

Chapter 9

The c-Abl/YAP/p73 Apoptotic Module and the HIPPO Pathway

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Abstract The HIPPO pathway is an evolutionarily conserved pathway that regulates cell proliferation and organ size. The canonical pathway is triggered by cell–cell contact, which leads to a series of signaling events that culminate in the nuclear exclusion of the downstream effectors, the pro-proliferative transcription coactivators YAP and TAZ. However, while the canonical role of YAP and TAZ is to promote proliferation, DNA damage leads to a switch in the role of YAP from pro-proliferative to pro-apoptotic. The mechanisms leading to YAP-mediated apoptosis will be discussed in this chapter, focusing on the role of the non-receptor tyrosine kinase c-Abl. c-Abl activity is needed for the switch of YAP from anti- to pro-apoptotic activity, as well as for the regulation of YAP and p73 accumulation. This switching mechanism introduces a certain level of complexity in our attempt to categorize onco- and tumor suppressor genes. p73, YAP, and TAZ are highly disordered proteins, an attribute of key regulatory proteins that interact with many partners. Disordered proteins undergo proteasomal degradation through both ubiquitin-dependent and -independent mechanisms. This double mechanism ensures an optimal HIPPO pathway proteostasis.

Keywords YAP • p73 • c-Abl • Apoptosis • Default degradation • 20S proteasome • Ubiquitin-independent degradation • Nanny model • IDP • Intrinsically disordered protein

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9.1 Introduction

The canonical HIPPO pathway controls cell proliferation and organ size through inhibition, via phosphorylation by LATS, of the transcription coactivators YAP and TAZ. However, noncanonical roles have also been established for these players, and thus these activities must be considered when approaching the system as a whole. The YAP coactivator can play diametrically opposed roles depending on its transcription factor partner. YAP association with the TEAD family of transcription factors leads to transcription of genes promoting cell proliferation, epithelial-to-mesenchymal transition (EMT), inhibition of apoptosis, and tumorigenesis. In contrast, YAP association with p73, a p53 tumor suppressor paralog, promotes apoptosis. In this chapter, we will review the apoptotic pathway mediated by YAP and p73, and discuss how regulation by the non-receptor tyrosine kinase c-Abl leads to the switching of YAP from anti- to pro-apoptotic activity.

YAP and TAZ, like many other key regulators, are intrinsically disordered proteins. This attribute is needed for multiple protein–protein interactions and intensive protein modifications such as phosphorylation. Indeed the number of proteins identified as interacting with YAP and TAZ and the sites of YAP and TAZ modification has increased since their discovery. In addition to modification by phosphorylation, the downstream effectors of the HIPPO pathway are regulated at the level of protein accumulation. c-Abl regulates the stability of p73 and YAP. This is achieved through protection from ubiquitin-dependent proteasomal degradation. However, YAP and p73 are also substrates of ubiquitin-independent degradation, and c-Abl stabilization of YAP and p73 may also be mediated through this pathway. Although regulation of protein levels by ubiquitin-independent degradation is often overlooked, recently the importance of this mode has garnered increased recognition. We will discuss how the ubiquitin-independent degradation pathway should be considered when studying the HIPPO pathway, which includes several known and predicted substrates.

9.2 YAP and p73 in Apoptosis

YAP interacts with many partners via distinct domains. Several of the partners are transcription factors, including the TEAD/TEF (Vassilev et al. 2001) and RUNX (Yagi et al. 1999; Zaidi et al. 2004) families. Association of YAP with TEAD/TEF leads to the transcription of genes that promote proliferation, EMT, tumorigenesis, stem cell renewal, and inhibition of apoptosis (Lian et al. 2010; Zhao et al. 2008a; Zhang et al. 2009; Ota and Sasaki 2008; Sawada et al. 2008). YAP association with RUNX leads to transcription from promoters such as osteocalcin (Yagi et al. 1999; Zaidi et al. 2004) and Itch (Levy et al. 2008a). In 2000, the Yaffe group noted that a number of transcription factors including p73 bear the sequence motif, PPxY, capable of binding the WW domain of YAP and TAZ (Kanai et al. 2000). In 2001, Strano

et al. (2001) reported that YAP associates with p63 and p73, the p53 paralogs. Since the interaction is mediated through the YAP WW domain and the PPPPY motif of p73, YAP interacts only with the long isoforms p73 α , p73 β , and p63 α , which contain the PPPPY motif, and not with p73 γ . RUNX also interacts with YAP through the YAP WW domain (Yagi et al. 1999), but the interaction of YAP with TEAD does not rely on the WW domain. Rather, this interaction is based on a TEAD-binding domain at the N-terminus of YAP, and a C-terminal region in TEAD (Vassilev et al. 2001; Li et al. 2010).

In contrast to the target genes induced by YAP/RUNX or YAP/TEAD, association of YAP with p73 leads to a dramatically different outcome. YAP functions as a coactivator of p73 (Strano et al. 2001), and YAP is important for the induction of apoptosis in response to DNA damaging agents (Basu et al. 2003; Levy et al. 2008b; Strano et al. 2005; Hamilton et al. 2009). YAP association with p73 imparts selectivity in p73 apoptotic targets, leading to transcription of pro-apoptotic targets such as BAX and p53AIP1, rather than the cell cycle arrest target p21 (Strano et al. 2005). In contrast to TEAD that bears a weak transcription activation domain (TAD), p73 contains a strong TAD; therefore, the role of YAP as a transcription coactivator of p73 might not be the whole story. Indeed YAP in the context of p73 plays some other roles as well, such as inhibiting p73 degradation (see below).

P73 and YAP are regulated at the level of subnuclear compartmentation. PML (promyelocytic leukemia protein) is a major organizer of PML nuclear bodies, which serve a scaffolding and regulatory role for cellular processes including apoptosis, senescence, DNA repair, and antiviral defense (Lallemand-Breitenbach and de The 2010; Bernardi et al. 2008; Salomoni et al. 2012). PML is needed for the apoptotic response by p73/YAP (Strano et al. 2005). PML interacts with p73, and inhibits ubiquitin-dependent degradation of p73. This is mediated through p73 acetylation by p300, which is dependent on PML (Bernassola et al. 2004). Interestingly, PML bodies are also needed for YAP coactivation of p73. Coactivation of p73 by YAP is dependent upon PML and localization to nuclear bodies, and YAP also contributes to the accumulation of p73 in response to DNA damage, and its acetylation by p300 (Strano et al. 2005). However, the underlying mechanisms of how p73 and YAP target PML have not yet been resolved, neither has the PML function in this process. PML is conjugated by a ubiquitin-like protein named SUMO. PML conjugation by SUMO plays a critical role in recruitment of proteins, many of which are sumoylated as well (reviewed in Lallemand-Breitenbach and de The 2010). The question of whether YAP and p73 undergo this modification prior to PML association, although important to substantiate the role of PML in this process, remains open.

YAP regulation of p73-dependent apoptosis and p73 levels does not occur spontaneously; rather, it occurs in response to DNA damage. Thus, DNA damage causes a switch in YAP activity, from promoting proliferation to promoting apoptosis. This switch is mediated through the non-receptor tyrosine kinase c-Abl, which is activated by DNA damage.

9.3 The Non-receptor Tyrosine Kinase c-Abl; Domain Structure and Modes of Activation

c-Abl is ubiquitously expressed in mammalian cells, and has both cytoplasmic and nuclear activities (Shaul and Ben-Yehoyada 2005; Pendergast 2002; Colicelli 2010). c-Abl possesses both NLS and NES motifs, and is thought to shuttle between nucleus and cytoplasm based on environmental signals, such as cell adherence to solid substrates (Taagepera et al. 1998). Human c-Abl has two alternatively spliced forms, 1a and 1b. The 1b isoform has a myristoylation site, which allows for membrane association, and is also involved in regulation of c-Abl autoinhibition (Nagar et al. 2003; Hantschel et al. 2003). The N-terminal region of c-Abl has several defined domains of the Src kinase family (reviewed in Pendergast 2002; Colicelli 2010) (Fig. 9.1). The SH3 (Src homology domain 3) binds to proline-rich sequences, with the consensus being PXXP. This domain is followed by an SH2 domain that preferentially binds phosphotyrosine residues. The tyrosine kinase domain (SH1) is followed by a unique long C-terminus. The C-terminal region contains proline-rich domains, the NES and NLS motifs, DNA-binding domain, and domains for binding to F- and G-actin. C-Abl folds into an autoinhibitory conformation, where the kinase domain is shielded by the SH3 and SH2 domains, and the conformation is secured by the interaction of the myristoylated N-terminus with the kinase domain (Pluk et al. 2002; Nagar et al. 2003).

Activation of c-Abl is achieved by opening of the autoinhibitory conformation. In the case of the constitutively active oncogenic forms of ABL, such as BCR-ABL, translocation creates a fusion protein where the N-terminus of BCR is fused to ABL, which prevents the folding into the autoinhibitory conformation. Activation of wild-type c-Abl is achieved through phosphorylation of the activation loop, either by other kinases, such as Src, or by autophosphorylation (reviewed in Colicelli 2010; Pendergast 2002). Phosphorylation of Y412 in the activation loop, and at Y245 in the kinase domain, is needed for full activation of c-Abl (Brasher and Van Etten 2000). C-Abl can also be activated by binding to adaptor proteins, such as the SH3-domain containing proteins Nck (Smith et al. 1999) and Crk (Shishido et al. 2001), which interact with proline-rich regions in the C-terminus of c-Abl. These and other proteins, which are also substrates of c-Abl, are involved in c-Abl regulation of actin dynamics, which is important for neural growth cone formation, cytoskeletal organization, and cell motility (reviewed in Pendergast 2002; Colicelli 2010).

C-Abl regulates cell proliferation and is regulated by mitogenic signals. C-Abl localized to the cell membrane is activated by growth factors EGF and PDGF, and this is mediated through Src kinases and phospholipase C- γ (Plattner et al. 1999, 2003). Both the effect of PDGF on actin dynamics, seen as increased dorsal membrane ruffling, and PDGF mitogenic capacity, are mediated through c-Abl (Plattner et al. 1999). Interestingly, while c-Abl is activated by PDGFR and promotes PDGF-mediated migration and proliferation, c-Abl phosphorylation of PDGFR acts in a negative feedback mechanism to inhibit PDGFR-mediated chemotaxis (Srinivasan

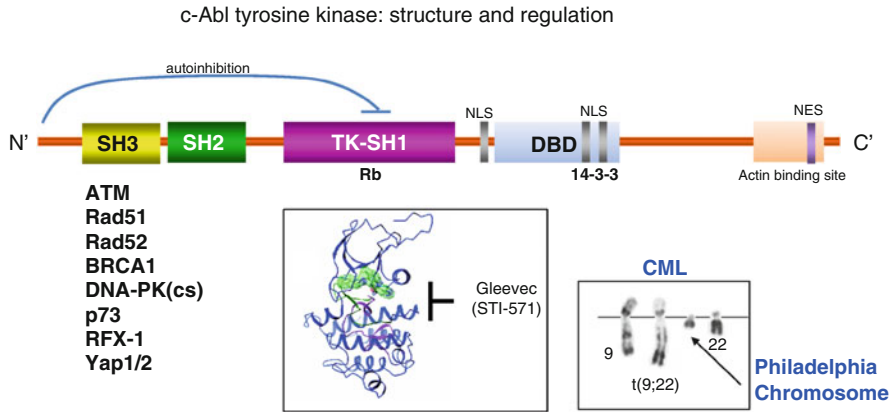


Fig. 9.1 c-Abl tyrosine kinase, structure and regulation. Schematic representation of c-Abl tyrosine kinase. *SH3* Src homology domain 3; *SH2* Src homology domain 2; *TK-SH1* tyrosine kinase, Src homology domain 1; *NLS* nuclear localization signal; *DBD* DNA-binding domain; *NES* nuclear export signal; and binding sites for actin are shown. Listed below are some of the proteins involved in DNA damage response shown to bind to the conserved domains. The structure showing interaction of the c-Abl inhibitor, Gleevec, with the c-Abl kinase domain is shown below the kinase domain. Also shown is the translocation involving ABL on chromosome 9 and BCR on chromosome 22, resulting in the Philadelphia chromosome, which causes chronic myelogenous leukemia, CML

et al. 2009). C-Abl is inhibited by binding of Rb to the kinase domain. As the cell moves from G1 to S phase, c-Abl is freed from Rb, and becomes activated (Welch and Wang 1993). While nuclear c-Abl is activated in S phase, the activity of cytoplasmic c-Abl is not affected by the cell cycle.

c-Abl is also active in stress response. Cytoplasmic c-Abl is activated by oxidative stress in a mechanism involving PKC- δ (Sun et al. 2000a, b) and in c-Abl deficient cells, H₂O₂-induced apoptosis is attenuated (Sun et al. 2000a). Compounds that induce ER stress, including tunicamycin, brefeldin A, or the calcium ionophore A 2318 activate c-Abl, and lead to translocation of ER-associated c-Abl to the mitochondria. Furthermore, apoptosis induced by ER stress is reduced in c-Abl-deficient cells (Ito et al. 2001). Oxidative and ER stress lead to apoptosis through release of mitochondrial cytochrome C in a c-Abl-dependent mechanism (Sun et al. 2000a; Ito et al. 2001).

C-Abl can translocate between the nucleus and the cytoplasm. However, phosphorylation of c-Abl by TTK/Mps1 on T735 (Nihira et al. 2008), creates a binding site for 14-3-3 (Yoshida et al. 2005), and leads to cytoplasmic localization of c-Abl. The T735 phosphorylation site is located between the second and third NLSs of c-Abl, and binding to 14-3-3 may mask the NLSs, impeding the nuclear localization of c-Abl (Yoshida 2007). Upon DNA damage, activation of JNK leads to the phosphorylation of 14-3-3, and the release of c-Abl, allowing the nuclear accumulation of c-Abl (Yoshida et al. 2005). Although YAP and TAZ are also sequestered in the cytoplasm through binding to 14-3-3 proteins (Kanai et al. 2000; Basu et al. 2003;

Zhao et al. 2007), it is not known whether JNK phosphorylation of 14-3-3 can lead to the nuclear localization of YAP and TAZ.

DNA damage by ionizing radiation and genotoxic agents leads to activation of nuclear c-Abl (Kharbanda et al. 1995a; Liu et al. 1996). This involves phosphorylation of c-Abl S465 by ATM (Baskaran et al. 1997; Shafman et al. 1997). Activation of c-Abl also relies on an intact mismatch-repair system, as c-Abl activation caused by different DNA damaging agents is impaired in cells deficient for mismatch repair (Nehme et al. 1999; Gong et al. 1999). The nonhomologous end joining (NHEJ) DNA repair protein DNA-PK also contributes to c-Abl activation (Kharbanda et al. 1997; Tang et al. 2012). Interestingly, c-Abl also phosphorylates, and is required for the full activation of ATM and ATR (Wang et al. 2011). Furthermore, c-Abl plays a role in activating JNK/SAPK and p38 MAP kinase pathways in response to DNA damage (Kharbanda et al. 1995a, b, 2000; Pandey et al. 1996). C-Abl has been shown to phosphorylate DNA-PK (Kharbanda et al. 1997) and other DNA damage response proteins, including RAD51 (Yuan et al. 1998), RAD52 (Kitao and Yuan 2002), and WRN (Cheng et al. 2003). In the case of DNA-PK, RAD51, and WRN, c-Abl phosphorylation inhibits their activities. This inhibitory activity toward DNA damage repair proteins is consistent with the finding that c-Abl inhibits the slow phase of DNA repair (Meltser et al. 2010). Meltser et al. showed that following ionizing radiation, most repair of double-strand breaks is concluded within 1–2 h, whereas breaks remaining after that period are repaired much more slowly (Meltser et al. 2010). C-Abl plays a role in down-regulating this later phase of repair, which is assumed to be less accurate than in the initial stage. One interpretation of this activity is that this paves the way for induction of apoptosis in cells with low likelihood of complete and accurate repair of their DNA. In this situation, active c-Abl is then poised to induce apoptosis, through activation of the p53-family member p73, and its coactivator YAP.

9.4 Regulation of p53 Family Proteins by c-Abl Tyrosine Kinase

The non-receptor tyrosine kinase c-Abl plays multiple roles in the regulation of the apoptotic pathway. Although later work showed that this role is primarily mediated through p73, early studies made connections between c-Abl and p53. Sawyers et al. demonstrated that nuclear expression of c-Abl led to cell cycle arrest, which was reminiscent of control by Rb and p53 (Sawyers et al. 1994). This group then showed that c-Abl bound p53, and c-Abl-induced cell cycle arrest was p53-dependent (Goga et al. 1995). Furthermore, c-Abl-mediated DNA damage-induced cell cycle arrest was shown to be dependent on p53 (Yuan et al. 1996a, b). C-Abl can phosphorylate Hdm2, the p53 E3 ligase, and the related p53 inhibitor Hdmx, and this inhibits their activities. In this way, c-Abl supports p53 accumulation and function (Zuckerman et al. 2009; Sionov et al. 1999; Goldberg et al. 2002).

However, c-Abl-dependent apoptotic response to DNA damage was found to occur in cells deficient for p53, indicating that c-Abl could operate through another mechanism (Yuan et al. 1997). This mechanism is mediated through the p53 family members p73, and p63 under certain cell contexts.

C-Abl activation affects the p73-dependent apoptotic response via several mechanisms. In response to DNA damage, activated c-Abl directly phosphorylates p73, which leads to p73 stabilization, and is needed for p73 apoptotic activity (Agami et al. 1999; Gong et al. 1999; Yuan et al. 1999). In contrast, c-Abl does not directly phosphorylate p53 (Ben-Yehoyada et al. 2003). P73 is phosphorylated by c-Abl on Y99 (Yuan et al. 1999), and the interaction between the c-Abl SH2 domain and phosphorylated p73 is needed for p73 stabilization (Tsai and Yuan 2003). Interaction between c-Abl and p73 depends on the c-Abl SH3 domain and a PxxP motif located in the linker region of p73 (Agami et al. 1999). Phosphorylation of p73 by c-Abl leads to the association of p73 with the nuclear matrix (Ben-Yehoyada et al. 2003). As PML is associated with the nuclear matrix (Lallemant-Breitenbach and de The 2010), c-Abl phosphorylation of p73 leads to increased association with PML, which, as mentioned above, leads to increased p73 stabilization due to PML-dependent acetylation (Bernassola et al. 2004), and increased apoptotic activity (Strano et al. 2005). Additionally, the prolyl isomerase Pin1, which recognizes phosphorylated serine or threonine residues that are followed by proline, is needed for stabilization of p73, and this mechanism is dependent upon c-Abl (Mantovani et al. 2004). Following DNA damage, c-Abl phosphorylation of p73 leads to subsequent phosphorylation of p73 by p38 MAPK (Sanchez-Prieto et al. 2002). P73 phosphorylated by p38 binds to Pin1, and this enhances acetylation of p73 by p300, and p73 stabilization (Mantovani et al. 2004).

9.5 Regulation of YAP/p73-Mediated Apoptosis by c-Abl Tyrosine Kinase

In response to DNA damage, c-Abl also phosphorylates YAP, at Y357 (Y391 in YAP2), leading to an increase in YAP levels (Levy et al. 2008b). The mechanism by which c-Abl phosphorylation increases YAP levels has not been revealed yet, but it may be achieved via two distinct mechanisms. The first involves YAP degradation via β -TrCP. YAP phosphorylation by LATS on S381 leads to subsequent phosphorylation by CK1 δ/ϵ , which marks the YAP phosphodegron as a substrate for β -TrCP-mediated ubiquitination, which is then followed by proteasomal degradation (Zhao et al. 2010). The c-Abl phosphorylation site, Y391, is adjacent to the DSG phosphodegron, leading to the possibility that phosphorylation of YAP by c-Abl inhibits YAP degradation by interfering with the association/phosphorylation of YAP by LATS, CK1 δ/ϵ , or with β -TrCP (Fig. 9.2). TAZ degradation is also mediated through a β -TrCP. However, in contrast to YAP, there are two consensus DSG phosphodegron motifs, with the C-terminal motif being more similar to the YAP DSG. Both

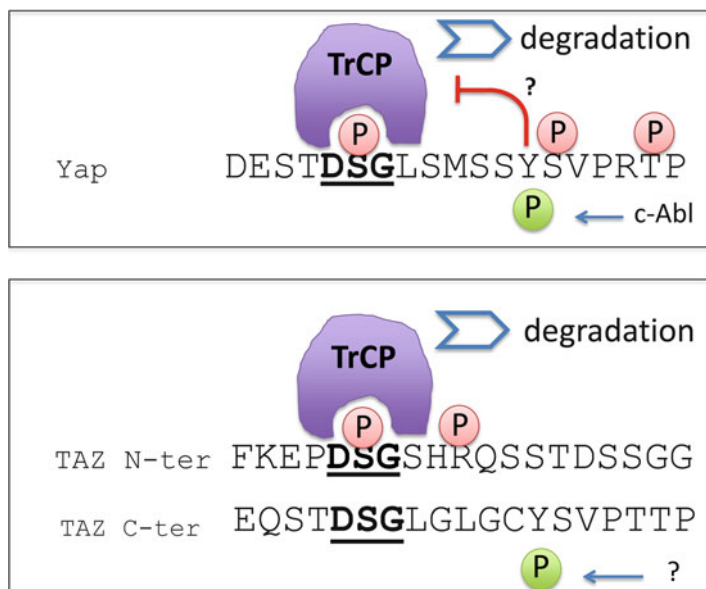


Fig. 9.2 YAP and TAZ phosphodegron motif. The phosphodegron DSG motif recognized by β -TrCP and surrounding sequence is shown. The tyrosine residue in YAP phosphorylated by c-Abl is indicated. TAZ has two consensus DSG motifs. The N-terminal motif has been shown to be the one targeted by β -TrCP in degradation of TAZ. Interestingly, the C-terminal motif is more similar to the YAP DSG motif, and possesses a putative tyrosine phosphorylation site

play a role in regulating TAZ levels under different conditions (Liu et al. 2010; Huang et al. 2012). In addition to potential modulation of β -TrCP-mediated YAP degradation, c-Abl phosphorylation of YAP may help in preventing YAP degradation through the ubiquitin-independent default degradation pathway (see below).

C-Abl phosphorylation not only increases YAP levels, but it also leads to an increased association of YAP with p73, leading YAP to preferentially associate with p73 instead of RUNX. The increased level of YAP, and its increased affinity for p73, enable the stabilization of p73 by YAP by preventing ubiquitination by the E3 protein ligase Itch, as described below (Levy et al. 2007; Danovi et al. 2008). Furthermore, YAP phosphorylated by c-Abl accumulates in the nucleus, and specifically associates with p73 on pro-apoptotic targets, such as Bax and PIG3, at the expense of non-apoptotic p73 targets, such as p21 (Levy et al. 2008b). Likewise, DNA damage-induced phosphorylation of YAP by c-Abl causes YAP to dissociate from RUNX, a regulator of Itch, the p73 E3 ligase. In this way, c-Abl enables the switching of YAP toward an apoptotic program (Fig. 9.3). It is, however, not clear whether under this condition tyrosine phosphorylated YAP is in association with TEAD transcription factors. Phosphomimetic YAP mutant is as active as wild-type

YAP in coactivating TEAD major target genes, suggesting that YAP modification is unlikely to modify the TEAD transcription program. Remarkably however, this YAP mutant is inactive in inducing cell transformation (unpublished observation), suggesting that the function of the new targets of the tyrosine phosphorylated YAP, such as those activated by p73 is dominant over the function of the YAP-TEAD transcription program.

The molecular mechanism of the c-Abl-mediated YAP target switch is still unknown. Particularly challenging is understanding the mechanism of YAP dissociation from RUNX at the level of the target genes. This is because it is unlikely that the whole YAP pool undergoes c-Abl-mediated tyrosine phosphorylation and the residual unmodified YAP should remain RUNX associated. The simplest explanation is that c-Abl directly targets the promoter-associated RUNX-YAP complex, although this remains to be shown experimentally. The fact that c-Abl is in association with promoters/enhancers has been demonstrated by a few studies. c-Abl binds to specific DNA sequences (Dikstein et al. 1992), and c-Abl that is associated with DNA is preferentially phosphorylated and activated (Dikstein et al. 1996). Also, a role for c-Abl has been shown in enhancing transcription through the phosphorylation of the CTD of RNA polymerase II (Baskaran et al. 1993, 1996). However, a role for this phosphorylation in induction of specific target genes is not known.

9.6 Regulation of HIPPO Pathway Proteostasis

A critical mode of regulation relies on mechanisms of protein homeostasis (proteostasis). The HIPPO pathway effectors are labile proteins, an attribute shared by many important regulators. Therefore, for better understanding of this pathway one needs to know the mechanisms of their degradation and how this process is modulated under different physiological conditions. Our knowledge on p73 is quite good. P73 is degraded in a ubiquitin-dependent manner, mediated by the ubiquitin ligase Itch (Rossi et al. 2005). P63, the p73 paralog, is also a substrate of Itch, and interaction is mediated in a manner analogous to the Itch/p73 interaction (Rossi et al. 2006). The interaction between p73 and Itch is mediated through the p73 PPPPY domain and Itch WW domains (Rossi et al. 2005). Notably, YAP also interacts with p73 through binding of YAP's WW domain to the p73 PPPPY motif. Thus, YAP-induced accumulation of p73 is due to its ability to compete with Itch for the binding to p73, thus preventing ubiquitination of p73 by Itch (Levy et al. 2007; Danovi et al. 2008) (Fig. 9.3). A similar mechanism would be predicted for protection of p63. In addition, c-Abl phosphorylation of YAP is involved in down-regulating Itch expression under DNA damage, as described in the previous section.

Interestingly, the HIPPO kinase LATS1, but not LATS2, is also a substrate of Itch (Salah et al. 2011; Ho et al. 2011). It is not yet known whether YAP can also protect LATS1 from Itch-dependent degradation, as it does for p73. What has been shown is that Itch overexpression leads to a reduction in LATS1 levels, leading to

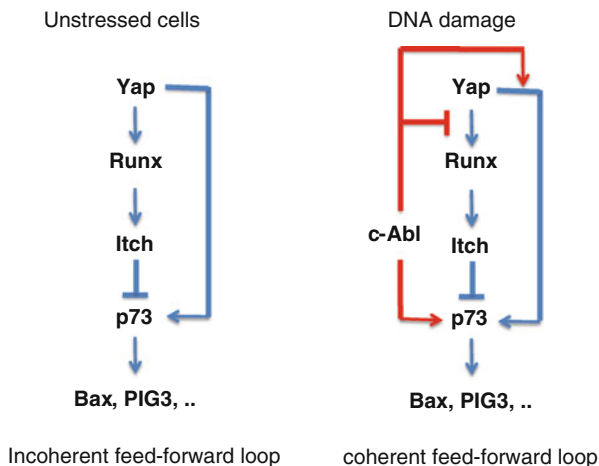


Fig. 9.3 Regulation of YAP/p73 mediated apoptosis. Under normal conditions, p73 undergoes proteasomal degradation mediated by the ubiquitin E3 ligase Itch. YAP coactivation of RUNX leads to higher levels of Itch, and reduced p73. Although YAP can also protect p73 from Itch, in the absence of DNA damage the net effect is p73 degradation. This represents an incoherent feed-forward loop. In the presence of DNA damage, c-Abl is activated, and this increases YAP levels and the propensity of YAP to associate with p73, rather than with RUNX. As a result, Itch levels are reduced, p73 levels increase, and p73/YAP activates pro-apoptotic target genes. Thus, activation of c-Abl switches the circuit to a coherent feed-forward loop

lower phosphorylation of YAP on S127, more nuclear localization of YAP, and more transcription of YAP pro-proliferative target genes. Knockdown of Itch leads to increased LATS1 and increased LATS-dependent apoptosis, as apoptosis in this situation was again decreased upon knockdown of LATS (Ho et al. 2011; Salah et al. 2011). Since Itch knockdown is also expected to lead to higher levels of p73, it is possible that apoptosis under this condition is also dependent on p73. This principle of regulation that is based on sequestration of the WW domain ligand sequence (PPxY, in the described examples) might have wider implications. For example, there are a relatively large number of WW domain containing proteins including a few other E3 ligases that their access to the substrate is eliminated by this mechanism (Shearwin-Whyatt et al. 2006).

Interestingly, YAP, by targeting RUNX, promotes the transcription of the Itch gene (Levy et al. 2008a). However, upon DNA damage YAP is phosphorylated by c-Abl, and this causes YAP to switch its association from RUNX in favor of p73. This leads to a reduction in transcription of Itch (Levy et al. 2008a). Thus, c-Abl also leads to the stabilization of p73 by reducing transcription of the E3 ligase Itch by disrupting the YAP-RUNX complex (Fig. 9.3). As LATS1 is also a target of Itch, it is predicted that activation of c-Abl by DNA damage would lead to an increase in LATS1 levels (Ho et al. 2011; Salah et al. 2011). However, this critical question has

not been challenged and an effect of DNA damage on levels of LATS has not been reported. The interactions of YAP, p73, Runx, Itch, and c-Abl can be summarized as shown in Fig. 9.3. In the absence of c-Abl phosphorylation, increased levels of YAP activate RUNX on the Itch promoter, leading to reduced p73 levels. This results in an incoherent feed-forward loop. In contrast, when YAP is phosphorylated by c-Abl, this causes YAP to dissociate from RUNX, leading to reduced Itch, and increased levels of p73. YAP also protects p73 from Itch-mediated degradation through binding to p73. Thus, in the presence of c-Abl phosphorylation of YAP, the circuit is transformed into a coherent feed-forward loop.

In the context of canonical activation of the HIPPO pathway by high cell density, MST and LATS ensure the nuclear exclusion of YAP. Yet, under other contexts, MST, LATS, Salvador, and RASSF1A promote apoptosis mediated by (nuclear) YAP and p73 (Matallanas et al. 2007; Donniger et al. 2011; Hamilton et al. 2009; Kawahara et al. 2008; Park et al. 2010; Yee et al. 2012). The details of this pro-apoptotic HIPPO cassette are presented in Chap. 7. Interestingly, MST1/2-promoted apoptosis is also subject to regulation by c-Abl. In response to oxidative stress in neurons, c-Abl phosphorylates MST1, leading to its stabilization and association with FOXO3, which then promotes apoptosis (Xiao et al. 2011). In addition, through a different mechanism, c-Abl is needed for MST2-mediated apoptosis. Here c-Abl phosphorylation of MST2 leads to its dissociation from Raf-1, enabling MST2 activation and induction of apoptosis (Liu et al. 2012).

YAP also associates with p63 (Strano et al. 2001). In oocytes, DNA damage leads to apoptosis that is dependent on c-Abl phosphorylation of p63 (Gonfloni et al. 2009). Full-length TA-p63 is implicated in this process, yet it is not known whether YAP plays a role in this response. Interestingly, c-Abl phosphorylation of the pro-survival Δ Np63 isoform leads to Δ Np63 stabilization (Yuan et al. 2010). Cisplatin treatment induces c-Abl phosphorylation of Δ Np63, and its association with YAP; however, these are implicated in protecting cells from cisplatin-induced cell death, rather than with inducing apoptosis, as is found with full-length p63 and p73.

In the previous sections we described mechanisms behind the DNA damage-induced stabilization of p73 and YAP. These mechanisms focused on escape from ubiquitin-dependent proteasomal degradation. The ubiquitin-proteasome system regulates the degradation of a vast array of cellular proteins, including those that are part of the HIPPO pathway. However, this system exists alongside ubiquitin-independent proteasomal degradation, a system that is often overlooked. While ubiquitin-dependent regulation requires modification of the substrate proteins by ubiquitin-E3 ligases, susceptibility of proteins to ubiquitin-independent degradation depends on the inherent characteristics of the given protein. Degradation of proteins by the proteasome necessitates a feeding of the protein into the catalytic core (20S particle) of the proteasome. The opening of this cylindrical core is small. Therefore, to enter the proteasome, proteins must present an unfolded region to the catalytic core of the proteasome (Smith et al. 2005; Kohler et al. 2001). Folded proteins are too large to enter the entry pore of the 20S proteasome. In the process of ubiquitin-dependent degradation,

folded, ubiquitinated proteins are recognized and bound by the 19S regulatory cap of the 26S proteasome. The cap structure has the ubiquitin-binding and deubiquitinase activities, as well as unfolding activity. Once it is deubiquitinated and unfolded, the protein can be fed into the 20S catalytic core of the proteasome, and degraded (Ruschak et al. 2010; Navon and Goldberg 2001). However, there are many examples of proteins that have regions that are intrinsically unstructured; their natural state is to be unfolded (Wright and Dyson 1999). These proteins are referred to as IDPs, intrinsically disordered proteins. Since these proteins possess unfolded regions, they are immediate substrates of the 20S proteasome, and require no modification prior to degradation. For this reason, degradation of these proteins occurs “by default” (Tsvetkov et al. 2009; Asher et al. 2006; Melo et al. 2011). Interestingly, many regulatory proteins are IDPs; their unstructured regions may give them more flexibility in terms of interaction with other proteins (Ward et al. 2004). In other words, the unstructured regions can be used to bind to different protein partners at different times, with the unstructured region adopting different conformations upon interacting with a specific protein partner. The interaction with other proteins also provides the means for regulating degradation by default. Interaction of an IDP with a protein partner protects the IDP from degradation by the 20S proteasome. The protein partner can be a permanent interacting protein, as in a functional complex, or to a more temporary binding protein, termed a “nanny” (Tsvetkov et al. 2009).

The ubiquitin-independent degradation pathway has shown to be a significant regulatory mechanism for many proteins, including those also degraded through ubiquitin-dependent means. These proteins include (but are not limited to) p53 (Asher and Shaul 2005, Asher et al. 2001, 2002a, b), ODC (Asher et al. 2005a), c-Fos (Adler et al. 2010), BIM(EL) (Wiggins et al. 2011), p21 (Touitou et al. 2001; Tsvetkov et al. 2008), BAF57 (Keppler and Archer 2010), thymidylate synthase (Melo et al. 2011), and others. Furthermore, p73 (Asher et al. 2005b), and the HIPPO proteins YAP and TAZ (Tsvetkov et al. 2012) are all subject to ubiquitin-independent degradation by default. YAP and TAZ are particularly sensitive to default degradation, when compared to other substrates of 20S proteasomal degradation (Tsvetkov et al. 2012). They possess a very high level of disorder. A schematic representation of YAP and TAZ disorder, as predicted by the program FoldIndex© (Prilusky et al. 2005) is shown in Fig. 9.4. As noted above, substrates of this type of degradation, degradation by default, can be protected from degradation by binding to a protein partner, or to a nanny (Asher et al. 2006). The protein NQO1 serves as a nanny for several IDPs, including p73 (Asher et al. 2005b), p53 (Asher et al. 2002b), and c-FOS (Adler et al. 2010). The interaction between YAP and p73, which is increased following c-Abl phosphorylation, may also serve to protect both proteins from default degradation. Thus, c-Abl phosphorylation may be affecting stability of YAP and p73 through this mechanism as well. There are other protein–protein interactions within the HIPPO network that may serve nanny functions for YAP, TAZ, or other HIPPO proteins. Interaction of YAP and TAZ with the 14-3-3 proteins (Basu et al. 2003; Zhao et al. 2007; Kanai et al. 2000), while serving

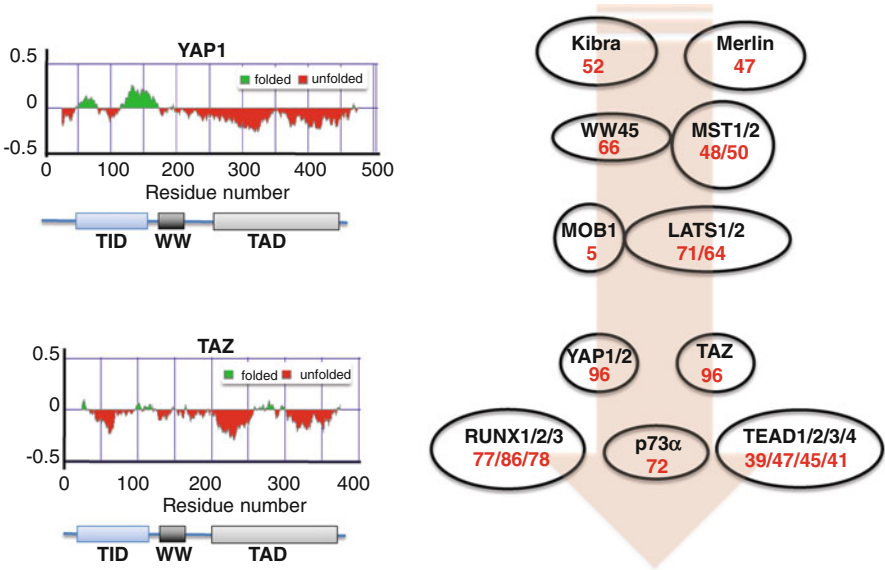


Fig. 9.4 Intrinsically disordered proteins of the HIPPO pathway. *Left panel:* Schematic representation of YAP and TAZ, and the predicted regions of disorder as analyzed by FoldIndex© (Prilusky et al. 2005). *Right panel:* Components of the HIPPO pathway are listed with the percentages of disordered regions, as calculated using IUPred (Dosztanyi et al. 2005a, b). The number represents the percent of amino acids in the protein with a disorder score above 0.4

to sequester them in the cytoplasm, may also be serving a nanny function, and allowing a protected reservoir of these proteins to remain undegraded. Similarly, YAP and TAZ interaction with LATS1/2 (Zhao et al. 2007; Huang et al. 2005; Hao et al. 2008; Lei et al. 2008), AMOT (Webb et al. 2011; Chan et al. 2011; Zhao et al. 2011) and ZO-2 (Oka et al. 2010; Remue et al. 2010), while having implications for cellular localization, may also be affecting YAP/TAZ levels by preventing default degradation. An important prediction is that the levels of YAP and TAZ change in direct correlation with the levels of the interacting proteins; namely the other HIPPO pathway components. Other HIPPO proteins may also be regulated through default degradation. Many of the HIPPO pathway proteins have disordered regions. Figure 9.4 shows HIPPO pathway components with the percentage of amino acids predicted to be in unstructured regions, as calculated by the program IUPred (Dosztanyi et al. 2005a, b). For example, Salvador (WW45), predicted to be 66% disordered, is also efficiently degraded in the ubiquitin-independent pathway (Tsvetkov et al. 2012). Thus, the fact that some of the HIPPO pathway components are unstructured and vulnerable to degradation by default unless they are in a complex, ensures an optimal HIPPO pathway proteostasis.

9.7 From Oncogene to Tumor Suppressor and Back Again

In trying to make sense of complex pathways, we tend to group proteins with similar functions and label them accordingly. Such is the case with “oncogenes” and “tumor suppressors.” Tumor suppressors protect cells from becoming cancerous. They prevent unbridled cell division, and will induce apoptosis when DNA damage threatens the integrity of the genome. When proteins are labeled this way, we make predictions about the activity of a protein under a given condition based on its assignment in this context. For example, with DNA damage, we assume tumor suppressors will favor apoptosis. However, this simplification leads to difficulty when the proteins switch roles. Such is the case with YAP, and *c-Abl* as well. *ABL* is a well-known oncogene when its N-terminus is fused through translocation, as in the case of chronic myelogenous leukemia (CML), to another protein, such as BCR (Sawyers 1999). In this situation, BCR-ABL is constitutively active, and is cytoplasmic, in contrast to wild-type *c-Abl*, which has both nuclear and cytoplasmic functions. The altered conformation of BCR-ABL, leading to altered localization, activation, and spectrum of substrates can be used to explain the oncogenicity of BCR-ABL. However, “switches” of wild-type *c-Abl* activity, causing wild-type *c-Abl* to be oncogenic, have also been observed. Activation of wild-type *c-Abl* has been implicated in certain cases of malignant solid tumors of lung and breast (Lin and Arlinghaus 2008). In the case of NSCLC, this may be due to the loss of an endogenous inhibitor of *c-Abl*, *FUS1* (Lin and Arlinghaus 2008). Whether improper activation of *c-Abl* plays a role in driving other cancers remains to be seen.

As noted above, with DNA damage, *c-Abl* is active in the nucleus, and phosphorylates YAP, which promotes p73-dependent apoptosis. In this situation, both YAP and *c-Abl* are tumor suppressors. In a study on breast cancer, YAP was shown to act as a tumor suppressor, and loss of YAP supported tumorigenicity, including increased invasiveness and increased tumor growth in nude mice (Yuan et al. 2008). Nevertheless, numerous mouse genetic studies and analysis of human tumors have shown YAP to be oncogenic (Huang et al. 2005; Overholtzer et al. 2006; Zhao et al. 2008b; Zeng and Hong 2008; Dong et al. 2007). In these models, the pro-proliferative activity of YAP clearly supersedes the pro-apoptotic. The question arises as to why this is true, and which *in vivo* conditions must prevail in order to support YAP pro-apoptotic activity. From a therapeutic standpoint, a method to switch YAP activity in cancer cells is a lucrative goal. However, in order to accomplish this goal more must be known about YAP regulation in different cell contexts. For example, the upstream HIPPO pathway components appear to have different effects on YAP under different cell contexts. Under high cell density YAP is nuclear excluded through the canonical HIPPO pathway components MST, WW45, and LATS. This prevents YAP coactivation of pro-proliferative genes. In contrast, these HIPPO pathway components, along with RASSF1, are known to promote apoptotic YAP activity in response to DNA damage and other insults (Matallanas et al. 2007). Here, YAP and the other HIPPO pathway proteins are all acting in tumor suppressor mode. The question remains as to what happens at high cell density, when YAP should be

excluded from the nucleus by HIPPO pathway proteins, thereby inhibiting its tumor suppressor activity. Under this condition, does the HIPPO pathway suppress apoptosis? Or, alternatively, is YAP nuclear exclusion suspended upon DNA damage, and if so, what is the mechanism?

Another anti-apoptotic role for YAP was revealed in its ability to compete with LATS for the binding to ASPP1. In this mechanism, LATS promotes the nuclear localization ASPP1 in response to oncogenic stress, and induces ASPP1/p53-driven apoptosis (Aylon et al. 2010). YAP association with LATS in the cytoplasm prevents LATS-mediated ASPP1 translocation. It is still unclear why certain stimuli promote YAP tumor suppressor activity, while others enable the anti-apoptotic activity of YAP. As shown for the case with DNA damage, part of the mechanism could be the status of YAP phosphorylation by c-Abl. However, other mechanisms, such as YAP localization, alternate phosphorylations, or association with different proteins are also likely to affect outcome. For example, c-Abl phosphorylation of $\Delta Np63$ increases its association with YAP and protects from DNA damage-induced apoptosis (Yuan et al. 2010), whereas c-Abl phosphorylation of TAp63 promotes apoptosis (Gonfloni et al. 2009). Phosphorylation of YAP on different sites also regulates its activity. In addition to phosphorylation by LATS (Zhao et al. 2007; Hao et al. 2008; Oka et al. 2008), Akt (Basu et al. 2003), and c-Abl (Levy et al. 2008b), YAP was shown to be multiply phosphorylated on serine and threonine residues in a p38- and JNK-dependent pathway in response to UV and cisplatin (Lee and Yonehara 2012). In addition, YAP activity is modulated by phosphorylation by Src and Yes (Zaidi et al. 2004; Tamm et al. 2011). These multiple modes of regulation enable the multiple functions of YAP. Unfortunately, this complicates our classification of YAP, and prevents easy assignment as either “tumor suppressor” or “oncogene.”

9.8 Conclusions and Future Directions

The Hippo pathway, which controls cell fate decisions regarding cell division and apoptosis, must be seen not as a linear route leading from a stimulus on one end, to a defined output at the other. Rather, the Hippo pathway is actually a network, with inputs impinging on the core players coming from different directions, and from different cellular pathways. This complexity means that a given Hippo pathway component’s behavior is not fixed; rather, it will be determined by localization, interactions with other proteins, protein level, and posttranslational modifications. Using the case of YAP and the DNA damage response, we see that YAP activity is transformed from pro-proliferative to pro-apoptotic, based on changes in its associations, which is largely regulated by phosphorylation by the non-receptor tyrosine kinase c-Abl. Interestingly, c-Abl regulates several other processes that are highly relevant to Hippo pathway function, including cell proliferation and actin dynamics (Colicelli 2010; Pendergast 2002). It is therefore predicted that c-Abl will be found to play a role in other aspects of Hippo pathway regulation.

The protein–protein interactions that govern activity also contribute to regulation of protein stability. This occurs through protection from ubiquitin-dependent as well as ubiquitin-independent proteasomal degradation. The use of common protein modules for interaction, such as the interaction of WW domains with PY domains, provides for interplay between E3 ubiquitin ligases and their substrates, and competing proteins with complementary protein modules. This scenario was shown for YAP/p73/Itch, and is likely to be a common mechanism for other Hippo pathway components.

Protein–protein interaction also provides a means for escape from ubiquitin-independent degradation, which degrades proteins with unstructured regions. As many regulatory proteins, including those in the Hippo pathway, possess these regions, this mode of degradation/stabilization should be considered when evaluating Hippo regulation.

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