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MYC as a target for cancer treatment

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ABSTRACT

The MYC gene which consists of 3 paralogs, C-MYC, N-MYC and L-MYC, is one of the most frequently deregulated driver genes in human cancer. Because of its high prevalence of deregulation and its causal role in cancer formation, maintenance and progression, targeting MYC is theoretically an attractive strategy for treating cancer. As a potential anticancer target, MYC was traditionally regarded as undruggable due to the absence of a suitable pocket for high-affinity binding by low molecular weight inhibitors. In recent years however, several compounds that directly or indirectly inhibit MYC have been shown to have anticancer activity in preclinical tumor models. Amongst the most detailed investigated strategies for targeting MYC are inhibition of its binding to its obligate interaction partner MAX, prevention of MYC expression and blocking of genes exhibiting synthetic lethality with overexpression of MYC. One of the most extensively investigated MYC inhibitors is a peptide/mini-protein known as OmoMYC. OmoMYC, which acts by blocking the binding of all 3 forms of MYC to their target promoters, has been shown to exhibit anticancer activity in a diverse range of preclinical models, with minimal side effects. Based on its broad efficacy and limited toxicity, OmoMYC is currently being developed for evaluation in clinical trials. Although no compound directly targeting MYC has yet progressed to clinical testing, APTO-253, which partly acts by decreasing expression of MYC, is currently undergoing a phase I clinical trial in patients with relapsed/refractory acute myeloid leukemia or myelodysplastic syndrome.

Introduction

MYC is one of the most widely investigated cancer-causing genes, being implicated in the formation, maintenance and progression of several different cancer types [1–3]. The MYC gene family consists of 3 members, C-MYC, L-MYC and N-MYC, all of which belong to the superfamily of basic helix-loop-helix leucine zipper (bHLHLZ) DNA binding proteins [1–3]. MYC proteins largely function as transcriptional modulators, regulating genes involved in several different cellular processes including cell growth, cell cycle, differentiation, apoptosis, angiogenesis, metabolism, DNA repair, protein translation, immune response and stem cell formation [1–4]. The specific effects exerted by MYC appear to be at least partly dependent on the cellular context as well as possibly on the cellular levels of MYC protein [5,6].

Overall, MYC proteins are believed to regulate greater than 15% of the human genome [7–10] and control transcription mediated by all 3 RNA polymerases, i.e., RNA polymerase I, II and III [11–13]. Between 2000 and 4000 different genes were found to be regulated by MYC [11,14]. Because of its ability to regulate widespread gene expression, MYC is sometimes referred to as a "master gene regulator". However, whether MYC is a general or specific regulator of gene expression is still unclear.

Although regulation of transcription is the best-established function of MYC, the oncoprotein has also been reported to play a role in DNA synthesis [15] and protein translation [16]. A specific protein potentially important in MYC-mediated tumorigenesis found to be regulated at the translational stage, at least in a liver cancer model, is the immune checkpoint molecule, programmed-death-ligand 1 (PD-L1) [17]. PD-L1, following binding to its receptor PD-1, promotes immune evasion, a process that is important in MYC-mediated tumorigenesis (see below).

Multiple studies extending back over several decades have shown that MYC is causally involved in the growth, progression and maintenance of cancers of diverse origins [1–3]. Indeed, dysregulation of MYC gene expression is believed to occur in up to 70% of human cancers [18,19]. Because of its widespread deregulation and causal role in cancer formation and/or progression, targeting MYC is a potential new

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strategy for treating malignancy. However, MYC, like RAS and TP53 (p53), has historically been regarded as an "undruggable" or a difficult to drug gene.

Despite been traditionally referred to as "undruggable", considerable progress has recently been made in the development of MYC inhibitors. Indeed, several compounds that directly or indirectly target MYC have recently been reported to possess anticancer activity in preclinical tumor models. The aim of this article is to critically review these developments and discuss the current status of MYC inhibitors for cancer treatment. First, however, we briefly review the structure of the MYC protein, its mode of action and its deregulation in malignancy. As C-MYC is the most widely deregulated form of MYC in cancer and the most extensively investigated, most of the article will focus on it. In this article, MYC will refer to C-MYC unless otherwise stated.

Structure of MYC protein

All 3 MYC proteins have essentially the same multi-domain-type structure and as mentioned above, all belong to the superfamily of bHLHLZ transcription regulators [1–3]. All contain 3 main domains, an N-terminal region containing the transactivation domain, a central region implicated in nuclear localization as well as stability control and a C-terminal region involved in interaction with its obligate partner, MAX as well as binding to DNA [20]. Dimerization with MAX is essential for MYC to regulate gene transcription [1].

A characteristic of the 3 MYC proteins is the presence of multiple highly conserved sequences, known as MYC or M boxes (MB) [20,21]. Five MB are present in L-MYC and 6 in both C- and N-MYC [21]. Extending from the N-terminal region, these 6 MB in C- and N-MYC are dubbed MB0, MBI, MBII, MBIIIa, MBIIIb and MBIV. L-MYC however, lacks the MBIIIa box. MB0, MBI and MBII are located within the transactivation domain of the MYC proteins, while the other M boxes are present in the central region of the proteins (Fig. 1) [21].

The different MB domains bind to different proteins and thus have distinct roles in MYC functioning. MB0 interacts with the TFIIF transcription elongation complex to regulate transcription and has been implicated in accelerating tumor growth [21,22]. MBI acts as a phosphodegron and is involved in the ubiquitination and proteasomal degradation of MYC (e.g. by FBW7) [23]. MBII is also required for MYC-mediated gene transcription. Activation of transcription occurs following MYC interaction with the TRRAP–HAT complexes [24], while repression can occur following binding to the G9a histone methyltransferase [25]. The MBII domain is also necessary for tumor initiation and in combination with MB0 was shown to be responsible for the cancer-inducing effects of MYC [21]. The MBIIIa domain has been reported to play a role in gene repression and regulation of apoptosis [26], while MBIIIb binds to the WD40-repeat protein WDR5 [27]. Interaction with WDR5 is necessary for MYC to attach to chromatin [27]. Finally, MBIV has been shown to play a role in chromatin binding, induction of apoptosis, G2 cell arrest and interaction with host cell factor-1 (HCF-1) [28]. The latter protein has been postulated to participate in cell cycle regulation [29].

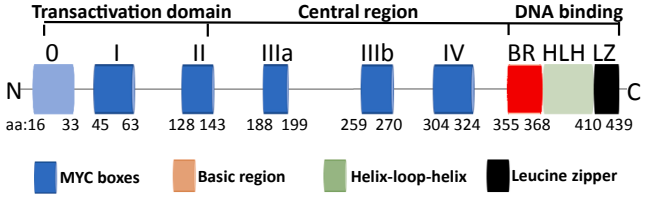

Fig. 1. Domain structure of C-MYC protein showing the transaction domain, MYC boxes, central region, basic region, helix-loop-helix domain and leucine-zipper domain.

Mode of action of MYC

Following MYC-MAX interaction, the dimeric complex preferentially binds to DNA response elements, known as enhancers or E-boxes containing the consensus DNA sequence, CACGTG (or related sequences) [30,31]. Although these sequences are abundant across the genome, they are particularly enriched at promoter sites of genes involved in regulating cell proliferation. Binding to these sites result in altered gene expression, with some genes being upregulated and others downregulated [25,32–34]. At least some of the genes downregulated result from MYC interacting with the zinc finger protein MIZ1 [34].

While binding of the MYC-MAX heterodimer to E-Box sequences in the regulatory regions of target genes appears to be the primary mechanism by which MYC regulates gene expression, MYC has also been reported to attach to non-E-box DNA regions [35]. Thus, MYC binds to the promoter on ribosome protein genes although such sites lack E boxes [36]. Furthermore, in some situations, MYC appears to be capable of acting independently of MAX. For example, in N-MYC amplified neuroblastomas, N-MYC was found to bind to p53, resulting in the regulation of novel p53 target genes [37].

Mechanisms activating MYC in cancer

In healthy adult tissues, expression of MYC is tightly controlled. However, in several different types of human cancers, MYC is overexpressed or structurally altered. Indeed, as mentioned above, such alterations in MYC genes have been reported to occur in approximately 70% of human malignancies [1–3]. Mechanisms giving rise to these alterations include gene amplification, chromosomal translocation, retroviral promoter insertion, activation of super enhancers, enhanced cell signalling, altered protein degradation and mutation (Table 1) [38–43].

Of these mechanisms, gene amplification appears to be one of the most frequent mechanisms for MYC activation in solid human cancers. Recent studies by The Cancer Genome Atlas (TCGA) network using approximately 9000 samples from 33 tumor types showed that 28% of human cancers have amplification of at least one of the MYC genes [38]. Amplification of c-MYC occurs most frequently in ovarian cancer (64%), esophageal cancer (45.3%) squamous lung cancer (37.2%) and breast cancer (30%) [38]. Prevalence of amplification in a specific cancer type, however, may depend on its molecular subtype. For example, in the basal/triple-negative form of breast cancer (TNBC), the most difficult form of breast cancer to treat, C-MYC is amplified in 34–44% of samples in contrast to only 7–13% in luminal A-type (ER/PR-positive) cancers [44] (tumor subtype with a favorable outcome).

In contrast to c-MYC, neither N-MYC nor L-MYC are frequently amplified in cancer (<7% overall) [38]. N-MYC however, can be amplified or overexpressed in tumors with neuroendocrine features such as neuroblastoma, retinoblastoma, medullablastoma, small-cell lung cancer and prostate cancer (neuroendocrine type) [45], while L-MYC was reported to be amplified in a small number of small-cell lung cancers [46].

While amplification of MYC is mostly found in epithelial-type

Table 1
Mechanisms of MYC activation in cancer.

Mechanism	Tumors	Refs.
Amplification	Ovarian, esophagus, uterine, breast	[38]
Translocation	B-cell lymphomas, including Burkitt lymphoma	[39]
Enhancer activation	B-cell lymphomas	[40]
Mutation	B-cell lymphomas	[41]
Altered protein stability	Multiple cancer types	[43]
Increased signalling	Multiple cancer types	[48–50]
Loss of p53	Mammary stem cells	[51]

tumors, activation by translocation is predominantly present in hematological malignancies. Burkitt lymphoma was the first cancer identified with such translocations. In this malignancy, 3 different MYC translocations have been identified, resulting in joining the long arm of chromosome 8 to the immunoglobulin heavy locus [IGH; t(8;14)(q24;q32)], to the kappa light chain locus [IGK; t(2;8)(p11;q24)] or to the lambda light chain locus [IGL; t(8;22)(q24;q11)] (39). The t(8;14)(q24;q32) translocation is found in approximately 80% of patients while the t(2;8)(p11;q24) and t(8;22)(q24;q11) translocations occur in approximately 15% and 5%, respectively. Other lymphomas with MYC translocations include diffuse large B cell lymphoma (5–15%), low grade follicular lymphoma (2–10%) and mantle cell lymphoma (<10%) [39]. Finally, MYC was found to be translocated in 36% of patients with multiple myeloma [47].

In cancers lacking MYC genetic alterations such as amplification or translocation, MYC mRNA and protein expression and/or stability can be increased as a result of enhanced signalling via the ERK, PI3K or β-catenin signalling pathways [48–50]. In addition to these signalling mechanisms, loss of p53 function was recently found to activate c-MYC [51]. Finally, MYC protein stability can be regulated by various post-translational modifications (phosphorylation, acetylation, sumoylation) as well as by E3 ubiquitin ligase recruitment (via FBW7 or SKP2) and proteasomal degradation [43,52].

Unlike other cancer-causing genes such as RAS and TP53, MYC genes are rarely activated by mutation in its coding sequence. This is consistent with the multiple observations showing that deregulation of MYC expression rather than the acquisition of neomorphic properties is the main mechanism by which MYC drives cancer growth [3]. MYC mutations however, are found in a subset of Burkitt lymphomas and diffuse large B cell lymphomas [41].

Role of MYC in tumorigenesis

Although decades of research have shown that deregulation of MYC is causally involved in cancer formation, maintenance and progression, the precise mechanism by which the oncoprotein plays a role in these processes is still unclear. Potential mechanisms by which it may do so include enhancing cell proliferation, inhibition of cell death, modulating metabolism, promoting angiogenesis and regulating stem cell formation [1–3]. In most if not all situations where MYC is involved in carcinogenesis, it does not act alone but in collaboration with other cancer causing genes, especially mutant RAS and mutant TP53 [53,54].

In addition to these cell intrinsic effects, MYC has also been shown to alter the tumor microenvironment and promote immune evasion [4,17,55–58]. Thus in a mutant KRAS mouse model of liver cancer, Xu et al [17] showed that upregulation of MYC resulted in an influx of inflammatory cells such as neutrophils and macrophages into tumors. This increased uptake of inflammatory cells led to enhanced angiogenesis, proliferation, metastasis and therapy resistance. In addition, upregulation of MYC resulted in increased expression of the checkpoint inhibitor, PD-L1 in tumor cells. Binding of PD-L1 to its receptor PD-1 on T cells resulted in immune suppression that in the liver cancer model investigated led to increased metastasis. Similarly, in other cancer models systems, upregulation of MYC was also shown to cause alterations in tumor inflammatory cells and result in immune suppression [4,56,58]. The specific effects of MYC on the tumor environment however, seem to vary depending on the specific tumor type. While MYC activation in a lung cancer model caused B cells exclusion [4], it led to B cell influx into the tumor periphery in a pancreatic cancer model [58]. As with the intrinsic effects of MYC mentioned above, the extrinsic effects of the oncoprotein on immune cell infiltration, in a least some situations, also depend on co-operating with mutant RAS [4,58].

In summary, it thus seems that MYC can induce tumorigenesis via multiple mechanisms, likely related to its broad ability to regulate expression of a wide number of different genes.

Consistent with MYC being a driver of tumorigenesis, suppression of its expression or inhibition of its function can reverse tumorigenesis [59–63]. This regression of tumorigenesis is mediated by reversal of the carcinogenic processes mentioned above, including, some or all of the following: promotion of cell cycle arrest, triggering of apoptosis, induction of senescence, promotion of differentiation, inhibition of angiogenesis, extrusion of tumor infiltrating inflammatory cells such as macrophages and neutrophils, influx of T and NK cells, reduced levels of PD-L1 and upregulation of an anti-tumor immune response [4,55–58]. Indeed, in some situations, even brief or partial suppression of MYC has been shown to reverse tumorigenesis [4,58,59]. For example, in mouse models of pancreatic and lung adenocarcinoma, deactivation of MYC triggered tumor regression after a few hours [4,58].

MYC as a therapeutic target for cancer

The experiments showing that turning off expression of MYC reverses tumorigenesis provides proof of principle that pharmacological targeting of the oncoprotein should block or decrease tumor cell growth. However, specific pharmacological targeting of MYC with low molecular weight compounds is difficult, as the protein possesses a largely intrinsically disordered structure, lacking a hydrophobic pocket or groove into which such compounds could bind with high affinity. Furthermore, MYC lacks catalytic activity and therefore, unlike several other cancer driver oncoproteins (e.g., EGFR, HER2, BRAF), it cannot be blocked with low molecular weight enzyme inhibitors. Finally, as MYC is located in the nucleus, it is difficult to target with large molecules such as the currently available monoclonal antibodies.

Despite these challenges, several different pharmaceutical-based strategies have recently been described for targeting MYC with the aim of blocking tumor growth [60–64] (Table 2). Of these, the most investigated are inhibition of MYC-MAX interaction, prevention of MYC expression and targeting of genes exhibiting synthetic lethality with overexpression of MYC. The current status of these different approaches is discussed below.

OmoMYC: The prototype and lead MYC antagonist

OmoMYC is a 90-amino acid peptide/mini-protein that mimics the bHLHLZ domain of C-MYC [63]. However, it differs from the naturally occurring bHLHLZ domain of MYC in containing 4 point mutations in its leucine zipper domain that were included to alter its dimerization properties [64]. OmoMYC appears to antagonize MYC and thus inhibit cancer cell growth *via* at least 2 mechanisms [65–69]. Firstly, OmoMYC forms homodimers with itself that prevent MYC-MAX heterodimers interaction with DNA and inhibition of MYC-mediated transcriptional [63–65,67]. Secondly, although OmoMYC interacts with both MYC and MAX it preferentially binds to the latter [69]. The binding to MAX

Table 2
Potential strategies with examples in targeting MYC for the treatment of cancer.

General mode of action	Example(s)	Refs.
Blocking MYC-MAX interaction	OmoMYC, 10054-F4, 10074-G5, KJ-Pyr-9, MYCMI-6, MYCi361 and MYCi975	[44,63,74–83]
Blocking MYC-MAX from binding to DNA/ preventing expression of MYC	OmoMYC, BET inhibitors (JQ1), CDK7 inhibitors (THZ1), ME4, G9a histone transferase inhibitors (UNCO638), MYC-N3A, cardiac glycosides (bufalin, oubain), cytoskeletal disrupters (dolastatins), G-quadraplex inhibitors (APTO-253)	[63–68,84–98]
Exploitation of synthetic lethal partners for MYC	Inhibitors of CDK1, PIM1 kinase, PARP, aurora B kinase, TRAIL	[107–113]
Preventing MYC translation	Dactolisib (BEZ235), silvestrol	[114,115]
Stabilizing MAX homodimers	NSC13728, KI-MS2-008	[116,117]

represses MYC-induced transcription by replacing MYC-MAX heterodimers with OmoMYC-MAX heterodimers [69]. Although OmoMYC inhibits MYC-mediated gene transactivation, it does not affect the MYC-MIZ-dependent promoter binding and gene repression [67].

Due to its size and peptide structure, OmoMYC was originally believed to be unsuitable for uptake and penetration into cancer cells. Its anticancer activity was therefore initially investigated as a switchable transgene. Using this approach, the OmoMYC was found to exhibit anticancer activity in several different animal tumor models (for review, see ref. 63). Consistent with the ability of MYC to promote immune evasion (see above), OmoMYC appears to induce tumor regression at least in part by altering the tumor microenvironment and inducing an anti-tumor immune response. Thus, Wang et al [72] found that intratumor injection in a TNBC model with OmoMYC linked to a penetrating Phylomer resulted in downregulation of the negative immune checkpoint protein, PD-L1 while Beaulieu et al [71] reported that administration of purified OmoMYC mini-protein to a mouse model of non-small cell lung cancer led to recruitment of T lymphocytes to the tumor site. Importantly, from a clinical point of view, only mild and fully reversible toxic side effects were observed with OmoMYC in preclinical studies reported to date.

The ability to systemically administer OmoMYC when combined with its ability to inhibit the growth of diverse experimental tumor types and cause minimal side effects on normal tissues [66,70–72] should now lead to the testing of OmoMYC in clinical trials [73]. However, since OmoMYC is a peptide/small protein, it is potentially susceptible to degradation in vivo [69]. It structure may thus have to be modified to prevent such degradation from occurring.

Blocking MYC-MAX interaction with low molecular weight inhibitors

Using high-throughput screening methodologies, several low molecular weight compounds have been identified that block the interaction between MYC and MAX [44,74–83] (Table 2). Consistent with their ability to interfere with MYC-MAX heterodimerization, these compounds have been shown to inhibit cancer cell proliferation in a diverse range of model tumor systems [43,74–83]. The compounds listed in Table 2 however, vary widely in structure, affinity for MYC and ability to inhibit tumor cell proliferation (i.e., have varying IC50 values). Few of the compounds have been investigated for anti-cancer activity in more than one type of animal model.

Amongst the more promising low molecular weight MYC antagonists are KJ-Pyr-9 [81], MYCMI-6 [43,82] and MYCi975 [83]. All of these compounds have been shown to inhibit MYC-MAX interaction and decrease cell proliferation in a broad range of cancer cell lines, usually with IC50 values < 10 μM. In addition, all have been shown to exhibit anticancer activity in *in vivo* MYC-dependent tumor models. Similar to OmoMYC, administration of MYCi975 was found to result in remodelling of the tumor environment and increased tumor uptake of immune cells (e.g., $CD3^+$ T cells, B cells and NK cells) [83]. Furthermore, combined treatment with MYCi975 and immunotherapy (pembrolizumab) resulted in synergistic tumor growth inhibition in a syngeneic prostate cancer model. Importantly, as with OmoMYC, treatment with MYCi975 did not appear to cause major short-term toxicity [83]. Outstanding questions with the MYC-MAX antagonists relate to their specificity and potential toxicity in vivo, especially long-term toxicity.

Preventing expression of MYC

Rather than directly inhibiting MYC function as described above, another widely investigated approach for targeting MYC involves blocking its expression. While this is an active area of investigation, it is unlikely that any of the compounds discussed below specifically downregulate only MYC. Thus, the potential exists for off-target effects and adverse effects *in vivo*. Although multiple different strategies are undergoing evaluation for silencing MYC expression, two of the more widely studied involve using inhibitors of bromodomain and extra-terminal domain (BET) proteins and use of compounds that stabilize G-quadruplex (G4) motifs in the MYC promoter.

BET inhibitors

BET proteins regulate transcription by associating with acetylated chromatin and facilitating the recruitment of transcriptional factors [84]. The family consists of 4 members; BRD2, BRD3, BRD4 and bromodomain testis-specific proteins. BRD4 was recently found to bind to the MYC promoter and regulate its transcription [84]. Several BET inhibitors, especially the BRD4 inhibitor JQ1, have been shown to downregulate MYC and suppress tumor growth in a diverse range of animal models exhibiting MYC activation [85–89]. However, while treatment with BET inhibitors in specific tumor models resulted in MYC downregulation, this association was not consistent across different tumor types [90]. Furthermore, BET inhibitors were found to downregulate expression of genes other than MYC such as the transcriptional factor, FOSL1 [90] and the signalling protein, ERK1 [91]. Thus, the precise role of MYC downregulation in mediating the anticancer activity of BET inhibitors is unclear and likely to vary, depending on the tumor cell type or cell context. Although several BET inhibitors are currently being investigated in clinical trials, preliminary results suggest that when used alone, the available compounds have limited efficacy as anticancer drugs [92].

Stabilization of G4 structures

G4 motifs are secondary DNA structures consisting of ≥ 3 guanine tetrads layers that are located in the promoter and 5′ untranslated regions of highly transcribed genes such as MYC (for review, see refs. 93,94). G4 structures can either positively or negatively regulate gene expression. A specific G4 structure in the nuclease hypersensitive element III region of the MYC promoter was found to downregulate its expression. Consequently, several compounds were identified that bound to and stabilized this structure, resulting in decreased expression of MYC. Consistent with the decreased expression of MYC, several of the compounds (GQC-05, SYUIO-05, DC-34, APTO-253) were shown to inhibit cell proliferation or induce apoptosis in cancer cell lines [93,95]. Of these, APTO-253 is the most investigated.

Using acute myeloid leukemia (AML) cell lines, APTO-253 was found to stabilize the G4 structure in the MYC promoter, decrease expression of MYC, induce cell cycle arrest and trigger apoptosis [95]. In addition, the compound has been shown to inhibit tumor growth in a wide range of *in vitro* and *in vivo* models as well as freshly isolated leukemic cells from bone marrow samples [95,96]. These findings led to a phase I clinical trial in which APTO-253 was investigated in 32 patients with diverse metastatic cancers (ClinicalTrials.gov Identifier: NCT123226). Overall, the drug was found to be well tolerated, with fatigue as the only drug-related adverse event reported to occur in greater than 10% of patients [97]. In 21 patients who completed 2 cycles of treatment, stable disease occurred in 5 (23.8%) with durations ranging from 3.6 to 8.4 months. APTO-253 is currently undergoing testing in a further phase I clinical trial involving patients with AML or myelodysplastic syndrome (MDS) (ClinicalTrials.gov Identifier: NCT02267863).

It is important to state that while APTO-253 decreases expression of MYC, the compound has also been shown to stabilize G4 structures in the *KIT* promoter, induce DNA damage and increase expression of the transcriptional factor KLF4 (involved in the regulation of proliferation, differentiation, apoptosis and somatic cell reprogramming) [98,99]. Whether any of these processes is secondary to the downregulation of MYC is unknown. Furthermore, the relative contribution of these different effects to the antiproliferative/pro-apoptotic actions of APTO-253 is unclear.

Other compounds downregulating MYC expression

Other compounds found to downregulate expression of MYC in model systems include the CDK7 inhibitor, THZ1 in MYC-driven tumors such as small cell lung cancer, neuroblastoma and TNBC [100–102], ME47 in breast cancer [103], MYC-N-A3 in neuroblastoma [104], cardiac glycosides (bufalin, oubain) in myeloma cells [105] and cytoskeletal disruptors (jasplakinolide and dolastatin) in myeloma cells [105].

Identification of synthetic lethal partners for MYC overexpression

A further potential approach for targeting MYC involves exploiting the concept of synthetic lethality. Synthetic lethality occurs when a defect (e.g., mutation) in either of 2 genes has little impact on cell viability but defects in both genes leads to cell death. The concept of synthetic lethality has been most successfully exploited in the use of PARP inhibitors for the treatment of patients with BRCA1/2 mutated ovarian and breast cancer [106]. In these cancers, the process of synthetic lethality is dependent on the inability of BRCA-mutated cancers to carry out homologous recombination repair of DNA while the PARP-mediated DNA repair process is blocked by specific inhibitors [106].

In the context of aberrant MYC expression, targeting a potentially synthetic lethal protein should theoretically kill only the malignant cells with aberrant MYC expression and spare normal cells. Goga and co-workers were one of the first to explore the synthetic lethality concept for targeting MYC for cancer treatment [107,108]. Using transgenic MYC-driven models of liver cancer, lymphoma or TNBC, these authors reported a synthetic lethal interaction between MYC overexpression and inhibition of CDK1, i.e., treatment of these MYC-dependent models with CDK1 inhibitors (purvalanol and roscovitine) decreased tumor growth and prolonged survival. These preliminary findings however, do not appear to have been further investigated, possibly because the CDK inhibitors used, lacked specificity for CDK1 and were subsequently found to be toxic [109].

More recently, overexpression of MYC was found to be synthetic lethal with PIM1 kinase inhibitors (also in TNBC) [110], with PARP inhibitors (in different cancer types) [111], with aurora B kinase inhibitors in lymphomas [112] and with TRAIL-induced apoptosis (in brain metastasis from breast cancer [113]. As with CDK1 inhibition, these results also have not been confirmed in additional model systems.

Other potential approaches for targeting MYC

Other potential strategies for targeting MYC for cancer treatment include inhibiting MYC translation [114,115], stabilizing MAX homodimers [116,117] and blocking interaction between MYC and interacting proteins other than MAX. As mentioned above, MYC interacts with several different proteins, in addition to MAX. Thus, it regulates transcription by interacting with co-regulatory proteins such as the TRRAP–HAT complexes [24] and the G9a histone methyltransferase [25]. Preliminary data has shown that low molecular weight inhibitors of G9a such as UNC0642 or A366 decreased proliferation of breast cancer cell lines *in vitro* [25]. Finally, as the oncogenicity of MYC depends on its interaction with WDR5, blocking this interaction is a further potential approach for targeting MYC [118].

Conclusion

It is clear from above that inhibiting MYC for cancer treatment is a highly active area of preclinical research. Indeed, as indicated, abrogating MYC activity or expression has been shown to result in reduced tumor growth in a diverse range of preclinical tumor models. Furthermore, based on available evidence, it appears that at least some of the MYC inhibitors mentioned above (e.g., OmoMYC) cause minimal toxicity to normal cells. However, it is important to point out that with the exception of OmoMYC, few of the findings with anti-MYC compounds have been reproduced by independent investigators or in multiple model systems. Furthermore, the specificity of the available compounds for MYC is unclear. For example, it is unclear if compounds preventing MYC-MAX interaction also target the bHLHLZ domain present on related transcriptional factors. A problem with available compounds preventing MYC expression is that they are unlikely to be specific in only downregulating MYC. Indeed, as mentioned above, the BET inhibitor, JQ1 has been shown to downregulate expression of multiple genes.

Future work should continue to investigate the most promising compounds discussed above (e.g., OmoMYC, MYCi975) in additional animal models to further establish efficacy, identify potential predictive biomarkers and assess toxicity. Only when confirmed evidence of efficacy and lack of serious toxicity is seen in several different animal model systems, can these inhibitors move into clinical trials. Finally, since there is increasing evidence that MYC deregulation depresses the immune response to tumors [4] and preliminary evidence that some MYC inhibitor, (i.e., OmoMYC and MYCi361), acts at least in part, by inducing an immune response [64], future work should establish the possible generality of MYC inhibitors for enhancing anti-tumor immunity.

Conflicts of Interest

MJD, SO'G and MT declare no conflicts of interest. JC has received honoraria from Eisai, Amgen, Puma Biothechnology, Seattle Genetics, Boehringer Ingelheim, Pfizer, Vertex and Genomic Health. He has acted in an advisory/consulting role to Eisai, Puma Biotechnology, Boehringer Ingelheim, Pfizer, Vertex, Roche. He also serves on the Speakers' Bureau for Pfizer, Eisai and Genomic Health and has received Research Funding from Roche, Eisai, Boehringer Ingelheim and Puma Biotechnology. In addition, he has received Travel, Accommodations, Expenses from MSD, Pfizer, Roche, AstraZeneca, Abbvie and Novartis. Finally, he is an employee of OncoMark, has stocks in OncoMark and is named on patent WO2020011770 (A1) - A method of predicting response to treatment in cancer patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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