[Frontiers in Bioscience, Elite, 8, 61-71, January 1, 2016]

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

George Z. Rassidakis[1,2,3], Elias Drakos[4]

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

TABLE OF CONTENTS

1. ABSTRACT

ALK+ anaplastic large cell lymphoma (ALCL). frequently carries the t(2;5).(p23;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).(p23;q35). resulting in aberrant expression and activation of NPM-ALK chimeric oncoprotein (2). The latter directly activates multiple oncogenic pathways including Ras, PLC-gamma, Jak/STAT, PI3K/AKT/mTOR, JNK/Jun and others (3). 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 (,). 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, oncogenic 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*

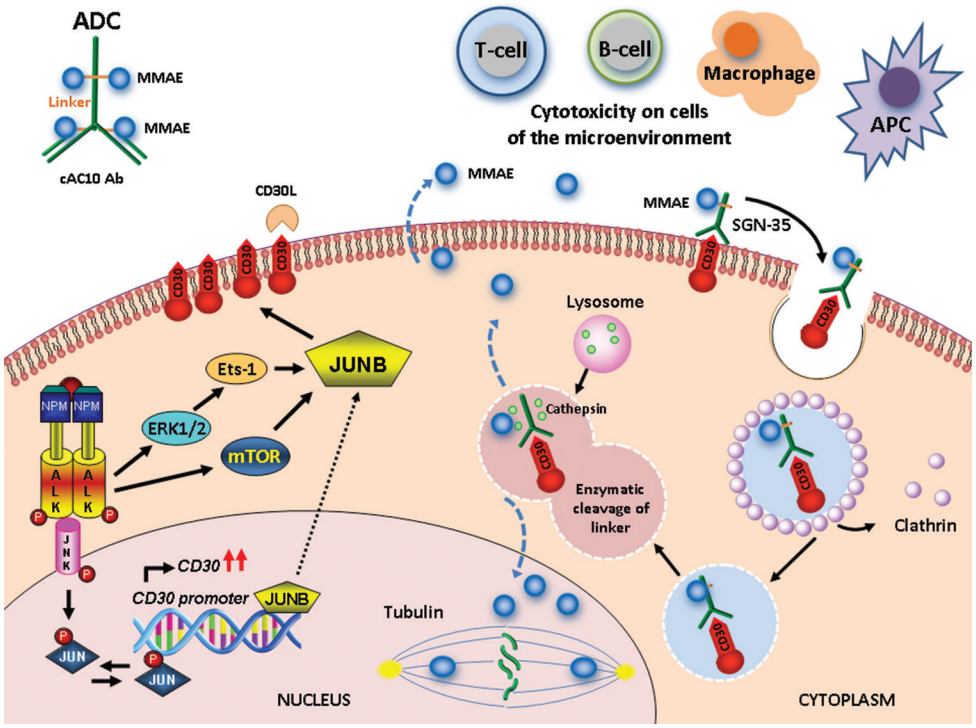

Figure 1. Based on several studies (see text), JunB seems to operate as an oncogene in the context of ALK+ ALCL and possibly other CD30+ lymphomas. JunB overexpression in ALK+ ALCL may be the result of gene amplification and NPM-ALK - associated mechanisms such as regulation of its transcription via 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 mictotubules 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

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 NFκB. 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 microtubule polymerization 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 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

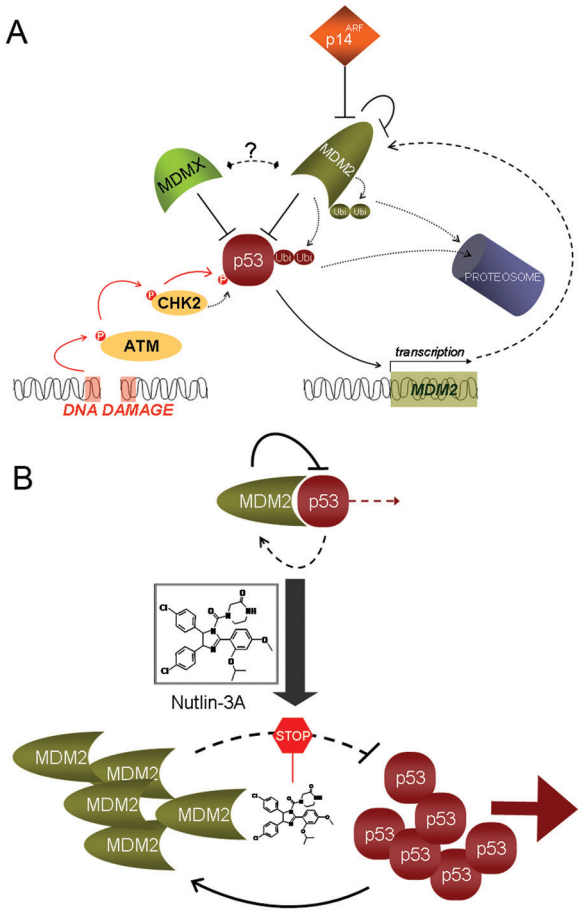

Figure 2. A) Outline of p53 regulation: Two of the most important regulators of p53 are the MDM2 and MDMX. MDM2 regulates the levels of p53 protein acting as E3 ubiquin ligase and facilitating the degradation of p53 from the proteosome. It also blocks p53 transactivation activity. In addition, MDM2 facilitates its own degradation and is a transcriptional target of p53. MDMX blocks the transactivation activity of p53 but does not seem to affect p53 protein levels. The reports about the influence of MDM2 on MDMX and vice versa are contradictory and it is not clear yet, if these effects are mediated directly, or indirectly. In addition, a variety of signals can modify the p53 protein influencing in this way its stability and activity. Only one of these signals, induced by DNA double strand brakes, is depicted. It involves the activation of kinases of the DNA damage response pathway, ATM and CHK2, and results in phosphorylation of serine amino acid residues at the N-terminal of the p53 protein enhancing p53 activation. The negative regulator of MDM2, p14/ARF, is also illustrated on the top. B) Mode of action of nutlin-3a: Nutlin-3a binds the p53-binding pocket of MDM2, blocking its interaction with the p53 protein. As a result, p53 is stabilized and its transactivation activity increases orchestrating the transcription of a large number of genes, including *MDM2* and inducing a variety of biologic effects, mediated specifically by the downstream p53 pathway.

rate of degradation (Figure 2) (46). The degradation of p53 is mainly regulated by the murine double minute 2 product (MDM2). that acts as an E3 p53-specific 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 phorphorylation 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 oligonuclotides, or rescuing the function of mutated p53 proteins though 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 (Figure 2) (56). Nutlins penetrate freely the cell membrane and their potency against MDM2-p53 binding is in the range between 100-300 nM, with nutlin-3a being the more potent (56). Both, *in vitro* and *in vivo* studies showed that nutlins can activate the p53 pathway and inhibit wt-p53 cancer cell growth inducing cell cycle arrest and apoptosis with potency in the range of 1-3 μM (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 p53 activation targeted the extrinsic apoptotic pathway, resulting in upregulation of the death receptor DR-5, downregulation of the apoptotic inhibitor c-FlipS/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 fuctional 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

1. G. Delsol, E. Ralfkiaer, H. Stein, D. Wright and E. S. Jaffe: Anaplastic large cell lymphoma. In: *World Health Organization classification of tumours. Pathology and genetics of tumors of haematopoietic and lymphoid tissues*. Ed E. S. Jaffe, N. L. Harris, H. Stein&J. W. Vardiman. IARC Press, Lyon, France (2008) No DOI found
2. S. W. Morris, M. N. Kirstein, M. B. Valentine, K. G. Dittmer, D. N. Shapiro, D. L. Saltman and A. T. Look: Fusion of a kinase gene, ALK, to a nucleolar protein gene, NPM, in non-Hodgkin's lymphoma. *Science*, 263(5151), 1281-4 (1994) DOI: 10.1126/science.8122112
3. R. Chiarle, C. Martinengo, C. Mastini, C.

Ambrogio, V. D'Escamard, G. Forni and G. Inghirami: The anaplastic lymphoma kinase is an effective oncoantigen for lymphoma vaccination. *Nat Med*, 14(6), 676-80 (2008) DOI: 10.1038/nm1769

4. U. Schwab, H. Stein, J. Gerdes, H. Lemke, H. Kirchner, M. Schaadt and V. Diehl: Production of a monoclonal antibody specific for Hodgkin and Sternberg-Reed cells of Hodgkin's disease and a subset of normal lymphoid cells. *Nature*, 299(5878), 65-7 (1982) DOI: 10.1038/299065a0
5. H. Durkop, U. Latza, M. Hummel, F. Eitelbach, B. Seed and H. Stein: Molecular cloning and expression of a new member of the nerve growth factor receptor family that is characteristic for Hodgkin's disease. *Cell*, 68(3), 421-7 (1992) DOI: 10.1016/0092-8674(92)90180-K
6. H. J. Gruss and S. K. Dower: Tumor necrosis factor ligand superfamily: involvement in the pathology of malignant lymphomas. *Blood*, 85(12), 3378-404 (1995) No DOI found
7. S. R. Wiley, R. G. Goodwin and C. A. Smith: Reverse signaling via CD30 ligand. *J Immunol*, 157(8), 3635-9 (1996) No DOI found
8. R. Chiarle, A. Podda, G. Prolla, J. Gong, G. J. Thorbecke and G. Inghirami: CD30 in normal and neoplastic cells. *Clin Immunol*, 90(2), 157-64 (1999) DOI: 10.1006/clim.1998.4636
9. S. Mathas, M. Hinz, I. Anagnostopoulos, D. Krappmann, A. Lietz, F. Jundt, K. Bommert, F. Mechta-Grigoriou, H. Stein, B. Dorken and C. Scheidereit: Aberrantly expressed c-Jun and JunB are a hallmark of Hodgkin lymphoma cells, stimulate proliferation and synergize with NF-kappa B. *EMBO J*, 21(15), 4104-13 (2002) DOI: 10.1093/emboj/cdf389
10. G. Z. Rassidakis, A. Thomaides, C. Atwell, R. Ford, D. Jones, F. X. Claret and L. J. Medeiros: JunB expression is a common feature of CD30+ lymphomas and lymphomatoid papulosis. *Mod Pathol*, 18(10), 1365-70 (2005) DOI: 10.1038/modpathol.3800419
11. E. Drakos, V. Leventaki, E. J. Schlette, D. Jones, P. Lin, L. J. Medeiros and G. Z. Rassidakis: c-Jun expression and activation are restricted to CD30+ lymphoproliferative disorders. *Am J Surg Pathol*, 31(3), 447-53 (2007) DOI: 10.1097/01.pas.0000213412.25935.e4
12. M. Watanabe, M. Sasaki, K. Itoh, M. Higashihara, K. Umezawa, M. E. Kadin, L. J. Abraham, T. Watanabe and R. Horie: JunB induced by constitutive CD30-extracellular signal-regulated kinase 1/2 mitogen-activated protein kinase signaling activates the CD30 promoter in anaplastic large cell lymphoma and reed-sternberg cells of Hodgkin lymphoma. *Cancer Res*, 65(17), 7628-34 (2005) No DOI found
13. M. Watanabe, Y. Ogawa, K. Ito, M. Higashihara, M. E. Kadin, L. J. Abraham, T. Watanabe and R. Horie: AP-1 mediated relief of repressive activity of the CD30 promoter microsatellite in Hodgkin and Reed-Sternberg cells. *Am J Pathol*, 163(2), 633-41 (2003) DOI: 10.1016/S0002-9440(10)63690-5
14. M. Watanabe, Y. Ogawa, K. Itoh, T. Koiwa, M. E. Kadin, T. Watanabe, I. Okayasu, M. Higashihara and R. Horie: Hypomethylation of CD30 CpG islands with aberrant JunB expression drives CD30 induction in Hodgkin lymphoma and anaplastic large cell lymphoma. *Lab Invest*, 88(1), 48-57 (2008) DOI: 10.1038/labinvest.3700696
15. E. Shaulian: AP-1--The Jun proteins: Oncogenes or tumor suppressors in disguise? *Cell Signal*, 22(6), 894-9 (2010) DOI: 10.1016/j.cellsig.2009.12.008
16. T. Deng and M. Karin: JunB differs from c-Jun in its DNA-binding and dimerization domains, and represses c-Jun by formation of inactive heterodimers. *Genes Dev*, 7(3), 479-90 (1993) DOI: 10.1101/gad.7.3.479
17. E. Passegue and E. F. Wagner: JunB suppresses cell proliferation by transcriptional activation of p16(INK4a) expression. *EMBO J*, 19(12), 2969-79 (2000) DOI: 10.1093/emboj/19.12.2969
18. E. Passegue, W. Jochum, M. Schorpp-Kistner, U. Mohle-Steinlein and E. F. Wagner: Chronic myeloid leukemia with increased granulocyte progenitors in mice lacking junB expression in the myeloid lineage. *Cell*, 104(1), 21-32 (2001) DOI: 10.1016/S0092-8674(01)00188-X

19. E. Passegue, W. Jochum, A. Behrens, R. Ricci and E. F. Wagner: JunB can substitute for Jun in mouse development and cell proliferation. *Nat Genet*, 30(2), 158-66 (2002)
DOI: 10.1038/ng790

20. S. Andrecht, A. Kolbus, B. Hartenstein, P. Angel and M. Schorpp-Kistner: Cell cycle promoting activity of JunB through cyclin A activation. *J Biol Chem*, 277(39), 35961-8 (2002)
DOI: 10.1074/jbc.M202847200

21. A. P. Szremska, L. Kenner, E. Weisz, R. G. Ott, E. Passegue, M. Artwohl, M. Freissmuth, R. Stoxreiter, H. C. Theussl, S. B. Parzer, R. Moriggl, E. F. Wagner and V. Sexl: JunB inhibits proliferation and transformation in B-lymphoid cells. *Blood*, 102(12), 4159-65 (2003)
DOI: 10.1182/blood-2003-03-0915

22. V. Leventaki, E. Drakos, L. J. Medeiros, M. S. Lim, K. S. Elenitoba-Johnson, F. X. Claret and G. Z. Rassidakis: NPM-ALK oncogenic kinase promotes cell-cycle progression through activation of JNK/cJun signaling in anaplastic large-cell lymphoma. *Blood*, 110(5), 1621-30 (2007)
DOI: 10.1182/blood-2006-11-059451

23. P. B. Staber, P. Vesely, N. Haq, R. G. Ott, K. Funato, I. Bambach, C. Fuchs, S. Schauer, W. Linkesch, A. Hrzenjak, W. G. Dirks, V. Sexl, H. Bergler, M. E. Kadin, D. W. Sternberg, L. Kenner and G. Hoefler: The oncoprotein NPM-ALK of anaplastic large-cell lymphoma induces JUNB transcription via ERK1/2 and JunB translation via mTOR signaling. *Blood*, 110(9), 3374-83 (2007)
DOI: 10.1182/blood-2007-02-071258

24. M. Watanabe, K. Itoh, T. Togano, M. E. Kadin, T. Watanabe, M. Higashihara and R. Horie: Ets-1 Activates Overexpression of JunB and CD30 in Hodgkin's Lymphoma and Anaplastic Large-Cell Lymphoma. *Am J Pathol*, 180(2), 831-8
DOI: 10.1016/j.ajpath.2011.10.007

25. F. Vega, L. J. Medeiros, V. Leventaki, C. Atwell, J. H. Cho-Vega, L. Tian, F. X. Claret and G. Z. Rassidakis: Activation of mammalian target of rapamycin signaling pathway contributes to tumor cell survival in anaplastic lymphoma kinase-positive anaplastic large cell lymphoma. *Cancer Res*, 66(13), 6589-97 (2006)
DOI: 10.1158/0008-5472.CAN-05-3018

26. X. Mao, G. Orchard, D. M. Lillington, R. Russell-Jones, B. D. Young and S. J. Whittaker: Amplification and overexpression of JUNB is associated with primary cutaneous T-cell lymphomas. *Blood*, 101(4), 1513-9 (2003)
DOI: 10.1182/blood-2002-08-2434

27. S. Hartmann, J. I. Martin-Subero, S. Gesk, J. Husken, M. Giefing, I. Nagel, J. Riemke, A. Chott, W. Klapper, M. Parrens, J. P. Merlio, R. Kuppers, A. Brauninger, R. Siebert and M. L. Hansmann: Detection of genomic imbalances in microdissected Hodgkin and Reed-Sternberg cells of classical Hodgkin's lymphoma by array-based comparative genomic hybridization. *Haematologica*, 93(9), 1318-26 (2008)
DOI: 10.3324/haematol.12875

28. V. Atsaves, L. Lekakis, E. Drakos, V. Leventaki, M. Ghaderi, G. E. Baltatzis, D. Chioureas, D. Jones, M. Feretzaki, C. Liakou, P. Panayiotidis, V. Gorgoulis, E. Patsouris, L. J. Medeiros, F. X. Claret and G. Z. Rassidakis: The oncogenic JUNB/CD30 axis contributes to cell cycle deregulation in ALK+ anaplastic large cell lymphoma. *Br J Haematol*, 167(4), 514-23 (2014)
DOI: 10.1111/bjh.13079

29. A. F. Wahl, K. Klussman, J. D. Thompson, J. H. Chen, L. V. Francisco, G. Risdon, D. F. Chace, C. B. Siegall and J. A. Francisco: The anti-CD30 monoclonal antibody SGN-30 promotes growth arrest and DNA fragmentation *in vitro* and affects antitumor activity in models of Hodgkin's disease. *Cancer Res*, 62(13), 3736-42 (2002)
No DOI found

30. C. G. Cerveny, C. L. Law, R. S. McCormick, J. S. Lenox, K. J. Hamblett, L. E. Westendorf, A. K. Yamane, J. M. Petroziello, J. A. Francisco and A. F. Wahl: Signaling via the anti-CD30 mAb SGN-30 sensitizes Hodgkin's disease cells to conventional chemotherapeutics. *Leukemia*, 19(9), 1648-55 (2005)
DOI: 10.1038/sj.leu.2403884

31. M. Duvic, S. A. Reddy, L. Pinter-Brown, N. J. Korman, J. Zic, D. A. Kennedy, J. Lorenz, E. L. Sievers and Y. H. Kim: A phase II study of SGN-30 in cutaneous anaplastic large cell lymphoma and related lymphoproliferative disorders. *Clin Cancer Res*, 15(19), 6217-24 (2009)
DOI: 10.1158/1078-0432.CCR-09-0162

32. A. Forero-Torres, J. P. Leonard, A. Younes, J. D. Rosenblatt, P. Brice, N. L. Bartlett, A. Bosly, L. Pinter-Brown, D. Kennedy, E. L. Sievers and A. K. Gopal: A Phase II study of SGN-30 (anti-CD30 mAb) in Hodgkin lymphoma or systemic anaplastic large cell lymphoma. *Br J Haematol*, 146(2), 171-9 (2009)
DOI: 10.1111/j.1365-2141.2009.07740.x

33. R. Schnell and P. Borchmann: SGN-30 (Seattle genetics). *Curr Opin Mol Ther*, 8(2), 164-72 (2006)
No DOI found

34. A. Younes, N. L. Bartlett, J. P. Leonard, D. A. Kennedy, C. M. Lynch, E. L. Sievers and A. Forero-Torres: Brentuximab vedotin (SGN-35) for relapsed CD30-positive lymphomas. *N Engl J Med*, 363(19), 1812-21 (2010)
DOI: 10.1056/NEJMoa1002965

35. J. Katz, J. E. Janik and A. Younes: Brentuximab Vedotin (SGN-35). *Clin Cancer Res*, 17(20), 6428-36 (2011)
DOI: 10.1158/1078-0432.CCR-11-0488

36. A. Rothe, S. Sasse, H. Goergen, D. A. Eichenauer, A. Lohri, U. Jager, C. Bangard, B. Boll, M. von Bergwelt Baildon, S. Theurich, P. Borchmann and A. Engert: Brentuximab vedotin for relapsed or refractory CD30+ hematologic malignancies: the German Hodgkin Study Group experience. *Blood*, 120(7), 1470-2 (2012)
DOI: 10.1182/blood-2012-05-430918

37. A. K. Gopal, R. Ramchandren, O. A. O'Connor, R. B. Berryman, R. H. Advani, R. Chen, S. E. Smith, M. Cooper, A. Rothe, J. V. Matous, L. E. Grove and J. Zain: Safety and efficacy of brentuximab vedotin for Hodgkin lymphoma recurring after allogeneic stem cell transplantation. *Blood*, 120(3), 560-8 (2011)
DOI: 10.1182/blood-2011-12-397893

38. A. Younes, A. K. Gopal, S. E. Smith, S. M. Ansell, J. D. Rosenblatt, K. J. Savage, R. Ramchandren, N. L. Bartlett, B. D. Cheson, S. de Vos, A. Forero-Torres, C. H. Moskowitz, J. M. Connors, A. Engert, E. K. Larsen, D. A. Kennedy, E. L. Sievers and R. Chen: Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory Hodgkin's lymphoma. *J Clin Oncol*, 30(18), 2183-9 (2011)
DOI: 10.1200/JCO.2011.38.0410

39. A. K. Gopal, R. Chen, S. E. Smith, S. M. Ansell, J. D. Rosenblatt, K. J. Savage, J. M. Connors, A. Engert, E. K. Larsen, X. Chi, E. L. Sievers and A. Younes: Durable remissions in a pivotal phase 2 study of brentuximab vedotin in relapsed or refractory Hodgkin lymphoma. *Blood* (2014)
DOI: 10.1182/blood-2014-08-595801

40. M. A. Fanale, A. Forero-Torres, J. D. Rosenblatt, R. H. Advani, A. R. Franklin, D. A. Kennedy, T. H. Han, E. L. Sievers and N. L. Bartlett: A phase I weekly dosing study of brentuximab vedotin in patients with relapsed/refractory CD30-positive hematologic malignancies. *Clin Cancer Res*, 18(1), 248-55 (2011)
DOI: 10.1158/1078-0432.CCR-11-1425

41. B. Pro, R. Advani, P. Brice, N. L. Bartlett, J. D. Rosenblatt, T. Illidge, J. Matous, R. Ramchandren, M. Fanale, J. M. Connors, Y. Yang, E. L. Sievers, D. A. Kennedy and A. Shustov: Brentuximab vedotin (SGN-35) in patients with relapsed or refractory systemic anaplastic large-cell lymphoma: results of a phase II study. *J Clin Oncol*, 30(18), 2190-6 (2011)
DOI: 10.1200/JCO.2011.38.0402

42. A. K. Gopal, N. L. Bartlett, A. Forero-Torres, A. Younes, R. Chen, J. W. Friedberg, J. V. Matous, A. R. Shustov, S. E. Smith, J. Zain, M. M. O'Meara and M. A. Fanale: Brentuximab vedotin in patients aged 60 years or older with relapsed or refractory CD30-positive lymphomas: a retrospective evaluation of safety and efficacy. *Leuk Lymphoma*, 55(10), 2328-34 (2013)
DOI: 10.3109/10428194.2013.876496

43. S. M. Ansell: Brentuximab vedotin. *Blood*, 124(22), 3197-3200 (2014)
DOI: 10.1182/blood-2014-06-537514

44. M. A. Fanale, S. M. Horwitz, A. Forero-Torres, N. L. Bartlett, R. H. Advani, B. Pro, R. W. Chen, A. Davies, T. Illidge, D. Huebner, D. A. Kennedy and A. R. Shustov: Brentuximab vedotin in the front-line treatment of patients with CD30+ peripheral T-cell lymphomas: results of a phase I study. *J Clin Oncol*, 32(28), 3137-43 (2013)
DOI: 10.1200/JCO.2013.54.2456

45. S. M. Horwitz, R. H. Advani, N. L. Bartlett, E. D. Jacobsen, J. P. Sharman, O. A. O'Connor, T. Siddiqi, D. A. Kennedy and Y. Oki: Objective

responses in relapsed T-cell lymphomas with single-agent brentuximab vedotin. *Blood*, 123(20), 3095-100 (2013)
DOI: 10.1182/blood-2013-12-542142

46. B. Vogelstein, D. Lane and A. J. Levine: Surfing the p53 network. *Nature*, 408(6810), 307-10 (2000)
DOI: 10.1038/35042675

47. J. Campisi and F. d'Adda di Fagagna: Cellular senescence: when bad things happen to good cells. *Nat Rev Mol Cell Biol*, 8(9), 729-40 (2007)
DOI: 10.1038/nrm2233

48. M. Schuler and D. R. Green: Transcription, apoptosis and p53: catch-22. *Trends Genet*, 21(3), 182-7 (2005)
DOI: 10.1016/j.tig.2005.01.001

49. Z. Feng, H. Zhang, A. J. Levine and S. Jin: The coordinate regulation of the p53 and mTOR pathways in cells. *Proc Natl Acad Sci U S A*, 102(23), 8204-9 (2005)
DOI: 10.1073/pnas.0502857102

50. S. Matoba, J. G. Kang, W. D. Patino, A. Wragg, M. Boehm, O. Gavrilova, P. J. Hurley, F. Bunz and P. M. Hwang: p53 regulates mitochondrial respiration. *Science*, 312(5780), 1650-3 (2006)
DOI: 10.1126/science.1126863

51. J. G. Teodoro, S. K. Evans and M. R. Green: Inhibition of tumor angiogenesis by p53: a new role for the guardian of the genome. *J Mol Med (Berl)*, 85(11), 1175-86 (2007)
DOI: 10.1007/s00109-007-0221-2

52. F. Toledo and G. M. Wahl: MDM2 and MDM4: p53 regulators as targets in anticancer therapy. *Int J Biochem Cell Biol*, 39(7-8), 1476-82 (2007)
DOI: 10.1016/j.biocel.2007.03.022

53. C. L. Brooks and W. Gu: p53 ubiquitination: Mdm2 and beyond. *Mol Cell*, 21(3), 307-15 (2006)
DOI: 10.1016/j.molcel.2006.01.020

54. W. Wang and W. S. El-Deiry: Restoration of p53 to limit tumor growth. *Curr Opin Oncol*, 20(1), 90-6 (2008)
DOI: 10.1097/CCO.0b013e3282f31d6f

55. L. T. Vassilev: MDM2 inhibitors for cancer therapy. *Trends Mol Med*, 13(1), 23-31 (2007)
DOI: 10.1016/j.molmed.2006.11.002

56. L. T. Vassilev, B. T. Vu, B. Graves, D. Carvajal, F. Podlaski, Z. Filipovic, N. Kong, U. Kammlott, C. Lukacs, C. Klein, N. Fotouhi and E. A. Liu: *In vivo* activation of the p53 pathway by small-molecule antagonists of MDM2. *Science*, 303(5659), 844-8 (2004)
DOI: 10.1126/science.1092472

57. A. Efeyan, A. Ortega-Molina, S. Velasco-Miguel, D. Herranz, L. T. Vassilev and M. Serrano: Induction of p53-dependent senescence by the MDM2 antagonist nutlin-3a in mouse cells of fibroblast origin. *Cancer Res*, 67(15), 7350-7 (2007)
DOI: 10.1158/0008-5472.CAN-07-0200

58. E. Cesarman, G. Inghirami, A. Chadburn and D. M. Knowles: High levels of p53 protein expression do not correlate with p53 gene mutations in anaplastic large cell lymphoma. *Am J Pathol*, 143(3), 845-56 (1993)
No DOI found

59. Z. Y. Xu-Monette, L. J. Medeiros, Y. Li, R. Z. Orlowski, M. Andreeff, C. E. Bueso-Ramos, T. C. Greiner, T. J. McDonnell and K. H. Young: Dysfunction of the TP53 tumor suppressor gene in lymphoid malignancies. *Blood*, 119(16), 3668-83
DOI: 10.1182/blood-2011-11-366062

60. G. Z. Rassidakis, A. Thomaides, S. Wang, Y. Jiang, A. Fourtouna, R. Lai and L. J. Medeiros: p53 gene mutations are uncommon but p53 is commonly expressed in anaplastic large-cell lymphoma. *Leukemia*, 19(9), 1663-9 (2005)
DOI: 10.1038/sj.leu.2403840

61. M. Boi, A. Rinaldi, I. Kwee, P. Bonetti, M. Todaro, F. Tabbo, R. Piva, P. M. Rancoita, A. Matolcsy, B. Timar, T. Tousseyn, S. M. Rodriguez-Pinilla, M. A. Piris, S. Bea, E. Campo, G. Bhagat, S. H. Swerdlow, A. Rosenwald, M. Ponzoni, K. H. Young, P. P. Piccaluga, R. Dummer, S. Pileri, E. Zucca, G. Inghirami and F. Bertoni: PRDM1/BLIMP1 is commonly inactivated in anaplastic large T-cell lymphoma. *Blood*, 122(15), 2683-93 (2013)
DOI: 10.1182/blood-2013-04-497933

62. E. Drakos, V. Atsaves, E. Schlette, J. Li, I. Papanastasi, G. Z. Rassidakis and L. J. Medeiros: The therapeutic potential of p53 reactivation by nutlin-3a in ALK+ anaplastic large cell lymphoma with wild-type or mutated p53. *Leukemia*, 23(12), 2290-9 (2009)
DOI: 10.1038/leu.2009.180

63. F. K. McDuff and S. D. Turner: Aberrant

anaplastic lymphoma kinase activity induces a p53 and Rb-dependent senescence-like arrest in the absence of detectable p53 stabilization. *PLoS One*, 6(3), e17854 DOI: 10.1371/journal.pone.0017854

64. P. Martinelli, P. Bonetti, C. Sironi, G. Pruneri, C. Fumagalli, P. R. Raviele, S. Volorio, S. Pileri, R. Chiarle, F. K. McDuff, B. K. Tusi, S. D. Turner, G. Inghirami, P. G. Pelicci and E. Colombo: The lymphoma-associated NPM-ALK oncogene elicits a p16INK4a/pRb-dependent tumor-suppressive pathway. *Blood*, 117(24), 6617-26 (2010) DOI: 10.1182/blood-2010-08-301135

65. Y. X. Cui, A. Kerby, F. K. McDuff, H. Ye and S. D. Turner: NPM-ALK inhibits the p53 tumor suppressor pathway in an MDM2 and JNK-dependent manner. *Blood*, 113(21), 5217-27 (2009) DOI: 10.1182/blood-2008-06-160168

66. Y. Zhao, A. Aguilar, D. Bernard and S. Wang: Small-Molecule Inhibitors of the MDM2-p53 Protein-Protein Interaction (MDM2 Inhibitors) in Clinical Trials for Cancer Treatment. *J Med Chem* 58(3):1038-52 (2015) 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