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REVIEW

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Family matters: How MYC family oncogenes impact small cell lung cancer

Johannes Brägelmann[a,b,§], Stefanie Böhm[a,b,§], Matthew R. Guthrie[c], Gurkan Mollaoglu[c], Trudy G. Oliver[c], and Martin L. Sos[a,b,d]

[a]Molecular Pathology, Institute of Pathology, University of Cologne, Cologne, Germany; [b]Department of Translational Genomics, Medical Faculty, University of Cologne, Cologne, Germany; [c]Department of Oncological Sciences, University of Utah, Huntsman Cancer Institute, Salt Lake City, UT, USA; [d]Center for Molecular Medicine Cologne, University of Cologne, Cologne, Germany

ABSTRACT
Small cell lung cancer (SCLC) is one of the most deadly cancers and currently lacks effective targeted treatment options. Recent advances in the molecular characterization of SCLC has provided novel insight into the biology of this disease and raises hope for a paradigm shift in the treatment of SCLC. We and others have identified activation of MYC as a driver of susceptibility to Aurora kinase inhibition in SCLC cells and tumors that translates into a therapeutic option for the targeted treatment of MYC-driven SCLC. While MYC shares major features with its paralogs MYCN and MYCL, the sensitivity to Aurora kinase inhibitors is unique for MYC-driven SCLC. In this review, we will compare the distinct molecular features of the 3 MYC family members and address the potential implications for targeted therapy of SCLC.

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MYC family members in small cell lung cancer

Lung cancer is the leading cause of cancer-associated deaths worldwide,[1] and accounts for more than 220,000 new cases annually in the US alone.[2] About 15% of lung cancer cases are histologically defined as small cell lung cancer (SCLC), which represents a highly aggressive manifestation that almost exclusively arises in smokers and is characterized by rapid growth and frequent metastasis.[3,4] Unfortunately, the major treatment options for SCLC – primarily platinum-based chemotherapy and radiation – have remained virtually unchanged for decades. While these treatment regimens achieve tumor regression in the majority of cases,[5] this initial response is followed by rapid relapse and chemoresistance in most patients, leading to a dismal 5-year survival rate of about 6%.[4,5]

Several recurrent genetic aberrations have been identified in SCLC, among which MYC family genes, including *MYC*, *MYCL* and *MYCN*, stand out as oncogenic drivers that may constitute novel therapeutically tractable targets.[6-8] The 3 MYC family proto-oncogenes are paralogs with regions of structural homology, but also functional differences. We were able to demonstrate that amplification of individual *MYC* family members is associated with phenotypic differences in SCLC. More specifically, we showed that the identity of the MYC family member determines the susceptibility toward the Aurora kinase inhibitor alisertib, where *MYC*-amplified SCLC cells are particularly sensitive.[9,10] Furthermore, recent studies suggest that *MYC*-amplified SCLC may be more sensitive to CHK1 inhibition as well.[11] This is in line with previous studies in myeloid 32D cells, where overexpression of MYC sensitizes cells to the chemotherapeutic agents adriamycin and camptothecin, while MYCL and MYCN-overexpressing cells are resistant.[12] This difference in drug susceptibility based on MYC family members also seems to occur in other tumor types such as neuroblastoma.[13] Thus, to successfully use MYC family members as biomarkers to predict treatment susceptibility in SCLC, it will be crucial to further dissect the molecular basis underlying the different phenotypes observed.

MYC family transcription factors

MYC family members are basic helix-loop-helix (bHLH) leucine zipper transcription factors that bind to the canonical E-box DNA element CACGTG and activate target gene expression as heterodimers with the small bHLH protein MAX.[14] As paralogs, MYC family members share highly conserved domains such as a transactivation domain that recruits the transcriptional machinery, a basic region for E-box-specific DNA binding, MYC homology boxes (MB) involved in protein turnover and functional regulation, and the C-terminal HLH-leucine zipper domain responsible for MAX dimerization (Fig. 1).[3,4,15-19] In the case of *MYCL*, 2 substantially differing transcripts have been found to be expressed in SCLC cell lines, and interestingly, the short isoform lacks the HLH domain.[20] All 3 MYC paralogs can complement an activated Ha-*ras* gene in transforming

CONTACT Trudy G. Oliver trudy.oliver@hci.utah.edu Department of Oncological Sciences, Huntsman Cancer Institute, University of Utah, Salt Lake City, Utah 84112, USA; Martin L. Sos martin.sos@uni-koeln.de Molecular Pathology, Institute of Pathology & Department of Translational Genomics, University of Cologne, 50937 Cologne, Germany.
[§]Equal contribution.

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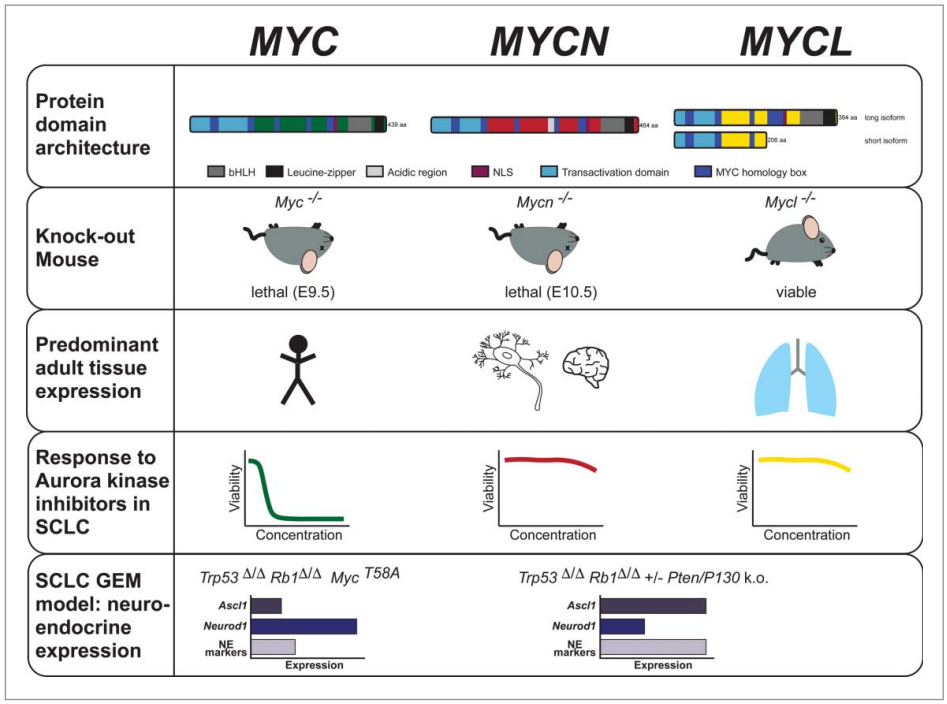

Figure 1. Schematic overview of major characteristics of the 3 MYC family paralogs with a focus on SCLC. Rows 1–3: Biochemical properties and physiological functions of MYC family members- protein domain architecture, phenotype of knockout mouse models and predominant distribution of MYC family member expression across tissues (broad expression of *MYC,* expression of *MYCN* primarily in neural and neuroendocrine tissues, and *MYCL* expression mainly in the lung). Row 4: Response of SCLC models to Aurora kinase inhibition with high sensitivity of *MYC* amplified/overexpressing cells. Row 5: Schematic differences of SCLC mouse models regarding genetic background, MYC family member activity/alteration and expression of neuroendocrine markers including the transcription factors *Neurod1* and *Ascl1*. (bHLH = basic Helix-Loop-Helix, NLS = nuclear localization sequence, GEM = genetically engineered mouse, NE = neuroendocrine).

primary rat embryo fibroblasts and are able to transform pre-neoplastic precursors of SCLC.[15-18] In addition, both *MYC* and *MYCN* induce proliferation and cell cycle progression in quiescent fibroblasts.[16,18,21] Taken together, these findings indicate a degree of redundancy between the family members. Indeed, during murine development, *Mycn* can partially complement for loss of *Myc*.[22] Moreover, a double knockout of *Myc* and *Mycn* in haematopoietic cells has a stronger phenotype than either knockout alone,[23] and both *Myc* and *Mycn* are essential genes, while *Mycl* is not (Fig. 1).[24-27] Albeit subtle, differential binding affinities of recombinant MYC, MYCN, and MYCL with MAX to different DNA consensus motifs have been reported *in vitro*,[28] and the transforming capacity of *MYCL* is lower than that of *MYC* in rat embryonic fibroblasts.[29] Furthermore, CRISPR-mediated inactivation of *Mycn* or *Mycl* in mouse tumor-derived SCLC cell lines reduces colony formation, while that of *Myc* does not.[30] This indicates that mechanistic differences between the family members likely exist. Interestingly, differential effects on transcriptional repression were discovered for heterotrimeric complexes of MYC family members with MAX and MIZ1.[31-34] Even though MYCN/MIZ1 complex formation was described in cell line models,[35,36] MYC/MIZ1 complexes were shown to be more readily detectable than MYCN/MIZ1 complexes and are considered to be relevant components for medulloblastoma subtype differentiation.[32] Even though this points to biological differences between MYC family members, most data are based on overexpression of exogenous MYC, MYCN and/or MIZ1, future studies are warranted to clarify complex formation at endogenous, physiological levels. Currently no data exists regarding complexes of MYCL with MIZ1 and the role of these complexes in SCLC is yet to be determined.

The tissue specific expression of *MYCN* and *MYCL*, in contrast to the more broad expression pattern of *MYC* (Fig. 1), also argues for functional differences between MYC family members. *Myc* is expressed in most developing tissues and sustained in many tissues in the adult mouse, while *Mycn* expression is restricted to early developmental stages, with elevated levels in forebrain, kidney, hindbrain and intestine of newborn mice.[37-39] *Mycl* is also developmentally regulated and expressed in embryonic brain, kidney and lung tissue.[40] Overall, this is largely consistent with the frequency of alterations in each paralog in human cancer types,[41-43] with *MYC* being widely affected across many blood-borne and solid tumors, *MYCN* being frequently altered in solid tumors of neuroendocrine and neuronal origin, and *MYCL* predominantly in SCLC. Specifically, *MYCN* deregulation is frequently found in neuroblastoma,[16] retinoblastoma,[44] medulloblastoma,[45] Wilm's tumors[46] and in prostate cancer with neuroendocrine differentiation,[47] while *MYCL* amplifications occur in SCLC,[41] Merkel cell carcinoma[48] and ovarian carcinoma.[49] In contrast to other known oncogenes such as *RAS* or *EGFR*, *MYC* (with the exception of Burkitt's lymphoma) is typically not mutated in cancer, but rather amplified or deregulated resulting in increased expression. Interestingly, in SCLC *MYC*, *MYCN* and *MYCL* are all found to be affected in a mutually exclusive manner.[3,5-8]

MYC function and regulation

MYC activates gene transcription in conjunction with MAX by several mechanisms, including the recruitment of basal transcription factors, histone acetylases, chromatin remodelling enzymes, and RNA polymerases.[50-55] MYC, the most frequently deregulated and best studied family member, mediates a transcriptional response that promotes cell growth and proliferation.[56,57] In numerous genome-wide studies in Drosophila and mammalian cells, MYC binding sites and regulated genes have been found to cover more than 15% of genomic loci,[58,59] while even regulating up to 1/3 of all transcribed genes in embryonic stem cells.[51] How exactly this transcriptional response is orchestrated remains a matter of ongoing debate, likely due to the complex feedback mechanisms involved. Two opposing models have been put forward, each substantiated by numerous lines of evidence: MYC as a global amplifier of existing transcriptional programs[51,60,61] or MYC as a regulator of specific target genes.[33,62,63] Support for the first model comes from the direct interaction between MYC and the CDK9/Cyclin T1 complex, which has been shown to mediate pause-release of RNA Polymerase II (Pol II) and thereby enhance transcription of all expressed genes, rather than recruiting Pol II to specific target genes.[51,64] Further studies in cell lines, including SCLC, demonstrate that MYC primarily acts by globally amplifying existing gene expression patterns, rather than specifically inducing a distinct set of target genes,[60] a finding that could explain some of the variation in reported MYC effects between different cell types. Providing evidence for the latter of the 2 models are studies combining global chromatin immunoprecipitation (ChIP) and gene expression analysis, which derived gene-specific MYC effects and defined dedicated MYC target gene sets, including genes involved in ribosome biogenesis, translation, cell cycle regulation and energy metabolism.[33,62,65,66] These 2 contrasting models may be reconciled by the recently postulated hypothesis that individual gene promoters exhibit varying affinities for binding and activation by MYC.[67] According to this model, transcription of high affinity genes, such as ribosomal constituents, whose promoters are bound by MYC with high affinity, occurs at low cellular MYC levels. In contrast, the expression of low-affinity genes, e.g. genes involved in TGF-β signaling, is induced only upon strong MYC overexpression. At extreme MYC levels, DNA-binding has been reported to become increasingly unspecific and to occur sequence-independently,[68] a phenomenon referred to as promoter invasion.[60,62] This is in line with evidence suggesting threshold-specific tumorigenic effects of MYC depending on its expression levels.[69]

In addition to its transcriptional role, MYC also controls S-phase entry and replication initiation in a non-transcriptional manner by interacting with the replication initiation complex and promoting recruitment of CDC45.[70-72] *MYC* overexpression induces activation of the DNA damage response (DDR) and results in increased genomic instability, likely a result of the well documented MYC-induced replicative stress caused by pre-mature origin firing and aberrant fork progression.[70,73,74] Similarly, *MYCN* has also been reported to induce DDR signaling in neuroblastoma cells,[13,75] which could be due to increased replicative stress.[76] No reports of similar effects of *MYCL* overexpression are available to date.

Intriguingly, despite its indisputable central role in promoting proliferation, high levels of *MYC* can also induce apoptosis,[77,78] and overexpression of all 3 MYC family members was found to induce apoptosis upon IL-3 withdrawal in 32D myeloid cells.[12] Moreover, an "apoptosis-primed" state has been described for *MYCN*-overexpressing neuroblastoma,[79] but also for physiological MYC levels during tissue development in young mice.[80] In part, gene repression by MYC/MIZ1 is important for induction of apoptosis,[81] as is MYC phosphorylation at T58,[82] and downstream activation of the p53 pathway.[83,84] Nonetheless, several examples of p53-independent MYC-driven apoptosis have been reported, such as during mitosis.[85,86]

Consistent with its central role in mediating proliferation and differentiation, *MYC* expression is tightly regulated in normal cells. Transcription of *MYC* is controlled by numerous transcription factors including CNBP, FuBP1, and TCF, as well as by structural DNA elements such as G4 quadruplexes.[87-90] *MYC* mRNA transport, stability and translation is in turn affected by multiple factors including miRNAs,[91-94] while MYC protein is post-translationally modified with ubiquitin, resulting in a short half-life of 15–30 min.[95-97] Phosphorylation controls the stability of both MYC and MYCN by affecting polyubiquitination and hence proteasomal degradation.[98-100] Serine 62 is phosphorylated by CDK1/CyclinA and CDK1/CyclinB1, leading to a transient stabilization of the protein, but also serving as the prerequisite for threonine 58 phosphorylation by glycogen synthase kinase 3 β (GSK3b).[98,101] This phosphorylation event triggers ubiquitination and subsequent degradation by the 26S proteasome. No such regulatory mechanism has been reported for MYCL to date. The relevance of these regulatory processes for the signaling of the 3 MYC family members in the context of SCLC remains to be studied.

Targeting MYC in small cell lung cancer

Due the fact that deregulation of MYC family members is one of the most frequent oncogenic events in cancer,[102] and the observation that MYC withdrawal in mouse models can lead to tumor regression,[103-106] MYC family members have been considered compelling therapeutic targets for decades. Compounds directly targeting MYC or the MYC/MAX interaction have been developed,[107-109] but overall this approach has proven challenging.[110] This is at least partly due to the lack of intrinsic enzymatic activity and their activation by overexpression, rather than by oncogenic mutations that could be directly exploited therapeutically. This precludes the application of strategies developed for compound discovery in the context of kinase inhibition, such as inhibitory substrate-analogs and targeting mutated proteins only.

In recent years, exploiting synthetic lethality has emerged as a promising approach to overcome such limitations, and several examples demonstrate that this may be a viable option for treatment of *MYC*-driven tumors. In MYC-driven SCLC, we and others identified Aurora kinases (AURK) as promising synthetic lethal targets,[9,10,111,112] which also emerged as potential candidate targets in other MYC-driven tumors.[99,113,114] An elegant explanation for the activity of Aurora kinase inhibitors in *MYCN*-amplified neuroblastoma is the observation that

Aurora kinase A (AURKA) binds to the MYCN/FBXW7 complex, reduces K48-linked ubiquitination of MYCN, and thus increases MYCN protein half-life.[99,114,115] This MYCN-stabilizing function of AURKA is independent of its catalytic activity and compounds such as alisertib or CD532 induce a perturbation of the AURKA/MYCN complex that results in a reduction of MYCN protein levels.[115] A similar stabilizing role of AURKA for MYC has also recently been proposed in NRAS-driven, MYC-expressing hepatocellular carcinoma.[113] This is in contrast to what we find in SCLC, where no strong decrease of MYC stability upon alisertib treatment was observed.[9,10] This indicates that additional mechanisms may sensitize MYC-overexpressing cells toward Aurora kinase inhibition independently of MYC protein abundance. Moreover, in contrast to neuroblastoma, *MYCN*-amplified SCLC cell lines were not particularly sensitive to AURK inhibition,[9,10] suggesting that lineage-dependent factors and/or the genomic background contribute to the specific sensitivity of *MYC*-driven SCLC to AURK inhibition.

In another study, CDK7, a cyclin-dependent kinase that phosphorylates Pol II, was proposed as a novel therapeutic target in SCLC.[116] Using the covalent CDK7 inhibitor THZ1, Christensen and colleagues demonstrated efficacy in *in vitro* and *in vivo* SCLC models. The increased THZ1-sensitivity in SCLC compared with NSCLC was in part explained by the impact of CDK7 inhibition on SCLC-specific super enhancers including those regulating MYC family members, leading to decreased MYC and MYCN levels.[116] Of note, THZ1 had previously been explored in the context of neuroblastoma, where it showed selective activity against *MYCN*-amplified, but not against non-amplified cell lines.[117] Similarly, MYC-dependent effects of CDK inhibition have been observed in other contexts. For example, *MYC*-addicted tumors are selectively responsive to CDK9 inhibition in hepatocellular carcinoma,[118] breast cancer,[119] and B-cell lymphoma.[120] In cell line models overexpressing different oncogenes, inhibition of CDK1 was demonstrated to induce apoptosis only in cells overexpressing *MYC*.[121] Whereas associations of MYC status and activity of CDK inhibition were shown in these contexts, it remains to be determined whether MYC status correlates with sensitivity to THZ1 or other CDK inhibitors in SCLC.

An alternative strategy to MYC inhibition is the targeted inhibition of epigenetic regulators such as BET proteins that may reduce MYC expression levels. The most extensively characterized bromodomain inhibitor is JQ-1,[122] which has been shown to reduce MYC family member expression and exhibits activity in *MYC*-driven acute leukemia,[123] Merkel cell carcinoma,[124] *BRD4-NUT* midline carcinoma[125] and *MYC*-amplified medulloblastoma.[126] Similarly, in a murine SCLC model, Jahchan and colleagues showed that *Mycl* activity is crucial for tumor-propagating SCLC cells and that their tumorigenic potential was significantly reduced after abrogation of *Mycl* activity by JQ-1-induced transcriptional repression or following *Mycl* knock-down.[127] JQ-1 was moreover shown to have antiproliferative effects in SCLC cell lines.[128,129] Interestingly, key targets with reduced expression upon JQ-1 treatment in SCLC cell lines were MYC family members[129] and ASCL1,[130] but currently biomarkers predicting JQ-1 sensitivity in SCLC are lacking. More recently, CHK1 inhibition has been identified as an additional drug target that elicits efficacy specifically in MYC-driven SCLC,[11] suggesting that MYC status is an important determinant of therapeutic response in SCLC.

Taken together, MYC family transcription factors are central signaling hubs, in one way or another affecting virtually all (proliferative) processes in a cell, which –together with their frequent deregulation- makes them attractive therapeutic targets in SCLC. However, to further define and eventually treat MYC-dependent SCLC, *in vivo* models that faithfully recapitulate the complexity of the human disease are crucial.

Reconstructing the role of MYC signaling in SCLC GEMM models

Multiple genetically engineered mouse models (GEMMs) for SCLC have been developed in the past decades. The first SCLC GEMMs were based on conditional loss of *Rb1* and *Trp53* as the key genetic alterations, leading to SCLC with high resemblance to the human disease both histologically and molecularly, albeit with long latency.[131] Importantly, tumors in this model frequently exhibit focal amplifications and/or high expression of *Mycl*.[132,133] Subsequent GEMMs incorporated the additional loss of Rb1 family member *Rbl2* (*p130*) or *Pten*, both of which are lost in a subset of SCLCs.[6,134-136] Loss of either tumor suppressor accelerates tumorigenesis, and has made these models more tractable for experimental use. A recent comprehensive histopathological review found that these GEMMs develop a spectrum of histopathologies including classic SCLC, NSCLC with neuroendocrine (NE) features and large cell neuroendocrine carcinoma (LCNEC).[137] Notably, tumors from these GEMMs that exhibit classic SCLC morphology are characterized by high expression of neuroendocrine markers and *Ascl1*, a transcription factor involved in neuroendocrine differentiation. In a mouse model, *Ascl1* has been shown to be required for tumorigenesis of classic SCLC,[138] and was demonstrated to be essential for the survival of neuroendocrine lung cancer cell lines including NE-NSCLCs.[139] Although *Mycl* amplifications observed in these original models occur stochastically, *Mycl* has been shown to play a significant functional role in SCLC tumorigenesis. Overexpression of *Mycl* in combination with *Trp53* and *Rb1* loss significantly decreases tumor latency,[140] and deletion of *Mycl* dramatically suppresses tumor formation and leads to more mixed and NSCLC morphologies, even when targeting neuroendocrine cells.[30] This suggests that beyond just driving proliferation, MYCL may play a role in SCLC differentiation.

The *Rb1/Trp53/Myc*^{T58A} (RPM) mouse is the first known SCLC GEMM driven by *Myc,* and expresses a non-phosphorylatable point mutant of MYC (T58A) causing substantially increased MYC protein levels.[9] Interestingly, tumors in this model exhibit reduced neuroendocrine gene expression, including *Ascl1,* but in contrast display high *Neurod1* expression. They thereby resemble a subset of human SCLC marked by low neuroendocrine markers, which is known as “variant” SCLC morphology.[141-143] Although it is still unknown whether variant SCLC depends on *Neurod1* in a similar manner as classic SCLC depends on *Ascl1*, it is conceivable that tumors may be addicted to their respective driver transcription factors. In addition to the variant morphology, some tumors in the RPM mice

were negative for both ASCL1 and NEUROD1, a phenotype also observed in human tumors and human SCLC cell lines.[9,138] The significance and the molecular mechanisms underlying these "double negative" SCLC cells are currently unclear. It is tempting to speculate that the "double negative" histological phenotype associated with high *MYC* expression may represent the most de-differentiated state of tumors and that MYC may be causally involved. However, whether/how MYC may control the differentiation of SCLC into the variant or "double negative" morphologies is yet to be fully understood.

Consistent with the human disease, MYC-driven murine SCLC is initially highly sensitive to the standard-of-care chemotherapy. In RPM mice, chemotherapy induces significant cell death, reduces tumor burden and increases survival. However, relapse is so rapid that animals only gain ~10 d in survival benefit compared with untreated animals.[9] We initially found that the AURK inhibitor alisertib is effective in *MYC*-driven human SCLC cell lines[10] and notably, mice with MYC-driven tumors had a significant increase in survival when alisertib was coupled with chemotherapy.[9] In line with these findings in GEMMs are reports from clinical trials for second-line SCLC treatment, which were designed to exploit such vulnerabilities discovered *in vitro*: 1) a phase II study investigating alisertib in pre-treated SCLC[144] and 2) a recent phase II trial of relapsed SCLC patients given paclitaxel with or without alisertib (NCT02038647). In the unselected cohort of SCLC patients, the addition of alisertib to taxane treatment did not significantly prolong survival.[145] However, evaluation of MYC expression by IHC revealed that in patients with high MYC levels, survival was significantly increased with the alisertib/paclitaxel combination compared with patients treated with paclitaxel only. This illustrates that *MYC* status may be a predictor of both SCLC subtype and therapeutic vulnerability in patients, and therefore, preclinical studies using these different GEMMs may be able to predict the outcome of clinical trials.

As mentioned above, *MYCN* is amplified in a small subset of SCLC patients and cell lines, but has not yet been clearly linked with variant or classic histopathology or to therapeutic response. Currently no SCLC mouse models driven by overexpression of *Mycn* have been published. However, David MacPherson has reported the generation of *Rb1/Trp53/Mycn* conditional mice (personal communication) and comparisons to existing GEMMs are awaited. It will be important to determine whether *Mycn*-driven SCLC GEMMs have similar or distinguishing molecular and phenotypic characteristics compared with *Mycl/Myc*-driven tumors.

Conclusions

Currently SCLC is treated as a homogeneous disease based on the stage at diagnosis.[146] However, growing evidence of heterogeneity among SCLC patient tumors, cell lines and GEMMs based on histology[147-149] and genomics[9,138,150] indicates that a more differentiated treatment stratification would likely prove beneficial. Deregulated MYC signaling may play a central role in the molecular and histological heterogeneity observed in SCLC. Apart from their association with histological subgroups, the central role of MYC family members in processes governing tumor maintenance offers new opportunities for targeted therapy, for example by exploitation of paralog-specific synthetic lethal interactions. As discussed above, the majority of functional characterization and identification of synthetic lethality has been performed for MYC and -to a lesser extent- for MYCN. In contrast, despite being the most frequently altered MYC family member in SCLC and the finding that *Mycl* inactivation leads to tumor suppression in mice,[30] very limited knowledge is available regarding MYCL, its basic biology, its role in cancer and potential synthetic lethal partners, and this deserves intensified investigation.

In the past, in-depth molecular analyses of human SCLCs were limited by the lack of tumor tissue due to the infrequent availability of biopsy samples. The improved development of patient-derived circulating tumor cell and tissue xenograft models (CDX and PDX, respectively) may be a means to broaden the scope of human tumor models. Nevertheless, GEM models are indispensable in complementing CDX/PDX studies. Because they provide autochthonous tumors in an immune-competent background, GEMMs allow the investigation of treatments in relation to an intact tumor microenvironment and offer the possibility to study immune-checkpoint modulation in conjunction with other treatment approaches.

Overall, several central questions remain open and need to be addressed: Are synthetic lethal interactions with *MYC* overexpression also relevant to *MYCN* and/or *MYCL*? What is the best strategy to discover novel synthetic lethal interactions in *MYCL* and *MYCN*-driven SCLC? How well do findings in *in vitro* and *in vivo* models translate into the clinic? To answer these questions, the investigation of human SCLC samples will certainly remain a cornerstone. However, integrative analysis of orthogonal tumor models including cell lines, GEMMs and CDX/PDXs will be an essential factor to gain biological insights and develop novel treatment strategies. Given the important phenotypic differences associated with different MYC family members in GEM models, it will be important to characterize MYC status in patients and model systems. A more complete understanding of the role of MYC family members in tumor phenotype and drug response ultimately holds great promise for improved outcome for patients with SCLC.

Disclosure of potential conflicts of interest

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