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p53 as a Therapeutic Target in T-ALL

Irene Riz[1], Wenjing Yang[2], Weiqun Peng[2] and Robert G. Hawley[1]
[1]*Department of Anatomy and Regenerative Biology*
[2]*Department of Physics, The George Washington University, Washington, DC*
USA

1. Introduction

TP53 is a central hub integrating stress signals from oncogenic genetic lesions and cytotoxic anti-cancer agents. The function of p53 as a regulator of transcription is well documented. More recently it was shown to directly interact with BCL2 family members and induce mitochondrial cell death. Stress-induced activation of p53 leads to cell cycle arrest that allows metabolic adjustments and repair mechanisms to take place prior to the next cycle; p53 may also induce senescence or apoptosis depending on the strength and nature of stress stimuli and/or cell type.

In 50% of human cancers, the TP53 gene is deleted or mutated with a high proportion of gain of oncogenic function mutations. It is noteworthy therefore that TP53 is rarely mutated in T-ALL. However, its tumor suppressor activity is circumvented by genetic lesions. We will discuss here the most frequent T-ALL genetic abnormalities of INK4A/ARF, NOTCH1 and PTEN genes and how they affect TP53 expression and function. Current understanding of the signaling pathways governed by these oncogenes is advanced enough to find points of intersection with p53 downstream targets and attempt to translate the accumulated knowledge to the clinic.

In addition, we will discuss the results of our analysis of publicly available expression profiling data indicating the existence of a TP53-anchored transcriptional program targeted by T-ALL oncogenes such as NOTCH, MYC and TLX1 in primary leukemic cells and how it can be exploited for cancer intervention.

Overall, the goal of this chapter is to describe how T-ALL pathobiology affects the p53-interacting network, highlighting some new potential therapeutic targets as well as some still unresolved questions.

2. INK4A-ARF inactivation circumvents oncogene-induced p53

Inactivation of INK4A-ARF occurs in 70% of T-ALL cases by mutations, biallelic deletions or hypermethylation (Hebert et al., 1994; Gardie et al., 1998; Sulong et al., 2009; Van Vlierberghe et al., 2008; Ferrando et al., 2002; Omura-Minamisawa et al., 2000). The locus encodes two stress-induced proteins with distinct tumor suppressing functions (Quelle et al., 1995): one, INK4A, targets cell cycle entry and another, ARF, inhibits cell cycle progression and cell survival. The two completely unrelated protein sequences derive from the same locus via expression of two alterative reading frames. This unusual feature was

suggested to be important for coordinate regulation of these gene products in response to stress signals (Gil & Peters, 2006; Popov & Gil, 2010). The tumor suppressor functions of INK4A and ARF are not redundant since animals with individually inactivated products of the locus showed less spontaneous tumors than the double knockouts (Sharpless et al., 2004). It is well established that the function of INK4A is to inhibit cyclin D-dependent protein kinases and thus suppress proliferation, loss of function contributing to signal-independent cell cycle entry (Serrano et al., 1993). Recently, INK4A was also implicated in regulation of thymocyte apoptosis in response to oxidative stress or gamma irradiation (Bianchi et al., 2006). An excellent review summarizing the biological functions of the INK4 family of proteins has been published (Canepa et al., 2007). Our focus will be on the ARF protein since, as shown in Figure 1, the best characterized activity of ARF is activation of p53. The mechanisms include direct inhibition of the enzymatic activity of the MDM2 E3 ubiquitin ligase and sequestering of the protein in nucleoli (Llanos et al., 2001; Honda & Yasuda, 1999): MDM2 binding is one of the major mechanisms keeping the apoptotic and growth-arresting function of p53 in check. MDM2 blocks p53 transactivation function and enforces its nuclear export and proteasomal degradation (Honda et al., 1997; Zhang & Xiong, 2001; Weber et al., 1999) (See Figure 1 for more details). In addition ARF was suggested to have p53-independent functions; for example, modulation of activity of transcription factors such as MYC, E2F and NFκB family members leads to their enhanced apoptotic activity or stress-induced inhibition of protein synthesis (Sherr, 2006; Qi et al., 2004).

ARF is regulated at multiple levels. Its protein stability and subcellular localization is controlled by the nucleolar phosphoprotein NPM1. ARF-NPM1 complexes are predominantly localized in nucleoli where ARF is more stable (Bertwistle et al., 2004; Brady et al., 2004). Its half life significantly decreases in the nucleoplasm via ubiquitination and proteasome-mediated degradation (Rodway et al., 2004; Kuo et al., 2004). Perhaps the most important aspect of ARF regulation is at the level of transcription. ARF is not expressed in most normal tissues; however, it can be activated in response to stress or aberrant hyperproliferative signals (e.g. RAS mutations, MYC overexpression, BCR-ABL translocation).

In adult hematopoietic stem cells and in immature thymocytes, the INK4A-ARF locus is silenced by the Polycomb-group gene BMI1 (Jacobs et al., 1999; Bracken et al., 2007). This epigenetic regulation is required for survival of normal T cell precursors (Miyazaki et al., 2008). However, ARF expression can be induced at this stage and activates apoptosis in cells with aberrant T cell receptor gene rearrangements or other genetic lesions leading to ectopic activation of protooncogenes. The most frequent T-ALL-associated oncogenic events, involving NOTCH1 (50%) and TAL1 (60%), as well as other less frequent genetic abnormalities, such as activation of LMO2 (9%), were directly demonstrated to cooperate with the loss of INK4A-ARF function (Shank-Calvo et al., 2006; Treanor et al., 2011). The response of the locus may be developmentally specific. For example, the responsiveness of the INK4A-ARF locus to the constitutively-active truncated form of NOTCH1 depends on the stage of development, with the locus being silent in hematopoietic stem cells but inducible in thymocytes (Volanakis et al., 2009). From that perspective, it is noteworthy that in immature T-ALL cases, the INK4A-ARF locus is predominantly found intact but kept inactive by epigenetic mechanisms (Ferrando et al., 2002). Thus these silencing mechanisms may serve as potential therapeutic targets in immature T-ALLs.

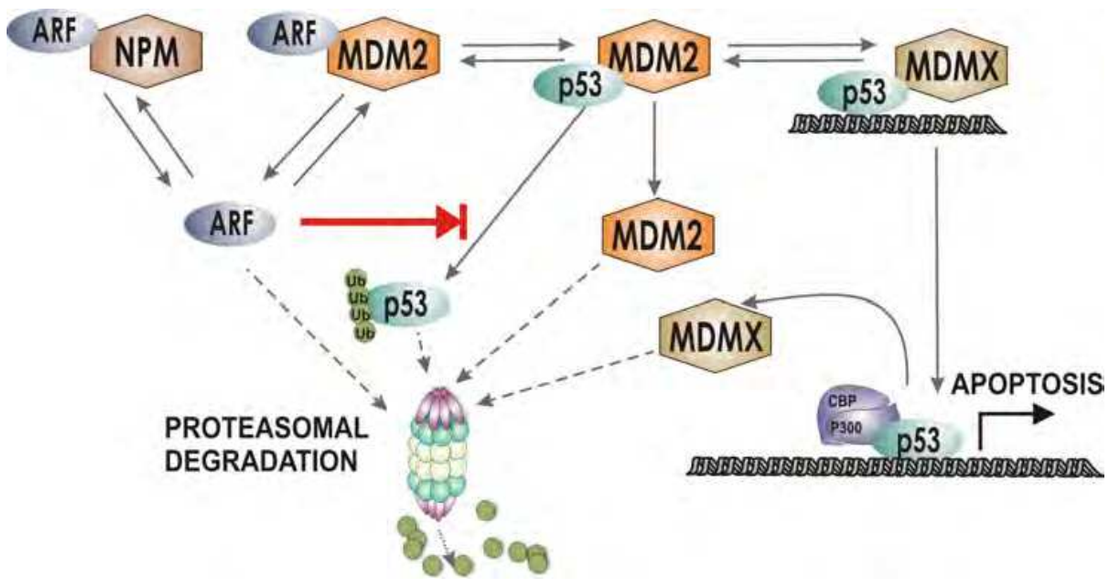

Fig. 1. Regulation of p53 protein stability via ARF and MDM2/MDMX. From left to right: nucleolar phosphoprotein NPM1 controls ARF protein stability and subcellular localization. ARF-NPM1 complexes are predominantly localized in nucleoli where ARF is more stable. Liberated ARF may be degraded by proteasomes or may associate with MDM2 and prevent degradation of p53 via direct binding to MDM2 and inhibition of its ubiquitin ligase activity. p53 is stabilized in MDMX complexes, but for full activation of p53-dependent transcription MDMX is replaced by transcriptional cofactors. MDM2 and MDMX are subjected to stress-induced proteasomal degradation.

Because the immature T-ALL subset represents the highest risk among T-ALL, we will describe in more detail BMI1 function and regulation to highlight potential therapeutic strategies aiming to reactivate the INK4A-ARF locus. In thymocytes, BMI1 binds directly to the locus and specifically maintains trimethylation of histone H3 at lysine 27 (3mH3K27 modification) (Miyazaki et al., 2008). For maintenance of the repressed state through multiple rounds of cell divisions, DNA methylation markers are necessary. Polycomb proteins interpret DNA methylation marks and translate them into histone modifications to initiate/maintain repression (Spivakov & Fisher, 2007). Thus it is not surprising, but may be very important for potential clinical translation, that inhibition of DNA methyltransferase (DNMT) was shown to derepress the INK4A-ARF locus by affecting this mechanism in human cord blood-derived multipotent stem cells. The authors used 5-azacytidine, an inhibitor of DNMT analogous to cytidine; they showed that loss of DNA methylation marks caused diminished recruitment of EZH2, a key histone methyltransferase, and decreased 3mH3K27 modification of the INK4A-ARF locus (So et al., 2011). Another attractive candidate for therapeutic intervention is Hedgehog signaling, required for survival and proliferation of early thymocyte precursors (El Andaloussi et al., 2006). Moreover, it was recently shown that Sonic hedgehog activates BMI1 expression during cerebellar development (Leung et al., 2004). Thus testing Hedgehog inhibitors such as cyclopamine or vismodegib on immature T-ALL samples might be a promising approach. The strategy of reactivating the INK4A-ARF locus is complicated, however, by the fact that the locus responds to the same oncogenic signals that support the survival and proliferation of

malignant cells. For example, a powerful pro-survival kinase AKT1 targets EZH2 and suppresses methylation of histone H3 at lysine 27 (Cha et al., 2005) while MAPKAP kinase 3, a convergence point downstream of activated ERK and p38, inhibits BMI1 association with chromatin (Voncken et al., 2005). For these reasons and because the INK4A-ARF locus is deleted in the majority of T-ALL cases, current therapeutic strategies are based on activation of p53 in an ARF-independent manner.

3. NOTCH-governed network affects ARF and p53

Mutations activating the developmental regulator NOTCH1 occur in more than 50% of T-ALL cases (Weng et al., 2004). NOTCH1 was initially implicated in T-cell leukemogenesis by the finding of rare chromosomal translocations that place a constitutively-active truncated form of NOTCH1 (NIC) under the T cell receptor (TCR) beta chain promoter (Ellisen et al., 1991). NOTCH1 is a transmembrane receptor (Kopan & Ilagan, 2009). The Delta-like and Jagged ligands activate proteolytic processing of NOTCH1 that releases its cytoplasmic portion allowing it to translocate to the nucleus. In the nucleus, NOTCH1 activates transcription via a DNA-bound protein CSL (Aster et al., 2008). Subsequently, a high frequency of NOTCH1-activating mutations were characterized that enhance its proteolytic processing and/or stabilize its intracellular portion (Weng et al., 2004). Thus in T-ALL, NOTCH signaling is represented by a broad spectrum of levels of activation that may still be ligand dependent and also inhibited by drugs targeting the NOTCH1 processing machinery (Lewis et al., 2007; Sulis et al., 2011).

NOTCH signaling is required for several consecutive stages of normal thymocyte development, from the earliest stage of T-cell fate commitment until the late cortical thymocyte stage with fully rearranged TCR genes (Tanigaki & Honjo, 2007). NOTCH1 provides survival and stimulates growth of normal thymocytes and leukemic T cells (Grabher et al., 2006; Ciofani & Zuniga-Pflucker, 2005). That said, the functional role of NOTCH1 in T-ALL cells undergoing chemotherapeutic treatment is less clear. As NOTCH1 promotes their survival, NOTCH1 mutations would be expected to confer enhanced drug resistance. Interestingly, however, mutations activating NOTCH1 were found to associate with good initial response to treatment (Kox et al., 2010; Asnafi et al., 2009). In this context, and consistent with these observations, it is worth mentioning that we and others observed that NOTCH1 inhibition decreases sensitivity of T-ALL cell lines to selected chemotherapeutic agents while NOTCH1 activation enhances the response (De Keersmaecker et al., 2008; Liu et al., 2009; Riz et al., 2011).

The function of NOTCH1 is mediated by several signaling hubs that in turn impact ARF and p53 function: among them, mTOR kinase, a key growth regulator constitutively activated in many cancers; eIF4E, a selective regulator of translation initiation; SKP2, an E3 ubiqutin ligase; and transcription factors such as MYC and NFκB (Chan et al., 2007; Mungamuri et al., 2006; Hsieh & Ruggero, 2010; Kao et al., 2009; Dohda et al., 2007; Murphy et al., 2008).

The accumulated evidence indicates that ectopic activation of NOTCH1 in premalignant thymocytes may lead to ARF induction. First, in T-ALL, NOTCH1 mutations frequently coincide with INK4A-ARF inactivation (Ferrando et al., 2002; Treanor et al., 2011). Second, in mice, progression to full malignancy in NIC-expressing thymocytes is associated with decreased ARF expression (Li et al., 2008). And finally, oncogenic cooperation of these

two genetic aberrations was directly demonstrated in a murine T-ALL model (Volanakis et al., 2009). Moreover, the authors showed indirect activation of the ARF promoter by expression of NIC. Thus these data demonstrated that NOTCH1 mutations may activate ectopic signaling that triggers the oncogene-induced stress response exemplified by ARF induction. However, there is also evidence suggesting that NOTCH1 may downregulate the tumor suppressor function of p53. In an elegant system allowing regulatable NIC expression, it was shown that downregulation of NIC levels in mouse lymphomas *in vivo* is associated with activation of p53 (Beverly et al., 2005). Other work also demonstrated that ectopic expression of NIC partially downregulates the p53-mediated apoptotic response to DNA-damaging drugs in human leukemic cell lines (Mungamuri et al., 2006). The effect was mediated by the mTOR kinase. The authors showed that mTOR inhibition by rapamycin prevented (and eIF4E overexpression restored) the NOTCH1 pro-survival effect. Subsequently, in experiments with loss or gain of NOTCH1 function, MYC was placed upstream of the mTOR-eIF4E pathway (Chan et al., 2007). In agreement with these findings, eIF4E-driven CAP-mediated translation was shown to be required for MYC transforming function (Ruggero et al., 2004; Lin et al., 2008; Barna et al., 2008). Other work indicated that the oncogenic function of the mTOR-eIF4E pathway is mediated at least in part by inhibition of p53 via enhanced translation of MDM2 (Kao et al., 2009). The authors reported that rapamycin increases the p53/MDM2 protein ratio by inhibition of MDM2 translation without affecting its mRNA expression or protein stability. Ectopic expression of eIF4E abrogated the effect. With some gaps yet to be filled, the accumulated data indicate the existence of a signaling axis in T-ALL cells connecting the following components NOTCH1-MYC-mTOR-eIF4E-MDM2-p53 (see Figure 2 for a complete representation of the pathway).

NOTCH1 was shown to positively regulate the ubiqutin ligase SKP2 and, as a result, downregulate the p27 Kip1 and p21 Cip1 cell cycle inhibitors in T-ALL cell lines (Dohda et al., 2007; Sarmento et al., 2005). Moreover, SKP2 was shown to inhibit p53 function by targeting the acetyltransferase p300 (Kitagawa et al., 2008). Notably, MYC protein is targeted for degradation by SKP2 (Kim et al., 2003; von der Lehr et al., 2003) and SKP2 is not required for the transforming function of MYC (Old et al., 2010). However, as mentioned earlier, MYC gene expression is directly activated by NOTCH1 (Weng et al., 2006; Sharma et al., 2007). It is possible therefore that NOTCH1-induced SKP2 counteracts the NOTCH1-mediated transcriptional activation of MYC to keep MYC protein levels within a pro-survival range. Recently published data suggest that this is indeed the case. It was reported (although not discussed by the authors) that downregulation of NIC in murine T-cell lymphomas expressing MYC under a NOTCH1-independent constitutive promoter showed very strong activation of MYC protein levels without affecting mRNA levels [see Figure 4A and C in (Demarest et al., 2011)]; of note, the process coincided with strong upregulation of p53 protein and tumor regression. Because overexpression of MYC was documented to activate oncogene-induced stress via p53 in ARF-dependent and -independent manners (Murphy et al., 2008), it is tempting to propose that another potential NOTCH1 survival function is mediated by SKP2 control of MYC protein levels. This mechanism may play a particularly prominent role in those cases when, as a result of chromosomal rearrangements, MYC transcription is constitutive and no longer dependent on NOTCH1.

Finally, it is important to note that NOTCH was shown to activate NFκB transcriptional function on multiple levels that includes upregulation of expression of NFκB subunits,

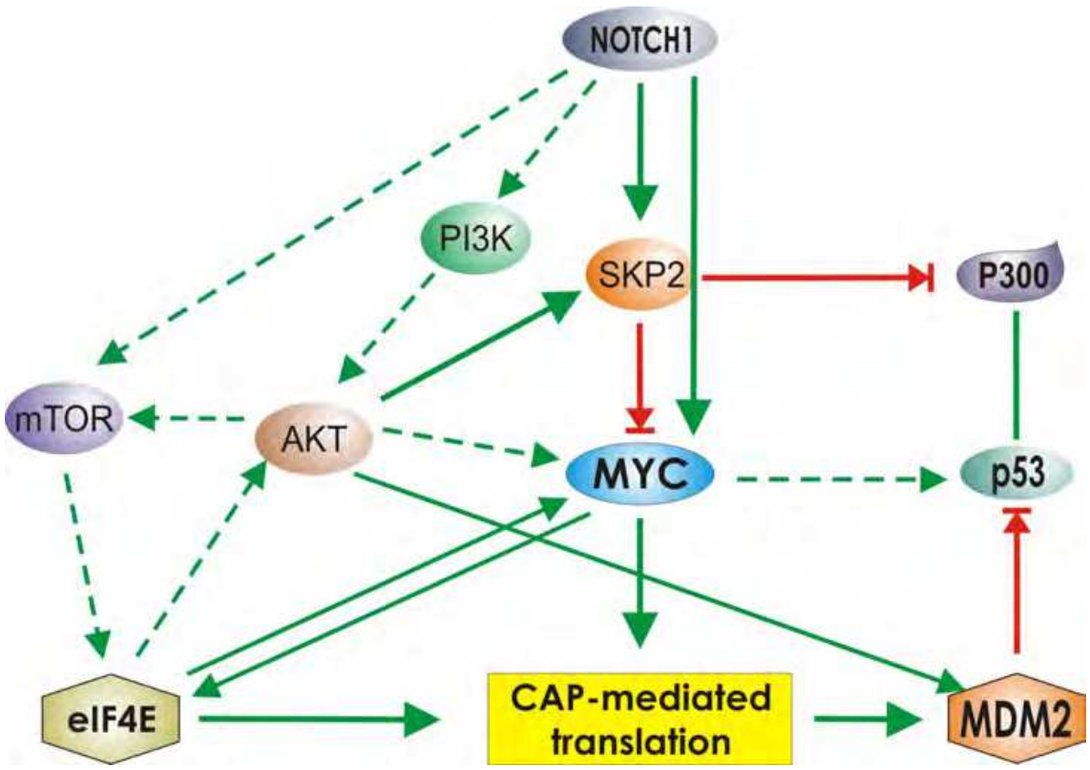

Fig. 2. NOTCH and p53 network. The function of NOTCH1 is mediated by several signaling hubs that in turn impact ARF and p53 function: NOTCH1 activates AKT, AKT directly activates MDM2. NOTCH activates SKP2 and Skp2 suppresses p300-mediated acetylation of p53 and the transactivation ability of p53. MYC gene expression is directly activated by NOTCH; MYC protein levels are controlled by SKP2 and AKT; ectopic MYC activation may cause activation of p53. NOTCH and/or MYC activate mTOR and eIF4E; eIF4E mediates protein synthesis of MYC and activators of AKT kinase; MYC and eIF4E promote CAP-mediated translation of MDM2. Solid arrows indicate direct interaction, dashed arrows indicate functional interaction via one or more intermediaries.

direct interaction with its upstream regulatory components such as IKK kinase, and inhibition of a negative loop of regulation (Osipo et al., 2008; Shin et al., 2006; Espinosa et al., 2010). NFκB and p53 exhibit a well documented history of cross-talk as well as synergistic interactions. For example, p53 and the p52 NFκB subunit coordinately regulate SKP2 gene expression (Barre & Perkins, 2010). NFκB is not only a pro-survival factor, it was shown to activate apoptosis in response to chemotherapeutic drug treatments (Radhakrishnan & Kamalakaran, 2006). Moreover, NFκB can induce p53 function, while p53 was shown to selectively inhibit the survival function of NFκB but to cooperate with the NFκB-mediated transcriptional activation of apoptotic genes (Meley et al., 2010; Ryan et al., 2000). Thus the functional outcome of NOTCH1-NFκB-p53 pathway interaction is not easy to predict; and, depending on the conditions (e.g., chemotherapy-induced stress levels), the NOTCH1-NFκB-p53 pathways may cooperate in promoting apoptosis. In addition, our data indicate that NOTCH1 may positively contribute to NFκB apoptotic function in a p53-independent manner.

We believe therefore that additional studies should be carried out to address the conflicting laboratory and clinical findings about the role of NOTCH1 activation in the regulation of T-

ALL cell survival in response to therapy. Briefly, as mentioned above, a number of preclinical studies have demonstrated a pro-survival role of NOTCH signaling in T-ALL; based on these studies, T-ALL clinical trials investigating the therapeutic potential of γ-secretase inhibitors have been initiated (ClinicalTrials.gov, NCT01088763; NCT00878189); so far, the drugs tested have demonstrated low anti-leukemic efficacy. A novel approach targeting NOTCH1 processing via inhibition of ADAM10 (a disintegrin and metalloprotease 10) was also suggested (Sulis et al., 2011). Moreover, on the basis of results obtained with T-ALL cell lines, in which inhibition of NOTCH signaling was reported to enhance glucocorticoid sensitivity, combination therapies of γ-secretase inhibitors and glucocorticoids were proposed (Real & Ferrando, 2009; Real et al., 2009). Clearly, the inclusion of γ-secretase inhibitors in T-ALL protocols needs to be reevaluated in light of the new clinical data showing that activated NOTCH1 is associated with a better initial response regardless of the type of treatment and particularly to prednisone (Kox et al., 2010). On the other hand, perhaps if it is not combined with conventional therapy, NOTCH1 inhibition may prove to be a successful approach; for example, in combination with Sonic hedgehog inhibition (Okuhashi et al., 2011) or mTOR and PTEN-PI3K/AKT modulation (see below).

4. PTEN: AKT-dependent and -independent activation of p53

Recurring oncogenic events in T-ALL involve inactivation of the PTEN tumor suppressor gene (Zhang et al., 2006; Palomero et al., 2008). The frequency of PTEN mutations was estimated to be about 20%; however, its functional downregulation is more common (Jotta et al., 2010; Silva et al., 2008). PTEN is a lipid phosphatase hydrolyzing phosphate in position 3 from phosphoinositides. In primary T-ALL, PTEN was suggested to be a major factor contributing to elevated levels of phosphoinositides and thus indirectly contributing to MYC protein stability (Silva et al., 2010; Bonnet et al., 2011).

Phosphoinositides, such as phosphatidylinositol-(3,4,5)-trisphosphate (PIP3), are membrane second messengers connecting cytokine and growth factor signaling with intracellular components such as the serine threonine protein kinase AKT (Carracedo & Pandolfi, 2008). PTEN dephosphorylates PIP3 while phosphoinositide-3 kinase (PI3K) reverses the reaction such that the levels of PIP3 are controlled by the balance of these two enzymes (Figure 3). PI3K is activated by various genetic lesions, the most common of which activate NOTCH1 (Sade et al., 2004). In addition, about 20% of mutations are in genes encoding upstream activators of the PI3K pathway; among them, IGF signaling components are the most prominent (Remke et al., 2009) while mutations directly affecting PI3K subunits are more rare (Gutierrez et al., 2009). Thus, as a result of PTEN inhibition and/or PI3K activation, close to 90% of T-ALL show elevated PIP3 levels (Silva et al., 2008). The signal from PIP3 is transmitted via membrane recruitment and activation of a member of the pleckstrin homology domain protein family, one of the best characterized being AKT kinase. Indeed in T-ALL, AKT levels were shown to be activated very frequently (close to 90%) (Silva et al., 2008). AKT phosphorylates about 100 different proteins and mainly promotes survival (by inactivating BAD, MDM2 and forkhead transcription factors) and growth (by inhibition of p27, GSK3 kinase), and regulates glucose homeostasis (by enhancing the glucose transporter GLUT4). Importantly, AKT regulates protein translation and ribosome biogenesis via activation of the mTOR pathway (Carracedo & Pandolfi, 2008). Therefore, the contribution of the PTEN/PI3K-AKT pathway is of central importance to the pathobiology of T-ALL, and especially with regard to p53 regulation.

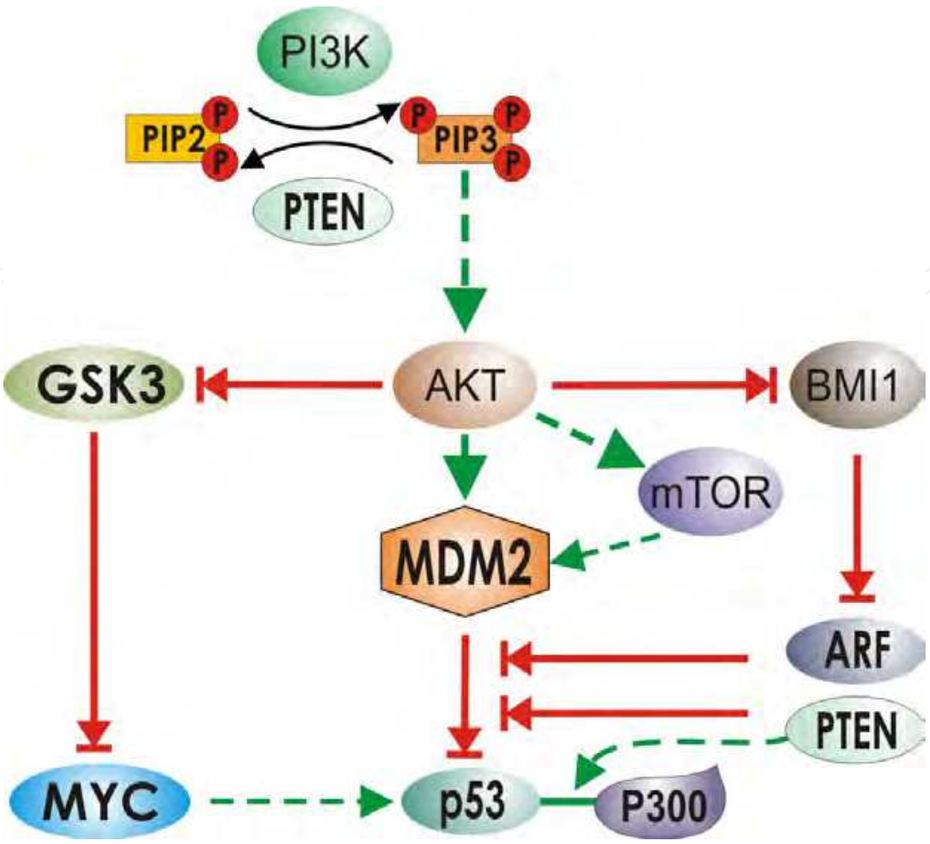

Fig. 3. Role of PTEN in p53 regulation. PTEN hydrolyses the phosphate group in the 3′ position from phosphatidylinositol 3,4,5-triphosphate (PIP3) to form phosphatidylinositol 4,5-biphosphate that counteracts PI3K function. PIP3 activates AKT. AKT phosphorylates and activates MDM2 directly and via mTOR pathways contributes to its protein synthesis. PTEN directly binds p53, enhancing its stability by antagonizing the p53-MDM2 interaction and promoting p300/CBP-mediated acetylation of p53. On the other hand, ectopic AKT activation may induce ARF function, and ectopic MYC activation may induce p53 in ARF -dependent and -independent ways. Solid arrows indicate direct interaction, dashed arrows indicate functional interaction via one or more intermediaries.

Most of the characterized downstream effectors of PTEN are AKT dependent; in T-ALL, they include p53, mTOR and MYC. p53 is regulated by AKT phosphorylation of MDM2 that leads to its nuclear translocation (Mayo & Donner, 2001). In addition, PTEN may directly bind p53 protein, enhance its stability by antagonizing p53-MDM2 interaction, and promote p300/CBP-mediated acetylation of p53 (Zhou et al., 2003; Freeman et al., 2003). Gain or loss of function experiments in T-ALL demonstrated that the PTEN-mTOR axis is important for the growth of the leukemogenic cells (Yilmaz et al., 2006). As previously mentioned, mTOR was also shown to enhance translation of MDM2. A recent publication addressing the frequency of MYC deregulation in T-ALL demonstrated that downregulation of PTEN function is one of the predominant features associated with enhanced MYC protein levels (Bonnet et al., 2011). MYC is regulated via AKT-dependent inhibition of GSK3 kinase. If it is not inhibited by AKT, this constitutively active kinase directly targets MYC protein for degradation (Gregory et al., 2003).

PTEN is a haploinsufficient tumor suppressor since the presence of a single copy does not prevent cancers (Salmena et al., 2008). On the other hand, biallelic loss of PTEN in primary thymocytes causes a cellular stress response resulting in the AKT-dependent induction of cell cycle arrest (Xue et al., 2008) via elevated expression of ARF and p53 proteins (Lee et al., 2010). The data are consistent with earlier work observing that loss of PTEN induces p53 function in other cell types (Chen et al., 2005b; Kim et al., 2007a). Together, the data strongly demonstrate that complete loss of PTEN may activate an oncogene-induced stress response and explains why it usually occurs in advanced cancers with inactivated p53 genes and poor prognosis (Jotta et al., 2010; Gutierrez et al., 2009).

Thus cancer intervention via modulation of PTEN function requires a precise knowledge of PTEN and p53 statuses. For p53 positive cases, PTEN inhibition was proposed as a therapeutic strategy (Mak et al., 2010). A more widely applicable approach is therapeutic restoration/activation of PTEN function. The activity of PTEN is directly inhibited by reactive oxygen species (ROS) oxidation of its catalytic center. Since leukemic cells frequently show increased levels of ROS, antioxidants may contribute to the restoration of PTEN function (Silva et al., 2008). For example, ascorbic acid or resveratrol treatment of T-ALL cell lines was associated with activation of p53; however, PTEN function was not addressed (Harakeh et al., 2007; Cecchinato et al., 2007). The levels of PTEN protein expression are tightly regulated. In T-ALL cells, CK2 was shown to control its protein levels and thus CK2 inhibition was suggested as a therapeutic strategy (Silva et al., 2010). Inhibition of PI3K, AKT and mTOR kinases was also suggested (Chiarini et al., 2010; Chiarini et al., 2009; Evangelisti et al., 2011a; Evangelisti et al., 2011b). However, despite a significant overlap in downstream targets, PTEN loss cannot compensate for NOTCH1 oncogenic function (Medyouf et al., 2010). Thus inhibition of both pathways was shown to cooperate in primary leukemic T cells and in mouse tumor models (Guo et al., 2011; Cullion et al., 2009). Finally, dual inhibition of PI3K and mTOR has been suggested as a therapeutic option for T-ALL (Chiarini et al., 2009).

5. TP53 coexpressed genes — potential chemotherapeutic targets

As discussed above, genetic aberrations may cause activation of a stress response. For example, deregulation of the NOTCH, PTEN, TAL1 or LYL1 loci causes activation of ARF in normal thymocytes. TP53 gene expression can also be induced in response to stress (Vilborg et al., 2010). Despite the secondary adaptive mutations preventing oncogene-induced apoptosis or senescence, cancer cells still frequently show elevated stress levels. The elevated stress together with enhanced growth is exploited in cancer therapies, which aim to selectively kill tumor cells while sparing normal cells. Knowing the transcription programs mediating the stress phenotype of cancer cells is important for the rational design of new "targeted" treatment strategies (Luo et al., 2009).

While analyzing publicly available expression profiles of primary T-ALL cells, we noticed that expression levels of TP53 varied greatly between patient samples. Moreover, in the majority of cases, TP53 was expressed at higher levels than in normal thymocytes, indicating that the complexity of aberrations in T-ALL manifests in various levels of oncogene-induced stress. We asked what transcripts are coregulated with TP53 with the expectation of identifying genes that functionally interact with it. We analyzed expression

profiles of primary T-ALL samples and normal thymocytes (Soulier et al., 2005). Genes were selected for analysis that were coexpressed with TP53 (Affymetrix probe set 211300_s_at U133A) based on similarity of their expression patterns (r>0.65) within about 100 T-ALL patient samples. As expected, the set of TP53-profile neighbors contained a number of genes encoding proteins that interact with TP53 at the mRNA or protein levels, regulating its stability and function (Figure 4). Interestingly, among them were genes that counteract p53 function, possibly reflecting neoplastic adaptation to high levels of TP53 gene expression. For example, inactivation of p53 at the level of protein stability is illustrated by PA2G4, PSME3 and HUWE1. Briefly, PA2G4 promotes p53 polyubiquitination and degradation; PSME3, encoding the 26S proteasome subunit, was shown to be required for p53 degradation (Zhang & Zhang, 2008); and HUWE1 (or ARF-BP1) E3 ubiqutin ligase directly binds to p53 and targets it for degradation in an MDM2-independent manner (Chen et al., 2005a). Other examples include G3BP1, which facilitates redistribution of p53 from the nucleus to the cytoplasm (Kim et al., 2007b); UBE2N (or UBC13), which inhibits formation of transcriptionally active p53 tetramers (Topisirovic et al., 2009); and CHD4, which deacetylates p53 and blocks p21 induction (Polo et al., 2010). Finally, inhibition of p53 transcriptional outcome is exemplified by YBX1, which is a component of the repressor complex blocking expression of p53 target genes (Shiota et al., 2008; Kim et al., 2008). Proteins cooperating with p53 function were also found among the set of p53-profile neighbors; for example, HNRNPF promotes p53 mRNA 3'-end formation (Decorsiere et al., 2011); DKC1 facilitates p53 translation; heat shock-induced stabilization of p53 occurs via direct binding to HSP90AA1; the purine biosynthesis enzyme GART is involved in p53- activating posttranslational modifications (Bronder & Moran, 2003); and SSRP1 is a component of the p53 transcriptional complex (Keller & Lu, 2002; Keller et al., 2001). There were also examples of genetic cooperation such as NOLC1 and SMARCC1. TP53 and NOLC1 cooperate in snoRNA-mediated ribosomal RNA editing, an important process for stress-induced stabilization of ribosomes (Krastev et al., 2011). Haploinsufficiency of both SMARCC1 and p53 cooperate to induce tumorigenesis in a mouse model (Ahn et al., 2011).

Because p53 is known to interact in some manner with a large portion of the genome, we asked if the enrichment of the p53-interacting genes in the set of TP53-profile neighbors is statistically significant. An empirical approach was used to determine the p-value. We generated 100 sets of 100 genes randomly selected from all annotated genes. For each set of 100 genes, TP53 was added to the set. The resulting simulated gene sets were subjected to Ingenuity Pathway Analysis and treated the same way as the list of T-ALL TP53-profile neighbors. The tabulated results of the number of p53 connections identified were used to estimate the p-value: this statistical approach indicated that the number of p53 connections within the set of T-ALL TP53-profile neighbors significantly exceeded the number of those within the simulated randomly-selected gene sets (p-value < 0.01). Importantly, our statistical analysis suggests that other less-studied genes among the T-ALL TP53-profile neighbors may also be important regulators of p53. This idea warrants further investigation because novel regulators of p53 might be found that may serve as potential therapeutic targets (Cheok et al., 2011). In support of this notion, certain of the known p53-interacting proteins, such as HUWE1, have already been suggested as possibilities for therapeutic intervention to restore p53 function in cancer cells (Chen et al., 2006).

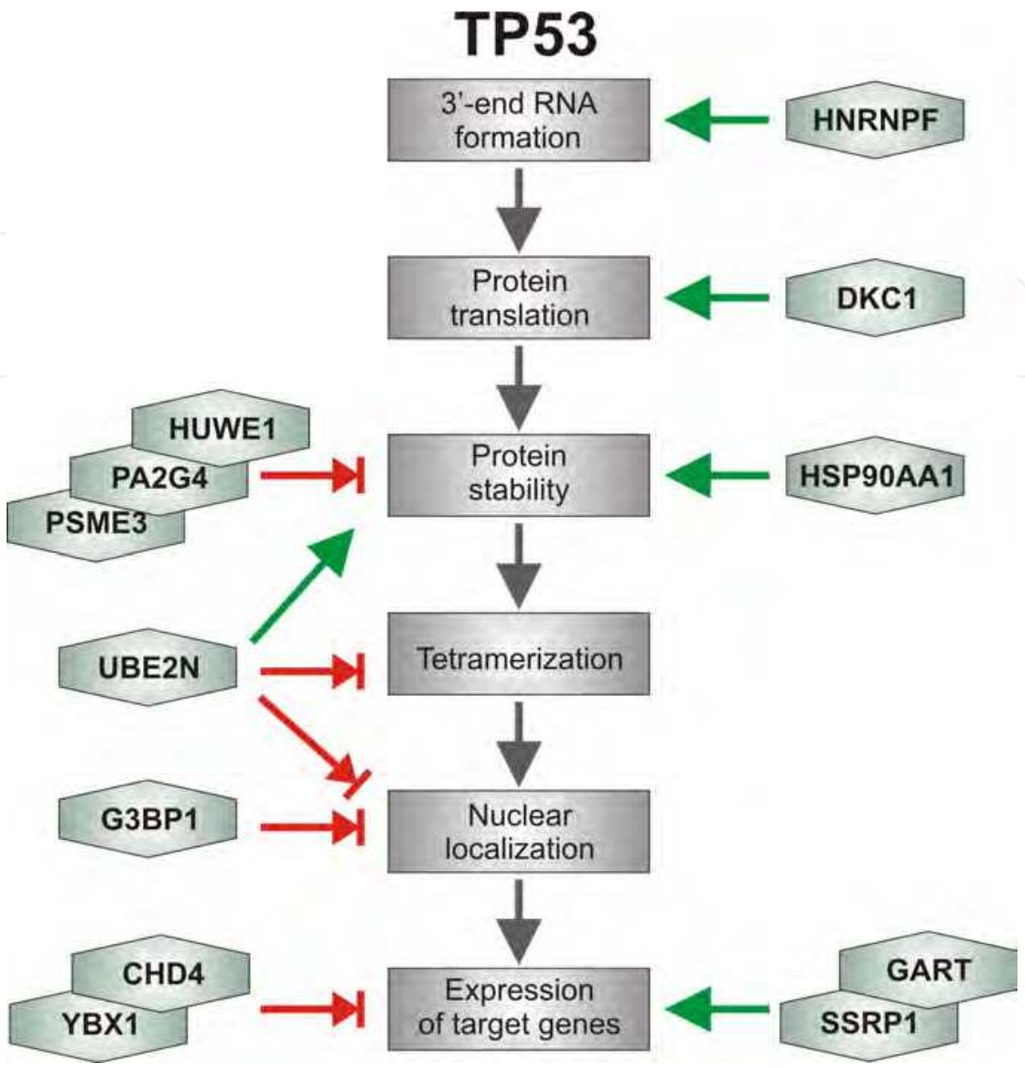

Fig. 4. TP53 profile neighbors in T-ALL regulate its function. Shown are examples of the TP53 profile neighbors known to target sequential steps of p53 activation.

The enrichment of p53-interacting genes and common expression signature also indicated that the set of TP53-profile neighbors is deregulated as a result of leukemogenesis and may be targeted by common T-ALL oncogenes. To ask which oncogenes may be involved in regulation of the set of TP53-coexpressed genes in T-ALL, we used genome-wide chromatin immunoprecipitation data previously published by others (Margolin et al., 2009; De Keersmaecker et al., 2010) to identify direct MYC or TLX1 targets. We found that the set of T-ALL TP53-coexpressed genes is significantly enriched for direct MYC and/or TLX1 targets, accounting for 70% of the set. Specifically, out of 16,697 genes represented on the array, 8,404 of them were bound by either MYC or TLX1. On the other hand, out of the 99 genes found to be coexpressed with TP53 in T-ALL, 69 of them were bound by either MYC or TLX1. Using the hypergeometric distribution, we determined that the p-value for the frequency of MYC or TLX1 target genes within the set of T-ALL p53-profile neighbors is 7×10^{-5}. Notably, NOTCH1 targets were within the subsets of MYC and/or

TLX1 targets. Moreover, the remaining 30% of the genes showed similar expression profiles and functional classification, arguing that they are regulated by one of NOTCH1, MYC or TLX1, but indirectly via downstream transcription factors. Promoter analysis revealed that the incidence of glucocorticoid receptor (GR) binding sites was 10 times more frequent in this set versus the genes directly targeted by MYC and TLX1, suggesting that these genes are potential targets of GR, and that GR may be the transcription factor contributing to the oncogene-induced stress response. A number of observations support this hypothesis. First, TLX1-positive T-ALL cases are characterized by high GR mRNA expression levels (Ferrando et al., 2002). In this regard, we found that shRNA-mediated knockdown of TLX1 in the T-ALL-derived ALL-SIL cell line was associated with increased resistance to glucocorticoid-induced cell death (manuscript in preparation) indicating that TLX1 may contribute positively to GR function. Moreover, recent clinical studies have demonstrated that activation of the NOTCH1 oncogene is associated with a superior initial therapeutic response to glucocorticoids (Kox et al., 2010) indicating that NOTCH1 may also cooperate with GR-induced killing. Finally, we and others observed that ectopic activation of MYC may cause transcriptional induction of pro-apoptotic BIM (Riz et al., 2011), which is a known mediator of GR induced apoptosis in T-ALL cells. Thus we hypothesize based on our analysis that an interacting network of transcription factors—NOTCH1-MYC-TLX1—may activate the TP53-anchored transcriptional program of an oncogene-induced stress response, predominantly via direct binding to promoters and in part via activation of GR function. We hope that our hypothesis will help to stimulate further studies seeking novel therapeutic targets to restore p53 function and to understand the intricate relationships between NOTCH1 and GR, two major targets of T-ALL therapeutic intervention.

6. Interaction of T-ALL mutations and p53 downstream targets

It is important to appreciate that not only p53 function but also execution of p53-governed transcriptional programs is often compromised by T-ALL mutations. For example, NOTCH1 via activation of SKP2 decreases the levels of p21 and thus counteracts one of the best characterized activities of p53 (Sarmento et al., 2005). As discussed above, the pathways downstream of NOTCH and PTEN intersect at the level of PI3K-mTOR. A set of p53 target genes controls this pathway as well (Feng et al., 2005). PTEN itself was shown to be a p53 target gene about 10 years ago (Stambolic et al., 2001). Since then, it has become appreciated that PTEN is activated by p53 in response to high-dose chemotherapy as part of a p53-governed transcriptional program committing cells to apoptosis. NOTCH1 was shown to inhibit PTEN via upregulation of the transcription factor HES1, which directly represses the PTEN promoter (Palomero et al., 2007). Among upstream modulators of PI3K, p53 induces IGF-BP3 (Buckbinder et al., 1995). IGF-BP3 binds to IGF1 or IGF2 and prevents their interaction with the receptor. Mutations involving components of IGF signaling are frequent contributors to PI3K activation in T-ALL (Remke et al., 2009). Other p53 targets affecting the mTOR pathway include TSC2, AMPK beta1, sestrins 1 and 2 and REDD1, all of which contribute to negative regulation of mTOR by targeting the TORC1 complex (which counteracts AKT function) (Feng et al., 2007) (Figure 5).

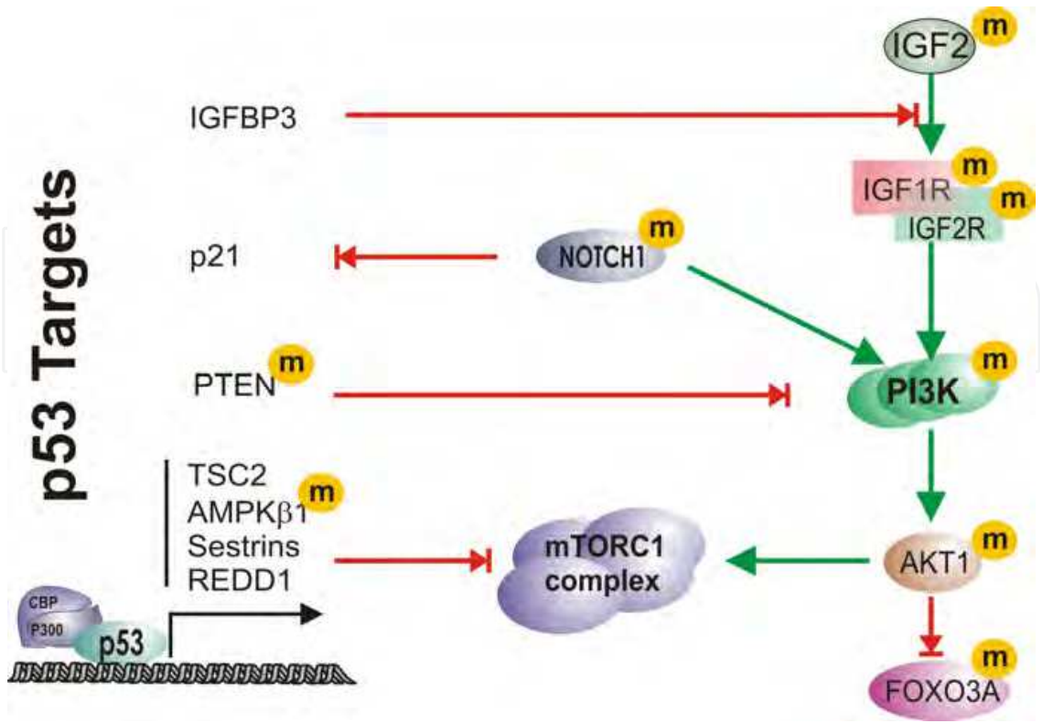

Fig. 5. T-ALL-associated genetic lesions compromise the function of p53 downstream targets. Alterations of NOTCH1 and PTEN loci are complemented by less frequent mutations in the growth-promoting IGF-PI3K/AKT/mTOR network; mutant proteins are indicated by 'm'. By inhibiting this network, the p53 target genes shown adjust metabolic rates in response to stress conditions and stall cell cycle progression.

7. Conclusion

A plethora of inactivating mutations notwithstanding there is still a possibility for therapeutic restoration of p53 apoptotic function because of two major features typical to this cellular regulator: multiplicity of activating stimuli and redundancy of the activating modifications. p53 is activated in response to a variety of stresses such as lack of nutrients, energy deprivation, DNA damage, heat shock, hypoxia or enhanced oxidation, and ER protein overload. Importantly, the apoptotic function of p53 may be activated only in the presence of persistent irreparable stress. For example, while reparable DNA damage activates p53 only partially via Ser-15/20 phosphorylation (which is sufficient for cell cycle arrest), PTEN induction by p53 is triggered by persistent DNA damage and has an additional checkpoint that requires phosphorylation of Ser46 in p53 (Mayo et al., 2005; Zhang et al., 2011). Thus chemotherapeutic agents activating p53 beyond its growth-arresting function should be considered as an aid to p53 protein stabilizers such as blockers of MDM2 function (Hasegawa et al., 2009). Among these regulators, WIP1 phosphatase (PPM1D), a p53 target and negative loop of autoregulation of p53 was suggested as a possibility, however, not tested in T-ALL (Lu et al., 2008; Yoda et al., 2008). Even though the Ser46 phosphorylated form of p53 was shown to associate with apoptotic activity, point mutation substituting this amino acid to alanine did not prevent activation of p53 apoptotic function (Kurihara et al., 2007). This illustration, together with studies showing that the p53-

MDM2 interaction is not affected by single point mutations, supports the idea of p53 regulatory redundancy (Kruse & Gu, 2009).

At the onset of neoplastic development, p53 is often activated as part of an oncogene-induced stress response. It is noteworthy that TP53 is rarely mutated in T-ALL (De Keersmaecker et al., 2005). Despite adaptive genetic and epigenetic mechanisms disrupting its functional outcome [discussed herein and (Vilas-Zornoza et al., 2011)], the p53 pathway still stays partially activated in fully developed T-ALL. Thus selective reactivation of p53 tumor suppressor function in the malignant cells is possible in principle by overcoming the disrupted links of the pathway. The development of personalized medicine providing knowledge of the patient's cancer genome should facilitate efforts to devise the appropriate strategy to activate wild-type p53 function in T-ALL. We believe that combining conventional cytotoxic therapy with molecular targeted approaches restoring p53 activity to its full potential will improve current protocols and prevent relapse. In this regard, there are several small molecule inhibitors of the p53-MDM2 interaction that are currently being investigated (Cheok et al., 2011), at least one of which (RG7112) is undergoing clinical trials in T-ALL patients (ClinicalTrials.gov, NCT00623870).

In spite of over 30 years of p53 research and investigation into the molecular basis of T-ALL, surprisingly little is known about the role and function of p53 in T-ALL. At time of writing, 43,847 PubMed articles were found by searching for "p53 and cancer" whereas only 146 articles could be retrieved for "p53 and T-ALL". T-ALL represents 15% of pediatric hematological malignancies which are the most common cancers in children. So, we believe that the subject is significantly underrepresented. We hope that by summarizing the current state of the art, this chapter will bring more attention to this issue and pave the way for new therapeutic strategies for patients with this disease.

8. Acknowledgments

We thank Sana Ahmad for assistance determining the statistical significance of p53 connections within the set of TP53-profile neighbors and Ian Toma for help preparing the figures. This work was supported in part by an American Cancer Society Pilot Grant for Junior Faculty from The George Washington University Cancer Institute (IRG-08-091-01) and a Pilot Project Award from the Clinical and Translational Science Institute at Children's National Medical Center (NIH UL1RR031988) (I.R.); and by NIH Grants R01HL65519 and R01HL66305, an Elaine H. Snyder Cancer Research Award and a King Fahd Endowment from The George Washington University School of Medicine (R.G.H.). Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Center for Research Resources or the National Institutes of Health. Correspondence: I.R. (anaixr@gwumc.edu) or R.G.H. (rghawley@gwu.edu)

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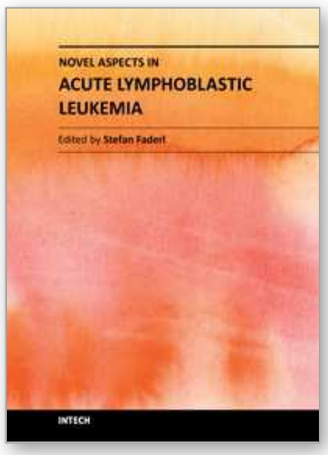

Novel Aspects in Acute Lymphoblastic Leukemia

Edited by Dr. Stefan Faderl

ISBN 978-953-307-753-6
Hard cover, 258 pages
Publisher InTech
Published online 16, November, 2011
Published in print edition November, 2011

Acute lymphoblastic leukemia (ALL) has turned from a universally fatal to a highly curable disease in little more than four decades. Even though differences in outcome continue to exist between children and adults, intense efforts are under way to overcome this discrepancy and improve the prognosis of adult patients as well. This exemplary progress in ALL therapy has been possible by the combination of an increasingly better understanding of the biology of the disease, availability of a range of effective drugs, and astute designs and relentless executions of many clinical trials. ALL is a complex disease requiring complex therapy. Whereas this book cannot provide a comprehensive review of every one of its many facets, the chapters from many investigators from around the world nevertheless cover a number of relevant topics: aspects of the epidemiology of ALL in Hispanics, ophthalmologic manifestations of ALL, overviews of current therapy and drug-resistance mechanisms, novel biological pathways and targets, new drugs in development, and long-term consequences of CNS prophylaxis and therapy. The publishers and editor therefore hope that the prospective readers will find enough insight and information for their own endeavors.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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