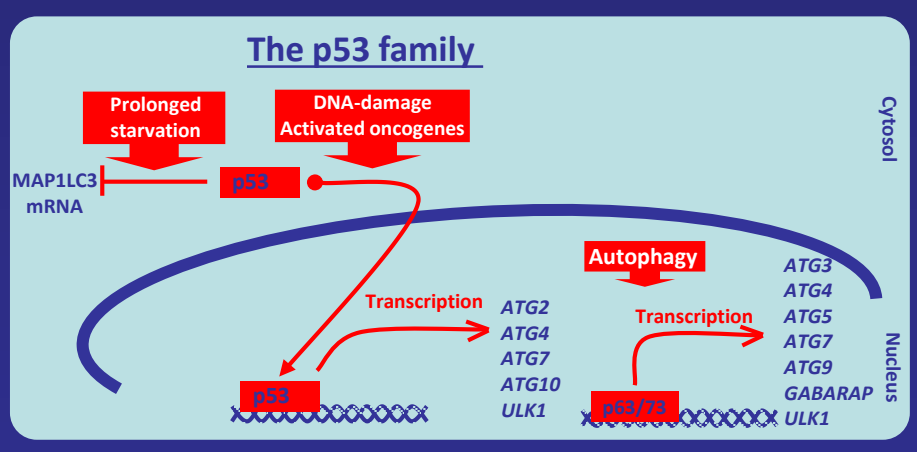
The FOXO family



• When activated, FOXOs translocate to the nucleus to induce the expression of a number of ATG genes. GATA-1 acts with FOXO3 to upregulate autophagy. Alternative splice variants of XBP1 either inhibit autophagy by degrading FOXO1, or induce autophagy by transactivating *BECN1*. In the cytosol, acetylated FOXO1 binds and activates ATG7.

• FOXK1 counteracts FOXO3 by occupying an overlapping set of promoters.

The p53 family

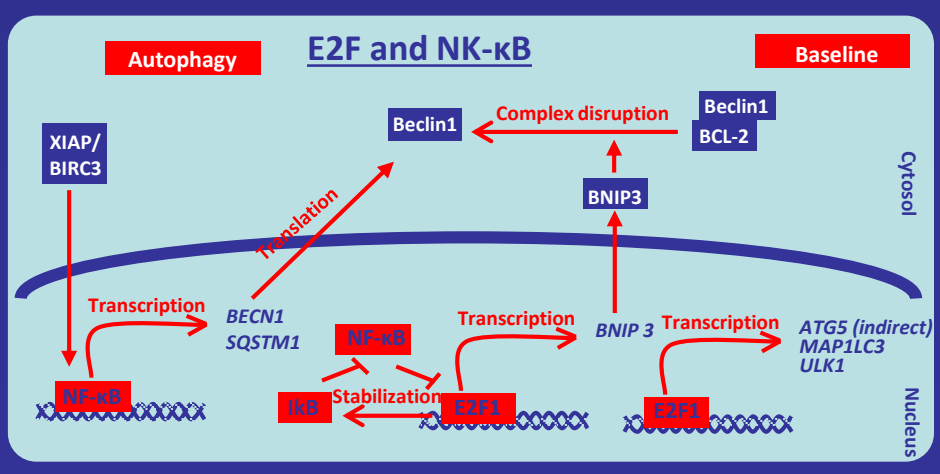


• Inducers of autophagy enhance the transcriptional activity of p53 leading to the expression of several ATG genes.

• The p53 family members, p63 and p73, are able to partly compensate for the loss of p53.

• Under prolonged starvation, cytoplasmic p53 inhibits autophagy through posttranscriptional down-regulation of MAP1LC3.

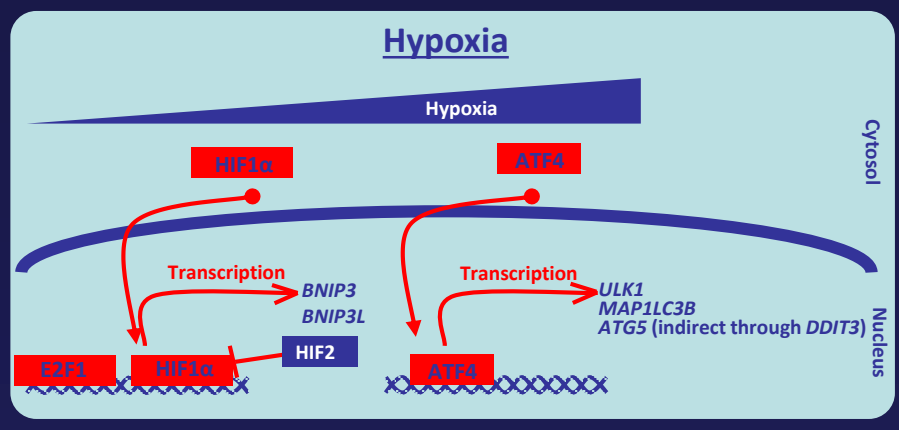
E2F and NK-κB



• E2F1 and NF-κB mainly regulate autophagy by opposing effects on BNIP3 transcription. BNIP3 positively regulates autophagy by disrupting the BCL-2 mediated inhibition of Beclin-1.

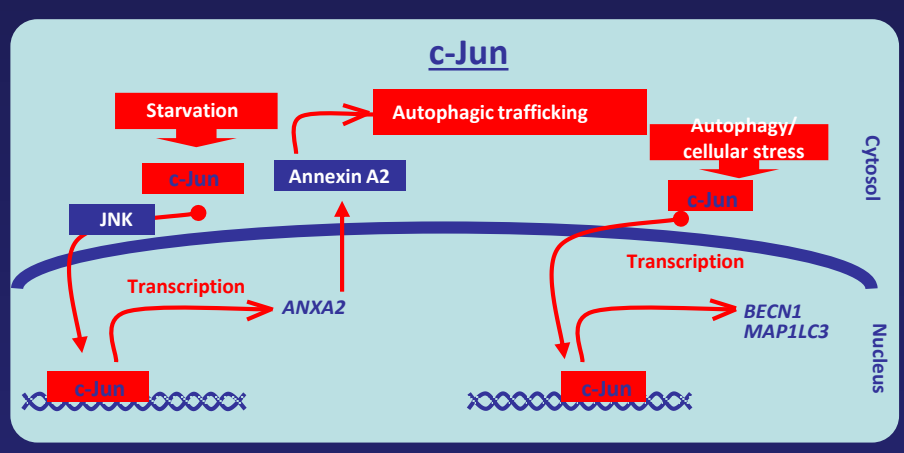
• NF-κB generally inhibits autophagy but can also induce autophagy-related genes including *BECN1* and *SQSTM1*. The amplification of two inhibitors of apoptosis proteins XIAP and BIRC3 induces autophagy through the up-regulation of *BECN1* transcription via NF-κB.

Hypoxia



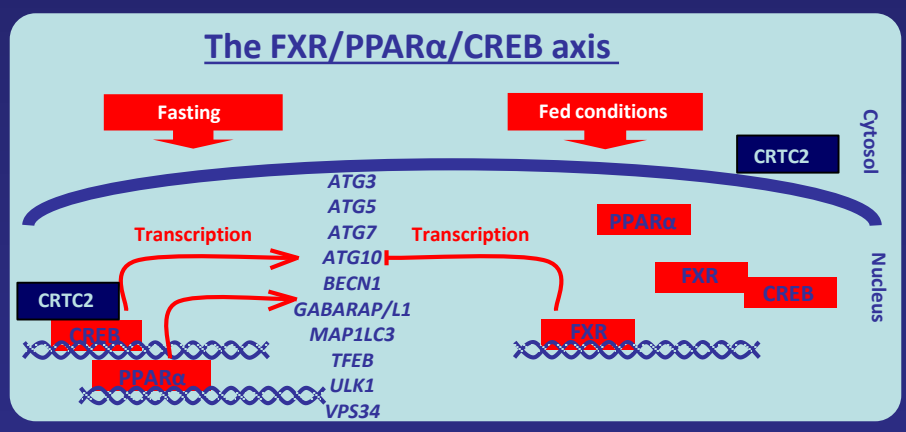
• Upon medium hypoxia, HIF1α activates *BNIP3* and *BNIP3L* transcription.
• Severe hypoxia leads to the activation of ATF4, which induces *ULK1*, *MAP1LC3B* and *ATG5*.

c-Jun



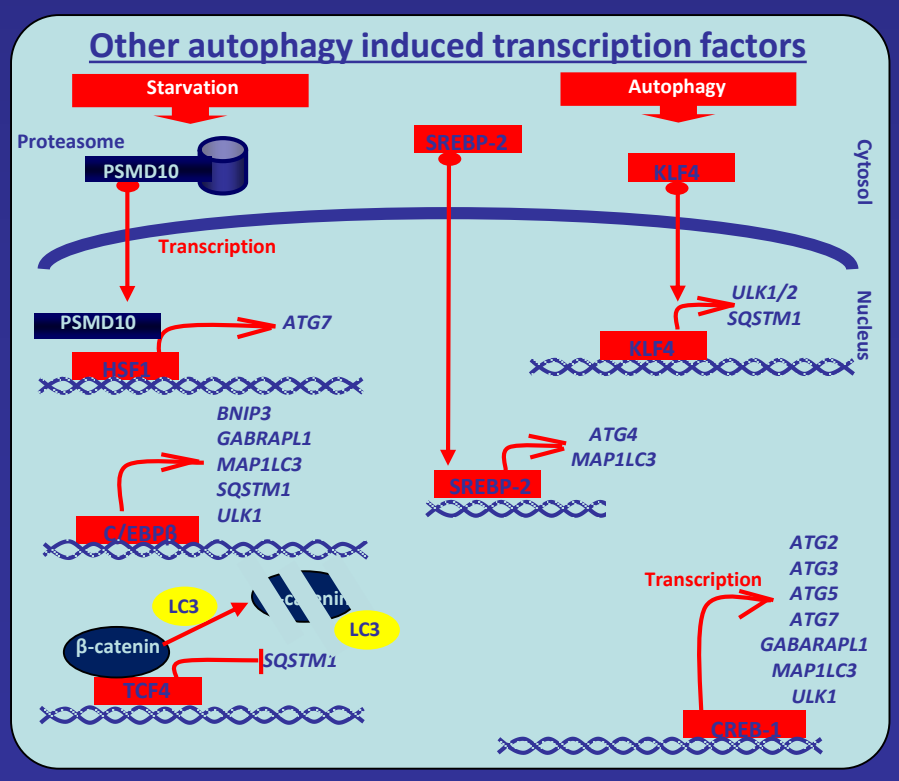
• Annexin A2 is involved in the vesicular trafficking of autophagy and is transcriptionally regulated by the JNK-c-Jun pathway under starvation.

The FXR/PPARα/CREB axis



• FXR was shown to repress most core ATG genes in the liver under fed conditions.
• The fasting transcriptional activator CREB and the nutrient-sensing regulator PPARα have both been described to work in opposition to FXR.
•CREB upregulates autophagy genes through the disruption of the functional CREB-CRTC2 complex.
• PPARα, activated by starvation, shares specific DNA binding sites with FXR. While FXR is active, the binding of PPARα is inhibited.

Other autophagy induced transcription factors



• The proteasome subunit PSMD10 translocates under starvation to the nucleus and binds the transcription factor HSF1 onto the *ATG7* promoter.
• C/EBPβ activates several ATG genes in the liver.
• CRE elements were found in the promoter of *GABARAPL1* and CREB-1 recruitment was required for *GABARAPL1* expression.
•β-catenin/TCF4 inhibit SQSTM1 transcription under baseline conditions. Upon autophagy-induction, MAP1LC3 binds β-catenin and leads to its degradation.
• Cell-sterol depletion increases SREBP-2 nuclear localization and ATG gene expression.