The emerging role of CD30 and p53 as novel targets for therapy in anaplastic large cell lymphoma

George Z. Rassidakis¹,²,³, Elias Drakos⁴

¹Department of Pathology and Cytology, Karolinska University Hospital and Karolinska Institute, Radiumhemmet, Stockholm, Sweden SE-17176, ²Department of Hematopathology, The University of Texas MD Anderson Cancer Center, Houston, Texas, ³European Research Initiative on ALK-related malignancies (ERIA), ⁴Department of Pathology, University of Crete Medical School, Heraklion, Crete, Greece

TABLE OF CONTENTS

1. Abstract
2. Introduction
3. The CD30 receptor and its ligand
   3.1. CD30 is linked to AP-1 transcription factors in lymphomas
   3.2. The JunB/CD30 axis in ALK+ ALCL
   3.3. CD30 contributes to cell cycle deregulation in ALK+ ALCL
   3.4. The CD30 receptor as a therapeutic target
4. The p53 tumor suppressor pathway
   4.1. Regulation of p53
   4.2. Targeted activation of p53: the development of nutlins
   4.3. The p53 pathway in ALK+ anaplastic large cell lymphoma
5. Acknowledgements
6. References

1. ABSTRACT

ALK+ anaplastic large cell lymphoma (ALCL), frequently carries the t(2;5).p(23;q35), resulting in expression of NPM-ALK oncogenic kinase, which is capable of activating multiple oncogenic pathways. ALK+ ALCL is also characterized by overexpression of CD30 receptor, a member of the tumor necrosis factor (TNF). receptor superfamily, which has been targeted for therapy using conjugated anti-CD30 antibodies with clinical success. Also, the tumor suppressor p53 is frequently non-mutated in ALK+ ALCL allowing for therapeutic modulation of p53 reactivation in this lymphoma type. Therefore, this review is focused on the role of CD30 receptor and p53 as novel targets for therapy in ALK+ ALCL, and also provides an update on their potential involvement in ALK+ ALCL pathogenesis.

2. INTRODUCTION

Anaplastic lymphoma kinase (ALK) + anaplastic large cell lymphoma (ALCL), is a distinct type of CD30+ T-cell non-Hodgkin lymphoma (1), which frequently carries the t(2;5).p(23;q35), resulting in aberrant expression and activation of NPM-ALK chimeric oncprotein (1). The latter directly activates multiple oncogenic pathways including Ras, PLC-gamma, Jak/STAT, PI3K/AKT/mTOR, JNK/Jun and others (2). ALCL is also characterized by overexpression of CD30 receptor, a member of the tumor necrosis factor (TNF). receptor superfamily. Recent evidence has uncovered the mechanisms underlying CD30 overexpression in ALCL and other CD30+ lymphomas suggesting that CD30 may have a role ALCL oncogenesis.

3. THE CD30 RECEPTOR AND ITS LIGAND

CD30 is a member of the nerve growth factor (NGF) /tumor necrosis factor (TNF). receptor superfamily (4,5). The extracellular domain of CD30 has 6 of the characteristic for the TNFR superfamily cysteine repeats, which mediate the formation of disulfide bonds and are probably important for the ligand (CD30L). binding. There appear to be two separate extracellular areas of the receptor, which are closely related: the distal to membrane CD30a and the proximal CD30b. As a type I glycoprotein, CD30 has also a transmembrane and an intracellular domain. The intracellular domain does not have any enzymatic activity nor does contain a death domain (DD). like the TNFR-I and the Fas, so by itself is unable to transmit a signal or to bind to death domain adaptor proteins such as TRADD and FADD. In order to mediate the signal, the CD30 has to associate with members of the TNFR Associated Factors (TRAfS), which bind to specific areas of the cytoplasmic domain of CD30 (6). CD30 molecules can also form heteromultimers with other TNFR members, which have been proposed to play a role in apoptosis through the death domains of these TNFR members. The CD30 ligand (CD30L or CD153) is a membrane protein with
an extracellular C-terminal domain and a cytoplasmic domain (7). In human lymphomas, CD30L is expressed by the Hodgkin and Reed Sternberg cells (HRS), of classical Hodgkin lymphoma (HL) which co-expresses CD30 as well as by inflammatory cells of the tumor cell microenvironment. CD30 is a lymphocyte activation marker and it is normally expressed in the parafollicular areas of the lymph nodes as well in the spleen and in areas of thymus surrounding the Hassal’s corpuscles. Peripheral activated lymphocytes also express CD30 and Th2 lymphocytes constitutively express CD30 (8).

3.1. CD30 is linked to AP-1 transcription factors in lymphomas

CD30 seems to be involved in the pathogenesis of ALK- ALCL (8). However, the underlined mechanisms are still under investigation. Earlier studies have demonstrated that increased activator protein-1 (AP-1), activity and overexpression of two of the members of AP-1 family, namely c-Jun and JunB, are found in CD30+ but not in CD30- lymphoma and leukemia cell lines and tumors including ALCL and classical HL (9-11). The mechanism underlying this strong association has been investigated in several studies. JunB, one of the AP-1 transcription factors, interacts with the CD30 gene promoter leading to increased transcription of CD30 gene. More specifically, Watanabe et al. in his first study on HRS cells of classical HL, showed, that JunB protein binds to the AP-1 binding sites of the microsatellite sequences (MS) of the CD30 gene promoter, thus releasing the inhibitory effect of the MS on the core CD30 promoter. As a result, CD30 transcription is induced leading to overexpression of the CD30 protein (12,13). Furthermore, CpG islands of the CD30 promoter are frequently unmethylated in ALCL and classical HL allowing for CD30 expression (14). Previous studies have shown that JunB, along with another member of the AP-1 family of transcription factors, c-Jun, are overexpressed in ALCL and classical HL, and more importantly, their expression is restricted only to CD30+ lymphomas (10,11).

The AP-1 transcription factors are involved in cell proliferation, growth control, oncocgenic transformation and apoptosis (15). Data from knock-out mouse models have shown that certain AP-1 genes (c-Fos, FosB, and JunD), are dispensable to embryogenesis while others including c-Jun and JunB are essential (15). JunB, a member of the Jun family, which also includes c-Jun and JunD, is mapped at 19p13 and encodes a 39kDa protein. Earlier studies have shown that JunB represses the transactivation and transformation capacity of c-Jun by forming inactive heterodimers with c-Jun (16). Thus, JunB initially was considered to function as a tumor suppressor (17,18). However, accumulating evidence suggests differential functions of JunB protein. For instance, JunB can substitute for c-Jun loss in mouse development and cell proliferation (19). Also, JunB transcriptionally regulates cyclin A, suggesting a cell cycle promoting function (20). Although transgenic expression of JunB inhibited proliferation and transformation in B (but not in T) lymphocytes, transformed B-cells eventually escaped from these inhibitory effects (21). As mentioned above, a casual association between AP-1 transcription factors and CD30 expression has been established, and therefore, the biologic activities of AP-1 transcription factors may be mediated, in part, through CD30 signaling in ALCL as described below. However, CD30-independent activities of AP-1 transcription factors do exist and seem to significantly contribute to uncontrolled cell cycle progression and tumor cell proliferation in ALK+ ALCL. For instance, cJun has been shown to be highly phosphorylated/activated in NPM-ALK+ ALCL because NPM-ALK physically binds to and phosphorylates/activates JNK kinase that, in turn, phosphorylates c-Jun (22). Phosphorylated (activated). cJun protein further increases its own gene transcription through increased DNA binding affinity to AP-1 sites of the c-Jun gene promoter, thus establishing a positive feedback loop. As a result, highly activated c-Jun leads to uncontrolled cell cycle progression mainly through repression of its transcriptional target, the cyclin-dependent kinase (CDK), inhibitor p21, but also through regulation of other cell cycle –associated proteins (22).

3.2. The JunB/CD30 axis in ALK+ ALCL

A line of evidence suggests that an active JunB/ CD30 axis, partly controlled by the NPM-ALK oncogenic kinase, operates in ALK+ ALCL. Staber et al (23), has shown that JunB expression is regulated via ERK1/2 at the transcriptional level and this is thought to be NPM-ALK dependent in ALCL. Furthermore, in a recent study, Watanabe and colleagues identified Ets1 as the transcriptional factor that mediates ERK1/2-dependent regulation of JunB in ALK+ ALCL (24). In addition, NPM-(,)-ALK upregulates JunB at the translational level through the mTOR pathway (23), which is highly activated in ALK+ ALCL (25). Of note, JunB gene amplification or gains of its chromosomal locus have been also reported in a subset of CD30+ cutaneous lymphomas (26) and classical Hodgkin lymphoma using comparative genomic hybridization methods (27). Therefore, it seems that multiple mechanisms at the genetic, transcriptional and translational level orchestrate JunB overexpression in ALK+ ALCL. The function of these multiple mechanisms resulting in JunB overexpression explains why JunB protein is constitutively expressed in all ALK+ ALCL tumors (10).

The biologic effects of JunB have been investigated in NPM-ALK+ ALCL. Based on JunB gene silencing experiments, our recently published data show that JunB contributed to uncontrolled cell cycle progression at G1-S and G2 through upregulation of cyclins A, D2 and D3 and downregulation of cyclin-dependent kinase (CDK), inhibitors p14 and p21 but not p27 (Figure 1). Interestingly, knocking down both JunB
CD30 and p53 in ALCL

Figure 1. Based on several studies (see text), JunB seems to operate as an oncogene in the context of ALK+ ALCL and possibly other CD30+ lymphomas. JunB overexpression in ALK+ ALCL may be the result of gene amplification and NPM-ALK associated mechanisms such as regulation of its transcription via ERK1-2/Ets1 or translation through PI3K/AKT/mTOR. JunB, in turn, interacts with the CD30 gene promoter leading to CD30 receptor upregulation. Activation of CD30 signaling may contribute to cell proliferation through cell cycle deregulation (not shown). In addition, JunB, as an AP-1 transcription factor might directly regulate cyclins, and CDK inhibitors also resulting in uncontrolled cell cycle progression. Therefore, an active JunB/CD30 axis seems to exist in ALK+ ALCL that may contribute to tumor cell proliferation and oncogenesis. Brentuximab vedotin (SGN-35) that targets the CD30 receptor is an cAC10 monoclonal antibody, which is conjugated with MMAE via a specific linker. Following binding of SGN-35 with the CD30 receptor, is internalization into the cytoplasm is mediated with clathrin-coated cytoplasmic vesicles. The lysosomal proteolytic enzymes release the active agent MMAE. As a result, MMAE is free to act by binding to microtubules during mitosis, thus preventing duplication of the neoplastic cell. In addition, free MMAE is released to the tumor cell microenvironment thus expanding the cytotoxicity to inflammatory cells such as reactive B and T lymphocytes, antigen presenting cells (APC) and macrophages.

and c-Jun simultaneously resulted in significantly lower colony formation than that observed after silencing of either JunB, or c-Jun gene alone suggesting that both AP-1 family members contribute to cell growth and proliferation of ALK+ ALCL cells. Therefore, it seems that JunB plays an oncogenic role, parallel of c-Jun in NPM-ALK+ ALCL. Furthermore, JunB overexpression seems to confer resistance to chemotherapy in NPM-ALK+ ALCL cells (28).

3.3. CD30 contributes to cell cycle deregulation in ALK+ ALCL

Although the transcriptional control of JunB on CD30 gene expression has been well established,(12,13), the potential role of CD30 protein in mediating oncogenic functions in NPM-ALK+ ALCL has been studied only recently (28). Knocking down CD30 gene resulted in a substantial decrease in cell growth associated with G1-S and, at a lesser degree, with G2-M cell cycle arrest. As for JunB, the effects on cell cycle were associated with upregulation of the same CDK inhibitors, p14 and p21, but not p27. Notably, AP-1 activity also was impaired following CD30 gene silencing (28). Interestingly, treatment with a neutralizing, non-conjugated anti-CD30 antibody (SGN-30), resulted in a concentration-dependent upregulation of CDK inhibitors p14 and p21 but not p27 associated with a significant decrease in S-phase of cell cycle. In addition to cell cycle changes, treatment of ALK+ ALCL cells with anti-CD30 antibodies resulted in apoptosis, as shown by several studies (28,29).

Based on its transcriptional activities, the oncogenic functions of JunB can be either CD30-dependent, as supported by the recently published data study showing common mediators of cell cycle regulation (p14, p21) (28), or CD30-independent (i.e. cyclins). Either way, the JunB/CD30 axis substantially contributes to cell cycle deregulation in ALK+ ALCL.

3.4. The CD30 receptor as a therapeutic target

As CD30 expression is restricted to distinct types of lymphomas, such as ALCL and classical HL, CD30 receptor has been a very attractive target for new therapeutic approaches in these neoplasms through
CD30 and p53 in ALCL

development of anti-CD30 antibodies during the last decade. The rationale behind the use of anti-CD30 antibodies initially was that specific binding of an anti-CD30 antibody to CD30 receptor would lead to TRAF2 degradation, thus avoiding activation of NFKB. However, it is now evident that the therapeutic results of the CD30-targeted approaches largely depend on the specific regimens tested. For instance, targeting CD30 receptor with the naked anti-CD30 antibody SGN-30 (Seattle Genetics, Bothell, WA) did not result in good clinical responses in relapsing ALCL and classical HL or other CD30+ lymphomas, besides the promising results in preclinical studies (29-33). By contrast, the development of the ADC (Antibody-Drug Conjugate), brentuximab vedotin (SGN-35), which also targets the CD30 receptor but it’s conjugated with a therapeutic agent showed significant tumor regression in up to 86% of patients with relapsed or refractory classical HL and ALCL lymphomas in the initial phase 1 trial (34). The mechanism of action of the clinically successful brentuximab vedotin is rather simple (35). (Figure 1). The SGN-35 is an cAC10 monoclonal antibody (IgG1), which is chemically conjugated through the sulfhydryl groups in cysteine residues with the therapeutic agent monomethylauristatin E (MMAE; 2-8 molecules of the drug) via a specific linker. Following specific binding of SGN-35 to the CD30 receptor, the antibody/receptor complex is internalized by clathrin-mediated endocytosis. Following clathrin release that is recirculated to the cell surface, the uncoated pits containing the internalized ADC are joined to the lysosomes where cathepsin cleaves the citroulin-valine dipeptides of the specific linker, thus releasing the active agent MMAE. As a result, MMAE is free to act by binding to tubulin during mitosis, thus preventing its polymerization and ultimately blocking duplication of the neoplastic cell. In addition, free MMAE is released to the tumor cell microenvironment thus expanding the cytotoxicity to inflammatory cells such as reactive B and T lymphocytes, antigen presenting cells (APC) and macrophages (Figure 1) (35).

A number of previous clinical trials have shown good response rates for brentuximab vedotin in classical HL, either as a single agent or in combination with standard chemotherapeutic agents, such as ABVD. In addition, brentuximab vedotin is safe and effective, not only after failure of an autologous stem cell transplantation, but, more importantly, after allogeneic stem cell transplantation, or as a bridge to an allogeneic stem cell transplantation (34,36-39). Several clinical trials of brentuximab vedotin included a sizable subset of patients with ALCL (34,40-43). In one of the largest studies of 58 patients with relapsed, or refractory ALCL treated with brentuximab vedotin, 50 patients (86%) achieved an objective response and 33 patients (57%) achieved a complete remission (CR). The median durations of overall response and CR were 12.6. and 13.2. months, respectively (41). Similar or even better responses were observed in the group of elderly ALCL patients (>60 years), treated with brentuximab vedotin in another study (42). Brentuximab vedotin, either as a single agent, or in combination with standard chemotherapy has been recently tested in CD30+ peripheral T-cell lymphomas (PTCL),(44,45), other than ALCL. Moreover, ongoing clinical trials are currently investigating the efficacy of CD30-targeted therapy in other CD30+ hematologic malignancies, such as CD30+ diffuse large B-cell lymphomas (DLBCL), and the results are expected to be published soon.

4. THE P53 TUMOR SUPPRESSOR PATHWAY

The central role of p53 in cancer development reflects the importance of cellular functions regulated by p53 (46). p53 is a transcription factor. Upon stimulation by a variety of cellular stress conditions including DNA damage, inappropriate growth promoting signals regulated by oncogenes, hypoxia and various metabolic alterations, p53 is tetramerized, and, mainly through its transcriptional activities, orchestrates a wide spectrum of cellular responses including activation of DNA repairing mechanisms, modifications of cellular metabolism, cell cycle arrest, autophagy and cellular senescence, or apoptosis induction (46).

An especially important transcriptional target of p53 is for influencing the cell cycle is p21 (46). Also, p21 upregulation is usually, but not always, observed during cellular senescence. However, the executive components of cellular senescence pathways are not fully understood (47). p53-induced apoptosis can be mediated by transcriptional mechanisms involving upregulation of the pro-apoptotic mitochondrial protein Bax, members of the pro-apoptotic BH3-only protein family, including Puma and Noxa, or upregulation of death receptors of the extrinsic apoptotic pathway including FAS (CD95). and Death receptor 5 (DR5, known also as TRAIL-R2 or KILLER), as well as by mechanisms independent of transcription involving translocation of p53 protein to the mitochondria (48).

p53 can also affect the metabolism (49). The Warburg phenomenon, the preferential extraction of energy by cancer cells through glycolysis, was recently partially attributed to the inactivation of p53 and downregulation of its downstream transcriptional target SCO2 (synthesis of cytochrome c oxidase 2) (50). Also, non-cell autonomous functions of p53 involving angiogenesis through transcriptional regulation of hypoxia-inducible factor (HIF), seem to be important for cancer biology (51).

4.1. Regulation of p53

The half life of p53 protein is less than half an hour and its stability is determined mainly by the
CD30 and p53 in ALCL

The degradation of p53 is mainly regulated by the murine double minute 2 (MDM2) that acts as an E3 ubiquitin ligase targeting p53 protein for proteosome-mediated degradation (46,52). MDM2, in addition of its ubiquitin ligase activity, blocks the transactivation activity of p53 by binding the p53 transactivation domain and facilitates, through its nuclear export signal, the export of p53 to the cytoplasm towards proteosome degradation (46,52). MDM2 is, also, a transcriptional target of p53, establishing in this way an autoregulatory loop (46,52). Also, MDMX (or MDM4), is a potent inhibitor of p53 transactivation activity by blocking the p53 transactivation domain, without affecting p53 protein levels (46,52). In addition to ubiquitylation, a number of protein modifications including acetylation, sumoylation, neddylation, and phosphorylation are involved in p53 regulation (53). These phosphorylations were shown *in vitro* to stabilize and increase the activity of p53 protein inhibiting its interaction with MDM2 (53).

4.2. Targeted activation of p53: the development of nutlins

In accordance with the importance of p53 inactivation in human cancer, intensive efforts and a multitude of strategies have been employed for restoring p53 function in cancer cells (54). Downregulation of MDM2 by MDM2-specific antisense oligonucleotides, or rescuing the function of mutated p53 proteins through small molecules including PRIMA-1 or ellipticine represent alternative strategies (54).

Another strategy focuses on disrupting the MDM2-p53 protein interaction for restoring the function of wt p53 (55). Biochemical and genetic studies enabled the identification and construction of small molecules for specifically disrupting MDM2-p53 protein interaction (56). Among the more promising of these agents are the imidazoline derivatives called nutlins discovered by Vassilev and colleagues in a Roche research facility located at the Nutley town (56).

In contrast, normal cells respond to nutlin-3a treatment mostly with reversible cell cycle arrest induced by activation of p53 pathway but without evidence of cell death (56,57). However, nutlin-3a-induced cellular senescence mediated by p53 activation is a recent finding meriting further investigation (57).

4.3. The p53 pathway in ALK+ anaplastic large cell lymphoma

Already from the era before the discovery of ALK kinase, combined immunohistochemical and genetic studies showed that p53 is frequently expressed, but rarely mutated in anaplastic large cell lymphoma (ALCL). tumors, a phenomenon observed, also, in classical Hodgkin lymphoma tumors (58,59). Later studies confirmed that, although almost 2/3 of ALK+ ALCL tumors express p53 protein by immunohistochemistry at a level...
of 10% of the tumor cells or above only 7% of the tumors harbor mutated (mt) p53 gene (60). Similar results were obtained from a more recent study employing high through-output genetic techniques, showing that only approximately 9% of ALK+, ALCL tumors and a larger percentage, approximately 45% of ALK-, ALCL are characterized by genetic alterations of p53 gene (61). Immunohistochemical analysis of ALK+, ALCL tumors provided first evidence that non-mutated p53 may retain some activity in ALK+ ALCL cells, since it was shown that higher p53 expression levels correlate with higher intrinsic apoptotic rate and higher expression levels of Mdm2, and p21, known transcriptional targets of p53 (60). However, definite proof that the p53 tumor suppressor pathway in wild type (wt)-p53 ALK+ ALCL cells is potentially functional was provided by a recent study employing nutlin-3a that disrupts the p53–Mdm2 interaction resulting in p53 stabilization and activation. It was shown that nutlin-3a-mediated activation of p53 resulted in cell-cycle arrest and apoptosis of ALK+ ALCL cells carrying wild type (wt), or mutated, but partially functional (mt-pf), p53 (62). G1, and/or G2 cell-cycle arrest was associated with upregulation of the cyclin-dependent kinase inhibitor p21. Nutlin-3a-induced apoptotic cell death was accompanied by upregulation of the proapoptotic regulators Bax and Puma, transcriptional targets of p53, downregulation of the antiapoptotic regulators of the intrinsic apoptotic pathway Bcl-xl and survivin, and caspase-3 cleavage. In addition, nutlin-3a-mediated activation of p53 targeted the extrinsic apoptotic pathway, resulting in upregulation of the death receptor DR-5, downregulation of the apoptotic inhibitor c-Flip/S/L and synergistic cell death induction after combined treatment with nutlin-3a and TRAIL, or the FAS-activating antibody CH11 (62). Also, nutlin-3a synergized with the BH3-only mimetic YC-137, targeting the intrinsic apoptotic pathway, resulting in increased cell death of wt-p53 ALK+, ALCL cells (unpublished data). Nutlin-3a-induced cell death of ALK+, ALCL cells was depended on p53 transactivation activity, as well as non transcriptional mechanisms, involving direct targeting of mitochondria by p53 protein (62). Furthermore, nongenotoxic activation of p53 induced by nutlin-3a treatment combined with genotoxic activation of p53 induced by classical chemotherapeutic agents, like doxorubicin, resulted in enhanced cytotoxicity against ALK+ ALCL cells harbouring wt-, mt-pf-, or mt-p53, and this was associated with upregulation of the p53 homologue, p73 (62). Collectively, these data showed that targeted activation of the p53 pathway may overcome the oncogenic signals originating from the NPM-ALK initiating oncogenic event, resulting in collapse of wt-p53 ALK+, ALCL cells. Therefore, it is obvious that sustained inhibition of the tumor suppressor pathway p53 is essential for the oncogenic phenotype of ALK+, ALCL cells. Indeed, in vitro mechanistic studies in murine embryonic fibroblastic cells (MEF) transfected with npm-alk and in vivo studies of lymphomagenesis in npm-alk transgenic mice suggest that overcoming cellular senescence mediated, in part by p53 activity, is an essential, although not adequate step towards npm-alk-induced lymphoma development (63,64). But how is suppression of the p53 pathway accomplished in ALK+ ALCL cells? Studies of other types of tumors show that additional genetic alterations involving the p53 pathway, including MDM2, or MDMX amplification may contribute to functional inactivation of p53 (52). Such genetic alterations have not been studied in detail in ALK+ ALCL tumors. However, recent studies suggest that NPM-ALK may, indirectly, induce p53 activity suppression through MDM2 stabilization, JNK and PI3K activation, or through mechanisms involving the p16/Retinoblastoma pathway, although the exact mechanism remains elusive (63-65).

Taken together, these preclinical studies suggest that targeted activation of the p53 tumor suppression pathway seems a reasonable therapeutic strategy for patients with ALK+ ALCL. Clinical trials of p53 targeting agents are already in development for various types of malignancies, including lymphomas (66). It is probable that agents like nutlin-3a that disrupt the p53–mdm2 interaction may become part of more effective and less toxic combination therapies including other biologic, or classical chemotherapeutic agents for ALK+ ALCL patients.

5. ACKNOWLEDGEMENTS

G.Z. Rassidakis is a recipient of ‘ARISTEIA-II’ (code 4757) grant (Operational Program ‘Education and Lifelong Learning’ of the National Strategic Reference Framework (NSRF)—Research Funding Program: Investing in knowledge society through the European Social Fund). The present review was concerted inside the European Research Initiative of ALK-related malignancies (ERIA) (http://www.erialcl.net).

6. REFERENCES


3. R. Chiarle, C. Martinengo, C. Mastini, C.
CD30 and p53 in ALCL


CD30 and p53 in ALCL


63. F. K. McDuff and S. D. Turner: Aberrant
DOI: 10.1371/journal.pone.0017854

DOI: 10.1182/blood-2010-08-301135

DOI: 10.1182/blood-2008-06-160168

DOI: 10.1021/jm501092z

**Key Words:** CD30, p53, Anaplastic Large Cell Lymphoma, Cell cycle, Review

**Send correspondence to:** George Z. Rassidakis, Department of Pathology and Cytology, Karolinska University Hospital and Karolinska Institute, Radiumhemmet, Stockholm, Sweden SE-17176, Tel: 0046-8-51776162, Fax: 0046-8-51772061, E-mail: georgios.rassidakis@karolinska.se