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The *MYC* oncogene — the grand orchestrator of cancer growth and immune evasion

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Abstract

The *MYC* proto-oncogenes encode a family of transcription factors that are among the most commonly activated oncoproteins in human neoplasias. Indeed, MYC aberrations or upregulation of MYC-related pathways by alternate mechanisms occur in the vast majority of cancers. MYC proteins are master regulators of cellular programmes. Thus, cancers with MYC activation elicit many of the hallmarks of cancer required for autonomous neoplastic growth. In preclinical models, MYC inactivation can result in sustained tumour regression, a phenomenon that has been attributed to oncogene addiction. Many therapeutic agents that directly target MYC are under development; however, to date, their clinical efficacy remains to be demonstrated. In the past few years, studies have demonstrated that MYC signalling can enable tumour cells to dysregulate their microenvironment and evade the host immune response. Herein, we discuss how MYC pathways not only dictate cancer cell pathophysiology but also suppress the host immune response against that cancer. We also propose that therapies targeting the MYC pathway will be key to reversing cancerous growth and restoring antitumour immune responses in patients with *MYC*-driven cancers.

The *MYC* oncogene (also known as c-MYC) is part of a superfamily of genes with products that are among the most commonly activated in human cancers[1–4]. MYC is a master regulator of multiple biological programmes and mediates much of its function primarily

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Author contributions

R.D. and D.W.F. researched data for this manuscript. All authors contributed to the discussion of content and preparation of the manuscript.

Competing interests

D.W.F. is a consultant for Revolution Medicines, a company developing MYC pathway therapies, co-founder of Bachus and Molecular Decisions, and has had advisory roles for American Gene Technologies, Geron, Moderna and Regulus. The other authors declare no conflicts of interest.

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as a transcription factor that regulates the expression of thousands of genes, either directly or indirectly[5,6]. In addition, MYC exerts multiple biological effects on cellular programmes that influence both the cell-intrinsic biology as well as the host immunity and tumour microenvironment (TME).

MYC has two paralogues: *MYCL* and *MYCN*. The initially held view was that MYC is ubiquitously involved in human cancers (both haematological and solid), whereas L-MYC is associated with small-cell lung cancer and N-MYC with neuroblastoma. However, in the past few years, insights gained from genome-sequencing studies show a broader role for both N-MYC[7–10] and L-MYC[11–13] in many other cancers[3,4] (FIG. 1a). Thus, when considering the entire MYC family, most human cancers harbour the genetic activation of one of its members[1–4].

A multitude of reports have documented that MYC overexpression can cause tumorigenesis. In a landmark study, Adams et al.[14] demonstrated that transgenic overexpression of *Myc* in mice was sufficient for B cell lymphomagenesis. Subsequently, many other investigators documented that *MYC* overexpression can causally induce other types of cancer in humans[15–17]. Moreover, the use of conditional transgenic mouse models has enabled a refined understanding of how MYC activation causes tumorigenesis and how its inactivation can elicit tumour regression. Two general approaches have been used to modulate MYC in preclinical studies: conditional regulation of the expression of a *MYC* transgene using the *Tet* system[18–23] and conditional expression of a synthetic MYC inhibitor, Omomyc[24–26]. In these conditional transgenic mouse models, *MYC*-induced tumours regress rapidly and dramatically upon MYC inactivation[18–23]. Tumour regression occurs even without influencing physiological endogenous MYC expression or function, in a phenomenon referred to as oncogene addiction[27]. This phenomenon suggests that targeting MYC could be an effective approach to treat some human cancers. To date, however, no drug has demonstrated efficacious therapeutic targeting of MYC or the MYC pathway, although promising candidates are in development.

Cancer is a complex process that requires a multitude of genetic events and the acquisition of the hallmarks of cancer[28]. Importantly, MYC activation can contribute to many of these hallmarks, including proliferation, self-renewal, cell survival, genomic instability, metabolism and invasiveness as well as angiogenesis and immune evasion[29–31]. Thus, MYC seems to have crucial effects in newly transformed cancer cells and also enables an evolving tumour to remodel the TME and evade the host immune response[32,33]. Details on how MYC biologically modulates cancer cell-intrinsic programmes of cellular proliferation, differentiation, survival and death have been described elsewhere[34–38].

In this Review, we focus on the broad clinical importance of MYC and MYC-related oncogenic signalling in the pathogenesis of human cancers. In particular, we provide evidence that MYC is a major driver of human cancer through its effects on tumour cells and also by enabling cancers to evade host immune surveillance. We summarize the studies that have demonstrated rapid and sustained tumour regression in *MYC*-driven cancers upon MYC inactivation as a consequence of oncogene addiction. Finally, we provide a rationale for and examples of therapeutic strategies targeting the MYC pathway. We conclude that

MYC signalling is one of the most important, yet to be successfully targeted, oncogenic pathways in human cancer; thus, mechanistic insights into the tumorigenic roles of this gene family will be key to developing efficacious therapies for cancer.

MYC is often activated in human cancers

Genetic alterations affecting the *MYC* proto-oncogenes and the MYC-related signalling pathways are among the most common in human cancers[1–4] (FIG. 1). MYC can be activated in cancers through multiple genetic, epistatic, epigenetic and post-translational mechanisms (FIG. 2), which vary between cancer types.

Genomic alterations, including gene amplification, chromosomal translocations and mutations, can increase *MYC* expression[1,4,39] (FIG. 2a). A pan-cancer assessment of alterations in 33 human cancer types conducted as part of The Cancer Genome Atlas project revealed that *MYC* or its paralogues *MYCL* or *MYCN* are amplified in 28% of tumours[3]. An analysis encompassing 17 cancer types also showed that *MYC* is frequently amplified in extrachromosomal DNA during tumour evolution[40,41]. These amplifications can directly lead to *MYC* overexpression or, indirectly, to the activation of genes involved in the MYC pathway as demonstrated in 30 of the 33 cancer types analysed in The Cancer Genome Atlas pan-cancer study[3]. *MYC* is genetically amplified in many solid tumour types, including breast and liver cancers, and is frequently chromosomally translocated in B cell and T cell leukaemias and lymphomas[39,42,43] (FIG. 1). *MYC* expression can also be increased through the insertion of upstream enhancers by retroviruses[44] or epistatically and/or epigenetically through the activation of many other oncogenic pathways, such as those mediated by WNT–β-catenin, SRC, numerous receptor tyrosine kinases and Notch[45], or via the loss of tumour suppressors such as APC[46] and TGFβ[47] (FIG. 2b).

In addition, MYC can be activated posttranslationally through many mechanisms increasing protein stability[48,49] (FIG. 2c). MYC has a short half-life that is tightly regulated through phosphorylation and proteasomal degradation. Tumours with stable MYC expression have elevated levels of phospho-serine 62 (P-S62)-MYC and low levels of phospho-threonine 58 (P-T58)-MYC[49,50]. Mitogenic pathways, such as RAS–MEK–ERK signalling, can increase P-S62 levels and thereby increase MYC stability[51]. Moreover, *MYC* mutations affecting the T58 residue can lead to constitutive S62 phosphorylation[52]. Cancers can also down-regulate PP2A, a serine/threonine phosphatase complex that targets P-S62, leading to MYC accumulation[50,53–55]. The levels of PIN1, a member of the peptidyl-prolyl cis-trans isomerase (PPIase) family that functionally regulates MYC stability via isomerization, is overexpressed in multiple human cancer types, suggesting that this is another mechanism by which levels of MYC are increased in cancer cells[56,57]. Finally, FBW7 is a tumour suppressor that controls the proteasomal degradation of many proteins, including MYC[58]. FBW7 is frequently inactivated in human cancers, such as uterine (18%), colon (16%) or cervical cancer (13%), through deletion, mutation or epigenetic modification[59,60], which can promote cancer progression at least in part owing to the resulting increase in MYC levels[53].

The *MYC* superfamily also includes genes encoding multiple other proteins considered to function as transcription factors or co-regulatory proteins and which are very commonly

activated in human cancers[61]. These genes include *MAX*, which encodes an MYC heterodimer binding partner, and *MLX* as well as *MGA*, *MXD1*, *MXD3*, *MXD4*, *MXI1*, *MNT*, *MLXIP* and *MLXIPL*, which encode proteins that interact with MAX and/or MLX[61]. Interactions between different members of this superfamily can result in transcriptional activation or repression of specific genes that, in turn, regulate cell-cycle progression and/or cellular transformation. Mutations or deletions in these members of the *MYC* superfamily have also been reported in human cancers[62,63]. Therefore, the MYC pathway is dysregulated in the majority of human cancers[3,29,64,65]. Accordingly, we have suggested that MYC signalling is a molecular hallmark of cancer[66].

MYC activation alone is generally not sufficient to induce the neoplastic transformation of non-malignant cells. Indeed, the tumorigenic functions of oncogenic MYC are restrained by many physiological mechanisms that cause cell-cycle arrest, apoptosis and/or cellular senescence. For example, unrestricted *MYC* activation can induce the expression of *TP53* (REF.[67]) as well as of cell-cycle checkpoint genes (such as *CDKN2A*)[68] and/or regulators of apoptosis (such as *BCL2*)[69]. Correspondingly, the inactivation of genes such as *TP53* or *CDKN2A*, the activation of genes such as *BCL2*, or the deletion of pro-apoptotic genes (for example, that encoding caspase-8 (REF.[70])) cooperate with MYC signalling to block cell-cycle arrest, senescence and/or apoptosis, thereby driving cancer initiation. The progressive shortening of the telomeres after every cell cycle eventually halts cell division and is another cellular protective mechanism; however, MYC increases telomerase activity by inducing the expression of a telomerase reverse transcriptase, thus favouring cellular immortality[71].

Provocatively, despite activation of *MYC* signalling being one of the most common genetic events in human tumorigenesis, MYC might not always be essential for tumour initiation. Genetically engineered *Myc*-haploinsufficient ($Myc^{+/-}$) mice develop lymphomas at the same rate as *Myc*-wild-type mice, albeit with reduced cell proliferation and delayed tumour progression[72]. Regardless, members of the MYC superfamily are commonly activated and thought to be required for tumorigenesis in most human cancers.

MYC oncogene addiction

In 2002, Bernard Weinstein proposed that cancers are ‘oncogene addicted’[27] following evidence from both experimental mouse models of *MYC*-driven cancers and clinical studies of heterogeneous human tumours. A multitude of studies has demonstrated that *MYC* can act as a cancer driver and that suppression of MYC signalling can result in sustained tumour regression[18–23]. In transgenic mouse models of *MYC*-driven cancers (including lymphoma, leukaemia, osteosarcoma, hepatocellular carcinoma (HCC), renal cell carcinoma and lung adenocarcinoma (LAC)), sustained tumour regression can be observed upon *MYC* inactivation, although the specific consequences depend upon the particular type of cancer[18–23]. Furthermore, the reversible expression of a dominant-negative *MYC* mutant and MYC–MAX disruptor, Omomyc, leads to the rapid regression of lung tumours in mouse models[24–26]. Thus, extensive experimental evidence supports targeting MYC as a potential therapeutic approach against a multitude of human cancers. *MYC* activation drives cancer progression through two types of mechanisms involving either acquisition of hallmarks of

cancer that are intrinsic to tumour cells[2,66] or changes in the TME and anticancer immune response[32,73].

Effects of MYC activation

Cancer cell-intrinsic mechanisms.—MYC regulates cancer cell-intrinsic processes with several physiological roles such as cell growth, differentiation and metabolism[74–77]. Such processes are co-opted upon MYC activation in a cancer cell-autonomous manner, thus facilitating cellular transformation (FIG. 3). In non-malignant cells, the expression of MYC is tightly controlled. High levels of MYC expression are, in fact, associated with increased sensitivity to apoptosis[78,79]. However, *MYC* activation can overcome these physiological barriers and promote cancer through several interdependent cell-intrinsic mechanisms.

MYC overexpression enforces relentless cellular proliferation by enabling cancer cells to re-enter the cell cycle[79] and also accelerates progression through the cell cycle by inhibiting cell-cycle checkpoints[37,80,81]. In addition, MYC promotes cancer cell growth by inducing a substantial increase in ribosomal and protein biogenesis[82–85]. MYC alters cancer cell metabolism by globally rewiring multiple metabolic pathways to support rapid growth and proliferation[35,86]. This function is partially accomplished by facilitating nutrient uptake in cancer cells through transcriptional induction of glucose and glutamine transporters and also of genes involved in glycolysis and glutaminolysis[87–89]. MYC activates cellular survival programmes through specific effects on DNA replication. In particular, MYC can directly activate the DNA replication machinery[90]. Of note, *Myc* is one of the four factors that enable stemness and embryonic programmes of self-renewal in induced pluripotent stem cells[91]. In addition, MYC can bypass and/or transcriptionally repress cell-cycle checkpoint proteins, such as p15 or p21, in some contexts, thus preventing cellular senescence even in the presence of DNA damage[92]. MYC activation can also result in genomic instability owing to many types of genomic damage, including DNA breaks, chromosomal translocations, chromosomal gains or losses, aneuploidy, and polyploidy. The mechanisms by which MYC induces genomic damage involve overriding cell-cycle checkpoints (such as transcriptional repression of p21) and blocking DNA double-strand break repair[21,93–96] as well as mitochondrial reactive oxygen species generated during MYC-driven cell proliferation[97–99]. MYC activation also can induce proliferative arrest and endoreduplication as well as genomic instability in vivo[100,101].

The ability of oncogenic *MYC* to elicit cell proliferation seems to depend upon the specific tissue lineage and the developmental context. For example, *MYC* overexpression in liver cells of embryonic or neonatal mice results in rapid cellular proliferation and rapid formation of hepatoblastomas (a paediatric neoplasm), whereas *MYC* overexpression in liver cells of adult mice results in cellular hypertrophy, endoreduplication and late-onset HCC[100]. In summary, MYC activation contributes to both the initiation and maintenance of tumorigenesis through several cancer cell-intrinsic mechanisms.

Effects on the immune response and TME.—Preclinical studies have revealed many mechanisms by which MYC influences the TME, involving effects on host stromal cells,

vascular endothelial cells, innate and adaptive immune cells, and, in some cases, specific cytokines and their receptors (FIG. 4).

MYC expression in cancer cells can influence host endothelial cells, resulting in reprogramming of the TME to support cellular proliferation and induction of angiogenesis[102–104] (FIG. 3). Moreover, MYC initiates and maintains tumorigenesis through a thrombospondin 1 (TSP1)-regulated angiogenic switch[105] (FIG. 3).

MYC-dependent perturbation of the host immune response is causally related to the mechanism of tumorigenesis and is an important mechanism underlying tumour regression upon MYC inactivation[106–108]. Characterized mechanisms include effects on $CD4^+$ T cells, macrophages, and natural killer (NK) cells and involve cytokines (such as TGFβ, interferons and TSP1) and key immunomodulatory molecules (such as PD-L1, CD47 and MHC class I (MHC I); FIG. 4)[106–112]. More than 30 years ago, a study described that MYC downregulates the expression of proteins involved in antigen presentation, such as MHC I, thus enabling immune evasion[113–115]. In addition, MYC induces the secretion of immune inhibitory cytokines from cancer cells, such as TGFβ, which in turn suppresses cytolytic T cell responses[116,117]. Furthermore, MYC has been found to upregulate the expression of immune-checkpoint proteins, such as PD-L1 and CD47, thus leading to T cell exhaustion[107,108,110,118,119]. In addition, MYC suppresses NK cell-mediated immune surveillance by transcriptionally repressing STAT1 and STAT2 and the type I interferon pathway[107,109,111]. Finally, MYC cooperates with TWIST1 to regulate the secretion of CCL2 and IL-13, thereby promoting the recruitment and polarization of immunosuppressive macrophages, which in turn facilitate metastasis[120] (FIG. 4).

Effects of MYC inactivation

MYC inactivation can cause tumour regression through effects on tumour cells as well as the host immune system and TME. In preclinical models[18–23], *MYC* inactivation results in a cascade of changes in both tumour cells and the TME that lead to rapid tumour regression and the restoration of regular tissue structures (FIG. 4). The specific kinetics and consequences of MYC inactivation seem to depend upon the tissue of origin of a cancer as well as on the specific genetic context. Thus, in mice with *MYC*-driven haematological cancers, such as T cell acute lymphoblastic leukaemia, MYC inactivation is associated with rapid proliferative arrest and very rapid tumour regression within a few days, together with robust induction of cellular differentiation, senescence and apoptosis[20]. By contrast, in mice with *MYC*-driven mesenchymal-derived tumours, such as osteosarcoma, MYC inactivation results in the robust terminal differentiation of bone cancer into bone[18,21]. Finally, in mice with *MYC*-driven epithelial-derived tumours, such as HCC, LAC and renal cell carcinoma, MYC inactivation results in tumour regression but a dormant population of otherwise histologically normal-appearing cells remains[19,121,122].

Cancer cell-intrinsic mechanisms.—MYC inactivation leads to the restoration of physiological cell-intrinsic checkpoints on cellular growth and differentiation. In mouse models of *MYC*-driven cancer, tumour cells undergo proliferative arrest, differentiation, senescence and/or apoptosis upon MYC inactivation[18–23,66]. These processes seem to occur

through the restoration of cell-cycle checkpoints, DNA repair and chromatin remodelling programmes. Thus, the knockdown of cell-cycle checkpoint proteins[66], such as p16, or DNA repair regulators, such as p53, impedes tumour regression elicited by MYC inactivation[21]. MYC inactivation also causes tumour regression through the loss of survival signals with the maintenance of death signals within cancer cells[123]. The mechanism involves both a TGFβ autocrine mechanism that elicits proliferative arrest and senescence upon MYC inactivation[116,123] and the modulation of microRNAs (such as miR17-92, miR-15 and let-7 family members) that epigenetically regulate genes required for cell survival and stemness[124–127]. Thus, MYC maintains tumorigenesis partially through the coordination of multiple cell-intrinsic biological programmes.

Effects on the immune response and TME.—MYC inactivation can also elicit tumour regression through effects on the host immune response and TME such as the suppression of angiogenesis[102,105]. Indeed, MYC has a known role in inducing the expression of cytokines that regulate angiogenesis. One such key regulator is the anti-angiogenic factor TSP1, which is transcriptionally repressed by MYC[128]. Upon MYC inactivation, the upregulation of TSP1 results in the death of endothelial cells within the tumour vasculature and the loss of mean vessel density[105].

Within a week of MYC inactivation, host innate immune cells (such as macrophages[107,120] and NK cells[111,129]) and adaptive immune effectors (including $CD4^+$ T cells[106,130] and B cells[23]) are recruited to the tumour bed (FIG. 4). All of these changes in host cellular compartments have been correlated and, in some cases, shown to be causally associated with changes in the levels of specific cytokines (such as CCL2 or IL-1β) and immune checkpoints (for example, PD-L1 or CD47)[103,107,108,120]. After several weeks of MYC inactivation, complete regression of the tumour occurs together with the restoration of regular tissue architecture and establishment of a durable immune response. Indeed, tumour regression upon MYC inactivation seems to be associated with long-standing immune rejection of the same tumour type[106].

Modelling oncogene addiction.—Of note, changes associated with oncogene addiction can be modelled mathematically. For example, one such model was developed to predict how relative changes in survival and death signals affect tumour growth[123]. In transgenic mouse models of LAC driven by *MYC* alone, *Ras* alone or both, oncogene addiction was found to be best described as a consequence of a reduced proliferative response rather than a net increase in apoptosis[123]. This observation is consistent with the ‘oncogenic shock model’, which proposes that, upon inactivation of oncogenic pathways, pro-survival signals dissipate quickly whereas pro-apoptotic signals persist for longer[123,131]. Indeed, the genetic context of a tumour and its sensitivity to undergo proliferative arrest and/or apoptosis influences the ability of MYC inactivation to elicit tumour regression. The inactivation of oncogenes other than *MYC*, such as *RAS* or *ERBB2*, can lead to similar phenotypical features of oncogene addiction, suggesting that the mechanisms involved are not necessarily unique to *MYC*[132–134]. Lastly, mathematical models have demonstrated mechanisms by which the TME contributes to tumour regression upon oncogene inactivation in transgenic mouse models[135].

Mechanisms of host immune evasion

MYC activation in cancer cells can impede the host immune response. Conversely, its inactivation seems to restore antitumour immunity in a sequential manner. In an experimental mouse model of pancreatic cancer, MYC activation led to the rapid induction of the potent pro-inflammatory cytokine IL-1β, driving the increased proliferation of endothelial cells[103]. CCL2 and CCL5 were also induced, thus triggering the recruitment of mast cells and delaying that of macrophages and neutrophils[136]. In 2020, Muthalagu et al. reported a novel mechanism whereby MYC and KRAS-G12D cooperatively promote pancreatic cancer progression in mice by repressing the type I interferon pathway[111]. Targeted suppression of MYC–MIZ1 complex formation restores the activation of this pathway and leads to CXCL13-mediated recruitment of antitumour B cells and NK cells[111]. Therefore, in multiple mouse models, MYC inactivation is associated with the restoration of an anticancer innate and adaptive immune response.

Some studies have revealed that MYC can regulate the immune response in a manner clearly dependent upon another driver oncogene. For example, in an experimental mouse model of HCC, MYC activation in the context of TWIST1 activation leads to transcriptional changes that confer macrophages from a pro-inflammatory to a prometastatic phenotype mediated by the secretion of CCL2 and IL-13 (REF.[120]). Importantly, levels of MYC, TWIST1, CCL2 and IL-13 were also directly correlated with a worse prognosis in 33 different human cancers. Moreover, measurement of CCL2 and IL-13 enabled prediction of the invasiveness of HCC in patients with this cancer type. Similarly, MYC and RAS cooperate to elicit an inflammatory phenotype in a mouse model of LAC[107] through a process characterized by increased production of CCL9 and IL-23 (REF.[107]). In this model, PD-L1^{+} macrophages inhibit T cells and induce angiogenesis. In summary, the specific features of the immune response regulated by MYC seem to be dependent on the specific type of cancer as well as on the genetic events associated with that tumour[137].

MYC regulates immune checkpoints

MYC affects the host immune response through the regulation of multiple immune checkpoints, including PD-L1 and CD47. MYC regulates PD-L1 in a complex manner involving multiple mechanisms, including direct transcriptional regulation as well as indirect post-transcriptional regulation[108,138,139]. In transgenic mouse models of haematological cancers, MYC binds to the promoter region and regulates the transcription of *Cd274* (encoding PD-L1)[108]. The constitutive retrovirally mediated expression of PD-L1 abrogated the ability of MYC inactivation to result in the inhibition of angiogenesis and the induction of cellular senescence and blocked tumour regression[108,72,107,140,141]. Similarly, in neuroblastoma and *ALK*-negative anaplastic large cell lymphoma cells, the in vitro inhibition of MYC expression with short-hairpin RNAs or small-molecule inhibitors reduces PD-L1 expression[142,143]. Thus, the transcriptional regulation of *CD274* expression seems to be a conserved mechanism by which MYC promotes immune evasion.

MYC can also regulate PD-L1 indirectly in cooperation with other oncogenes or through other key transcriptional regulators. For example, in a mouse model of triple-negative breast cancer, MYC and p65 cooperate to regulate *Cd274* transcription[110]. In mice with LAC,

MYC cooperates with KRAS to overcome translational repression of PD-L1 (REF.[107]). Increased protein stability of MYC is another mechanism of PD-L1 regulation. Indeed, in a transgenic mouse model of HCC, an engineered increase in MYC protein stability correspondingly increased PD-L1 expression and reduced the tumour infiltration of $CD8^+$ T cells[118]. In summary, MYC can increase the expression of PD-L1 in cancer cells through multiple mechanisms.

MYC can also regulate other receptors involved in the immune response such as CD47 and MHC I. CD47 is an immune regulatory molecule that provides a 'do not eat me' signal to immune cells expressing two types of ligands: TSP1 and tyrosine-protein phosphatase non-receptor type substrate 1 (also known as SIRPα)[144,145]. In human-derived lymphoma cells, MYC upregulated CD47 and inhibition of MYC signalling with the BET bromodomain inhibitor JQ1 reduced CD47 levels without affecting PD-L1 expression[146]. Similarly, in a mouse model of cutaneous T cell lymphoma, high levels of MYC induced the transcription of *CD47* (REF.[147]). Interestingly, CD47 has been shown to increase MYC expression in a feedforward loop[144,147].

Finally, MYC suppresses the expression of MHC I. More than 30 years ago, MYC was shown to downregulate MHC I in multiple cancers, including neuroblastoma, melanoma and lymphoma[113,115,148]. A subsequent study in mice showed that this downregulation is associated with a decrease in the recruitment of T cells and NK cells to LACs[107]. Of note, oncogenic RAS also seems to decrease MHC I expression; this process might occur through its known cooperation with MYC[149,150]. Together, these studies show that the regulation of immune checkpoints is a crucial mechanism whereby the *MYC* oncogene remodels the immune TME and facilitates immune evasion.

Immune regulation through metabolism

MYC regulates diverse metabolic pathways in cancer cells[151–154]. Importantly, immune function is also highly regulated by cellular metabolism[155–158]. More specifically, MYC influences the host TME directly and indirectly through its effects on metabolism.

MYC expression in cancer cells results in perturbations in metabolic pathways that lead to the release of immunomodulatory molecules. During tumour initiation in mouse models, *MYC*-driven proliferating cancer cells release metabolites (such as lactate[159] and glutamate[160,161]) that influence the local immune function within the TME. As the tumour grows, these effects could become more general and cause systemic disruption of anticancer immune responses[162,163].

MYC-driven cancers have dysregulated glucose, glutamine and lipid metabolism, which could affect the host metabolic homeostasis thereby indirectly influencing the immune system and immunoediting[152,164–166]. MYC enables a metabolic shift from oxidative phosphorylation to glycolysis (the Warburg effect), upregulates glutaminolysis and increases lipogenesis in cancer cells[151–154], which improves cellular fitness and confers a cell survival advantage. However, such an advantage could lead to a competition between cancer and immune cells for key metabolites, thus making immune cells ineffective[167]. Hence, MYC

could have both direct and indirect effects on the host immune system through its effects on cancer metabolism.

The MYC pathway as a therapeutic target

Despite substantial experimental evidence showing that targeting MYC can lead to tumour regression through both direct and indirect effects[18–26] and decades of effort towards clinical translation of these findings, MYC has not yet been successfully targeted therapeutically. The difficulties in targeting MYC have been described elsewhere[168,169]; briefly, some of the reasons include the highly disordered protein structure of MYC and the lack of a binding pocket or specific enzymatic activity. Nevertheless, a variety of strategies to inhibit MYC activity are currently being explored (FIG. 5) in preclinical cancer models or in clinical studies (Supplementary Table 1). Individual approaches have been comprehensively reviewed elsewhere[169–175]; herein, we provide a broad overview of different strategies for the therapeutic targeting of *MYC*-driven cancers.

Given that MYC functions as a heterodimer with MAX[176], small molecules that target the MYC–MAX interface, stabilize MAX–MAX homodimers or disrupt the binding of MYC–MAX to DNA have been used to inhibit MYC signalling. The MYC–MAX disruptors MYCi361 and MYCi975 (REF.[177]), the MAX–MAX stabilizer KI-MS2-008 (REF.[178]), disruptors of MYC–MAX binding to its canonical Ebox DNA sequence (such as ME47 (REF.[179])), the inhibitor of MYC–DNA binding and MYC transcriptional activity EN4 (REF.[180]), and Omomyc have all shown activity in preclinical models of *Myc*-driven cancers[24,25]. Some of the discovered small molecules and designed miniproteins show efficacy in various preclinical mouse cancer models but clinical evidence is not yet available. To date, Omomyc is the only promising candidate to have entered clinical trials.

Another approach to targeting MYC involves decreasing MYC biosynthesis or altering its stability. For example, inhibitors of the PI3K–AKT–mTOR signalling pathway suppress MYC translation and thus decrease tumoural levels of MYC in a mouse model[181]. Similarly, silvestrol, a small-molecule inhibitor of the translation initiator eIF4A, reduces MYC translation and inhibits tumour growth in a mouse model of colon cancer[182]. Moreover, inhibitors of Aurora kinases can induce MYC protein degradation and specifically inhibit MYC protein overexpression in cancer cells without affecting physiological MYC expression in non-malignant cells[183,184]. PLK1 also regulates MYC protein stability and is another promising therapeutic target[185]. Finally, PIN1 modulates MYC turnover and transcriptional activity[186]. Specific PIN1 inhibitors have shown promising therapeutic activity in preclinical models of MYC-driven cancers[187].

In the past few years, important developments have occurred in the design of specific protein degraders or proteolysis-targeting chimaeras (PROTACs). These approaches are based on cereblon-mediated protein degradation and provide a new means to directly and specifically target transcription factors, such as MYC and/or its interaction partners, for proteasomal degradation[188,189].

Reducing *MYC* mRNA stability in tumours is another potential strategy to target MYC-driven tumours[190]. Antisense oligonucleotides have been used in preclinical models to target *MYC*[191–193]. For example, a MYC-specific antisense oligonucleotide, MYC-ASO, impairs tumour progression and elicits an antitumour immune response in a primary transgenic mouse model of HCC[194].

Another strategy involves targeting upstream regulators to inhibit *MYC* transcription. For example, BET-motif inhibitors have demonstrated antitumour efficacy that might partially result from the inhibition of *Myc* transcription[195,196]. Drugs that stabilize the G-quadruplex structure in the *Myc* promoter region, such as IZCZ-3, can also inhibit *Myc* transcription[197–201].

Vulnerabilities that might be therapeutically targetable can be identified in screens for MYC-related synthetic lethal interactions — that is, of genes likely to be key mediators of MYC-driven cellular processes required for tumorigenesis. As a transcription factor, MYC drives the expression of a multitude of gene products that are required to initiate and/or maintain cancers[2,5,61,202,203], thus diversifying the arsenal of potential drug targets. Synthetic lethal screens[204–206] have identified multiple potential targets, such as cyclin-dependent kinases (CDKs)[207,208], SAE1/2-mediated sumoylation[204] and TNFRSF10B[205]. In addition, studies have demonstrated the dependency of MYC-driven cancers on a functional DNA damage response mediated by ATR, CHK1 and PRKDC[209,210]. A novel therapeutic synthetic lethal approach could address the transcription-independent role of MYCN in preventing replication stress-induced DNA damage. Indeed, in complex with Aurora kinase A, MYCN prevents R-loop formation and thus facilitates cell proliferation in a mouse model of neuroblastoma. This process could potentially be exploited therapeutically through the combined inhibition of Aurora kinase A and ATR[211]. In *Myc*-driven mouse models of B cell lymphomas or lung cancer, the anti-apoptotic protein MCL1 is a synthetic lethal vulnerability of MYCN. MCL1 inhibitors are currently being tested in clinical trials (Supplementary Table 1)[212,213]. Of note, these mechanisms are specific to MYCN.

Epigenetic modifiers, such as histone deacetylases (HDACs)[214–216] or histone methyltransferases (such as EZH2[217]), can also be used to target *MYC*-driven cancers. In non-small-cell lung cancer cell lines, the combination of DNA methyltransferase inhibitors with HDAC inhibitors led to the suppression of MYC signalling and consequent activation of an IFNα/β-based transcriptional programme accompanied by a CCL5-mediated antitumour T cell response[140]. These investigators were able to demonstrate that epigenetic therapy could deplete MYC, enabling tumours to reverse immune evasion[140]. Similarly, MYC can promote cancer through miR17-92-mediated regulation of chromatin remodelling[104,125,218]. The use of anti-miR-17 oligonucleotides delayed tumour progression in a mouse model of liver cancer[219]. Finally, given that MYC is a key regulator of cellular metabolism[19,35,152], targeting MYC synthetic metabolic vulnerabilities, such as SREBP1, is another potential therapeutic strategy[153,165]. Our laboratory is currently exploiting the concept of synthetic lethality with CRISPR-based functional in vivo genomic screening to identify novel molecular targets in *MYC*-driven cancers (A.D. and D.W.F., unpublished results).

A final therapeutic approach involves exploiting MYC-induced alterations of immune surveillance. For example, MYC regulates the expression of specific immunomodulatory molecules and cellular immune mechanisms in specific cancers and, thus, molecular and cellular therapies that restore these mechanisms might be particularly effective against *MYC*-driven cancers. Some evidence supports this strategy, at least experimentally, such that *Myc*-driven mouse cancers have been shown to be sensitive to the cytokine-mediated restoration of anticancer immune responses[220], reinstitution of NK cell-mediated immune surveillance[109] or immune-checkpoint inhibition[31,108].

Similarly, drugs that target the MYC pathway might sensitize tumours to specific immunotherapies. For example, MYCi361 has demonstrated promising synergy with anti-PD-1 antibodies in a mouse model of *Myc*-driven prostate cancer[177]. In addition, in a xenograft model of pancreatic ductal adenocarcinoma, the combination of an anti-PD-L1 antibody and JQ1 had synergistic effects[221]. Hence, MYC expression might predict response to immunotherapy and targeting the MYC pathway might sensitize cancers to and enhance the efficacy of immunotherapy.

In summary, many strategies can be used to either directly or indirectly target *MYC*-driven cancers. Ongoing early phase clinical trials are testing direct MYC inhibitors that either silence *MYC* gene expression, inhibit MYC protein biosynthesis or target MYC for proteasomal degradation (Supplementary Table 1). MYC can also be inhibited indirectly by targeting identified synthetic lethal interactions, with examples including HDACs, CDK4, CDK6, CDK7 and CDK9, DNA repair genes (such as CHK1 and ATR), and anti-apoptotic genes (for example, MCL1; Supplementary Table 1). Furthermore, small-molecule screens have identified compounds that directly target MYC–MAX. Nevertheless, most of these MYC–MAX inhibitors are yet to enter clinical trials. Strategies such as antisense RNA oligonucleotides have been tested in phase I clinical trials but, to our knowledge, have not been further pursued as cancer therapeutics[222,223]. To date, Omomyc is the only agent directly targeting MYC that has been tested in clinical trials[224] (Supplementary Table 1).

We believe that direct targeting of MYC is likely to be more clinically effective than indirect targeting strategies. Nevertheless, several drugs targeting MYC indirectly, either through synthetic lethal interactions or upstream signalling pathways, have reached the clinic (Supplementary Table 1). These agents include CDK4/6 inhibitors and mTOR inhibitors; however, such approaches are likely to be associated with therapeutic resistance. As we have described, MYC controls interconnected cell-intrinsic and cell-extrinsic programmes and, thus, cancer cells will probably be able to bypass the inhibition of any one specific mechanism. Therefore, even the brief or partial depletion of MYC can result in sustained suppression of tumorigenesis in preclinical models[18,105,225]. We believe that future efforts will make it possible to find agents that directly target MYC and that a therapeutic window exists in which these drugs have clinical activity against cancer while mitigating toxic effects in non-malignant cells.

Future directions

Insights on how MYC regulates both cancer cell-intrinsic processes, such as proliferation or metabolism, and cell-extrinsic phenomena, such as the host immune response and angiogenesis, have important practical implications for the development of therapeutics as well as guiding the selection of therapies. Agents that target MYC could be highly effective for the treatment of some cancer types or as individualized treatments for some patients. To date, no direct MYC inhibitors have been approved for clinical use, although we envision that such agents, once identified, will be effective either alone or in combination with other therapeutic agents to treat *MYC*-driven cancers. Furthermore, understanding and targeting those MYC functions that are independent of its transcriptional activity might provide alternative therapeutic strategies. Hence, molecular understanding of how MYC causes cancer should enable efforts to identify which patients with *MYC*-driven cancers are most likely to have a response to specific therapies such as direct MYC inhibitors, MYC synthetic lethal agents, MYC-guided immunotherapies and/or MYC-guided metabolic treatments (FIG. 6). Thus, we envision that patients with tumours could be assigned to MYC^{high} or MYC^{low} phenotypes defined by genomic events including *MYC* amplifications and translocations and/or expression of an MYC activation gene signature[226,227]. Subsequently, deep phenotyping of tumours using different approaches (including DNA and RNA sequencing, mass cytometry, or mass spectrometry) would guide the selection of therapeutic strategies to target MYC (FIG. 6). For example, patients with tumours harbouring *MYC* amplifications can potentially be treated with direct MYC inhibitors while those with enrichment of synthetic lethal targets of *MYC* would receive drugs targeting these specific gene products. MYC-directed therapies could be used to sensitize MYC^{high} immunologically ‘cold’ tumours to immunotherapies, whereas tumours in which MYC predominantly induces metabolic dysregulation can potentially be treated with drugs targeting metabolic pathways (such as lipid metabolism). In summary, discoveries from the past few years elucidating the specific mechanisms by which MYC drives cancer can potentially enable researchers to develop novel therapeutic strategies to target MYC.

Conclusions

MYC and other genes in the *MYC* superfamily are among the most commonly activated signalling mechanisms in human cancer. MYC initiates and maintains cancer through both tumour cell-intrinsic mechanisms and host immune and TME-dependent mechanisms. In experimental models, MYC inactivation can induce rapid tumour regression through effects on tumour cells, which occur as a consequence of oncogene addiction, as well as the restoration of immune responses. To date, however, the MYC pathway remains to be successfully targeted therapeutically. In this Review, we have described multiple approaches for targeting MYC or MYC-regulated pathways that are being evaluated in clinical trials (Supplementary Table 1). Furthermore, we propose that MYC and other members of the MYC pathway could serve as biomarkers to stratify patients for specific therapies (FIG. 6).

MYC is a particularly exciting therapeutic target because it regulates not only tumour cell-intrinsic growth but also the host immune response. Thus, immune surveillance might be restored by targeting the MYC pathway. For more than 30 years, MYC was presumed

to contribute to tumorigenesis through its direct effects on cancer cells. Nowadays, the role of MYC as a grand orchestrator of biological processes, not only inherent to tumour cells but also relating to the TME and the host immune system, has become apparent. MYC coordinates intercellular communications that occur between the cancer cells and specific immune cells, thus enabling tumour initiation, progression and metastasis. Experimentally, targeting MYC and the MYC pathway seems to both affect cancer cells and restore antitumour immunity. The evidence of MYC as a grand orchestrator provides further impetus to develop therapeutics to target this otherwise elusive oncogenic pathway.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key points

- The *MYC* oncogene is activated in the vast majority of cancers by genetic, epigenetic or post-translational mechanisms.
- In preclinical models, inactivation of MYC can result in sustained tumour regression owing to oncogene addiction.
- MYC activation drives cancer progression through mechanisms involving either the cell-intrinsic acquisition of hallmarks of cancer or dysregulation of the tumour microenvironment and host immune responses.
- MYC leads to cancer initiation and maintenance by regulating the host immune system through mechanisms involving immune checkpoints, specific receptors and secreted cytokines.
- Currently, no direct inhibitors of MYC are approved; however, many therapeutic agents targeting MYC are under development.
- We propose that therapies targeting the MYC pathway will be key to reversing cancerous growth and restoring antitumour immune responses in patients with MYC-driven cancers.

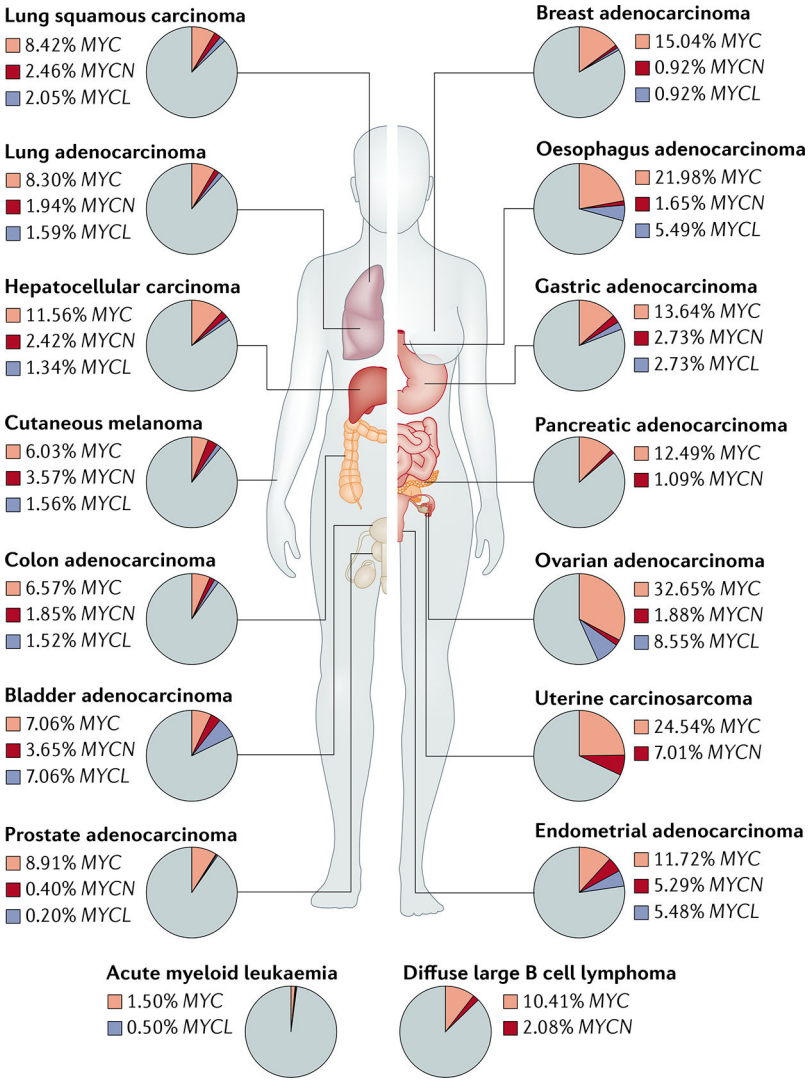

Fig. 1 |. Major genetic alterations involving *MYC* and its paralogues in human cancers.
Prevalence of gene amplification of the three *MYC* paralogues *MYC*, *MYCL* and *MYCN* across 16 major human cancer types in The Cancer Genome Atlas.

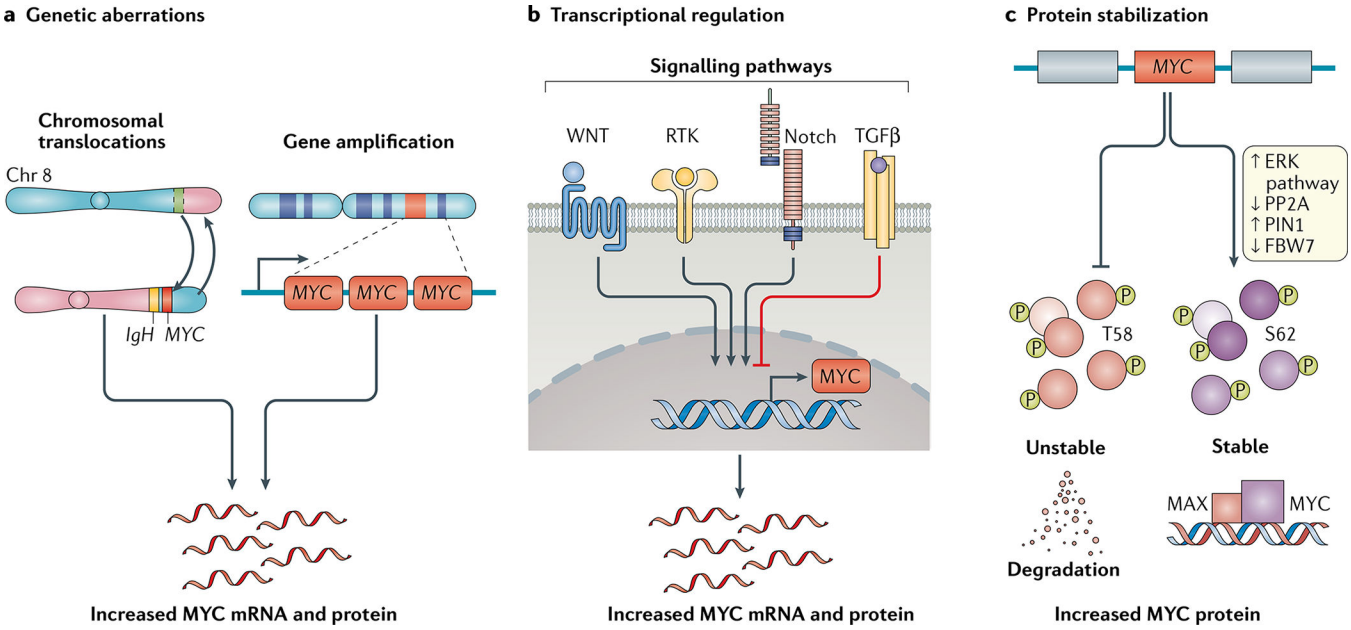

Fig. 2 |. Mechanisms leading to MYC activation in human cancers.

a | Genetic aberrations, such as chromosomal translocations and genomic amplifications, lead to increased *MYC* mRNA expression. **b** | Alteration of upstream regulatory pathways can lead to increased or decreased transcription of the *MYC* oncogene. **c** | Post-translational modifications of the MYC protein, such as preferential phosphorylation of the serine 62 (S62) residue versus threonine 58 (T58), can block degradation and promote stabilization of MYC, thereby enhancing activation of the MYC pathway.

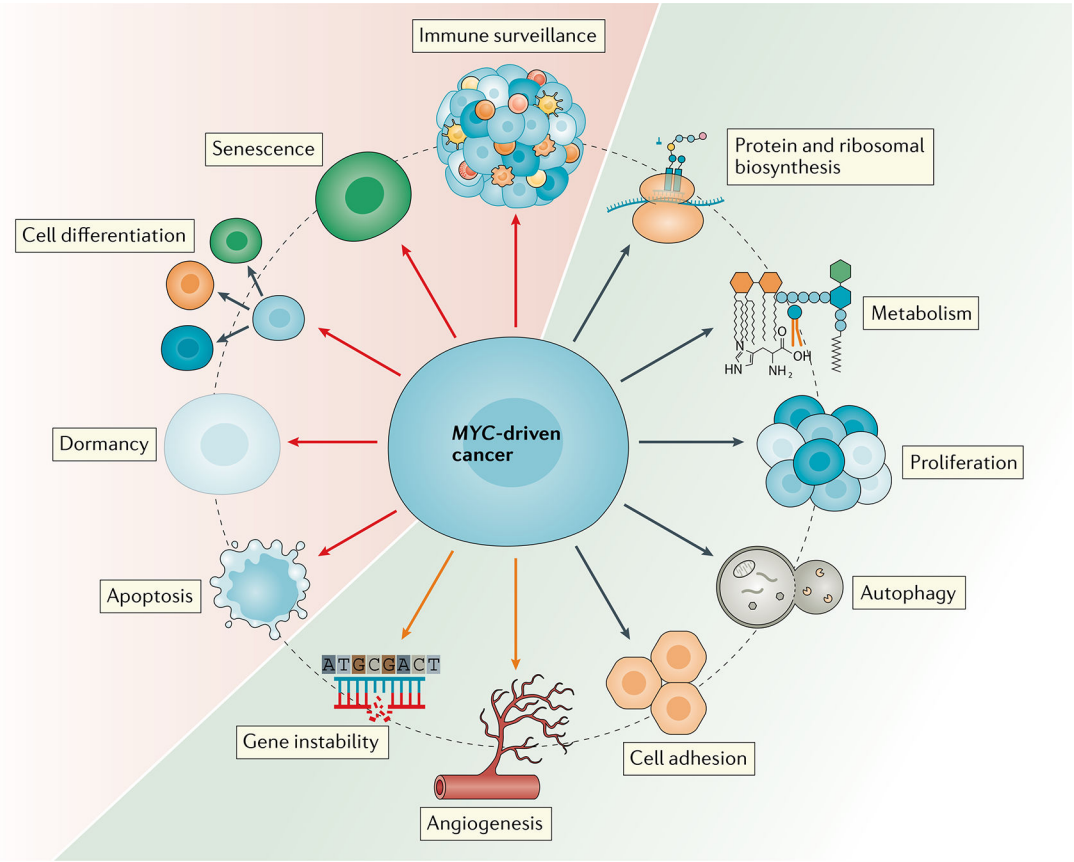

Fig. 3 |. MYC is a grand orchestrator of the hallmarks of cancer.

MYC regulates several cancer cell-intrinsic and host-dependent pathways to promote cancer cell growth and survival (green area). Cancer cell-intrinsic processes regulated by MYC include proliferation, metabolism, invasiveness, autophagy, and protein and ribosomal biosynthesis. MYC also simultaneously blocks other cellular protective mechanisms, such as differentiation or senescence, thereby promoting cancer progression (red area). Paradoxically, MYC also induces cellular processes, such as apoptosis and chromosomal instability, that can be detrimental to cancer cell survival (orange arrows). The delicate balance between these events and cellular context ultimately determines cell fate. Furthermore, MYC controls the ability of cancer cells to undergo dormancy and to overcome nutrient-low environments, eventually leading to tumour relapse. To maintain this quiescent state, MYC inhibits several cellular programmes, including cell differentiation and senescence. MYC activation in the cancer cells also drives enhanced angiogenesis, thus promoting tumour progression. Finally, one of the most important functions of MYC is to enable cancer cells to evade and inhibit immune surveillance to safeguard their survival. All of these hallmarks regulated by MYC work in unison to drive cancer progression.

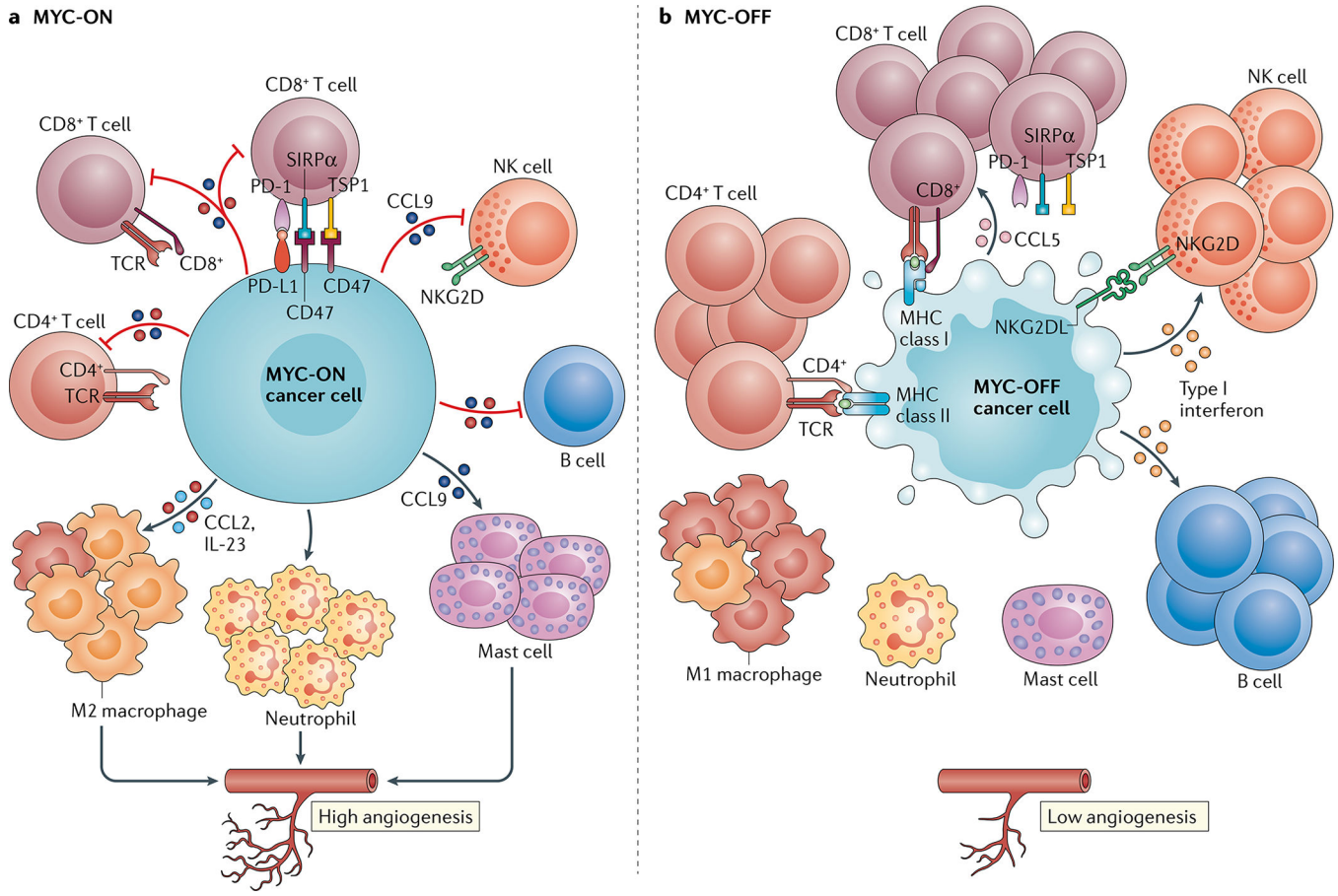

Fig. 4 |. MYC blocks immune surveillance.

MYC enables cancers to evade the immune system through several distinct mechanisms. **a** | MYC regulates the expression and production of several immune ligands or receptors and immune effector molecules, such as PD-L1, CD47, MHC classes I and II, and NKG2D. MYC also promotes the expression of several cytokines, such as CCL2, IL-23 and CCL9, which regulate the conversion of antitumour M1 macrophages to pro-tumour M2 macrophages and prevent the activation and recruitment of B cells, natural killer (NK) cells, and $CD4^+$ and $CD8^+$ T cells. CCL9 activates mast cells, which in turn induce angiogenesis. **b** | Upon inactivation of MYC, the downregulation of PD-L1 and CD47 results in the rapid recruitment and activation of $CD8^+$ T cells and NK cells. The inactivation of MYC also increases the levels of NKG2DL in cancer cells, resulting in NK cell recruitment. The production of most of the cytokines described above decreases upon MYC inactivation. By contrast, the expression of type I interferons and CCL5 increases upon MYC inactivation, resulting in the recruitment and activation of NK cells and B cells and of $CD8^+$ T cells, respectively. Thus, MYC controls the immune status of a tumour by creating an immunosuppressive ‘cold’ tumour microenvironment when activated, which reverts to an immune-sensitive ‘hot’ milieu when inactivated. TSP1, thrombospondin 1.

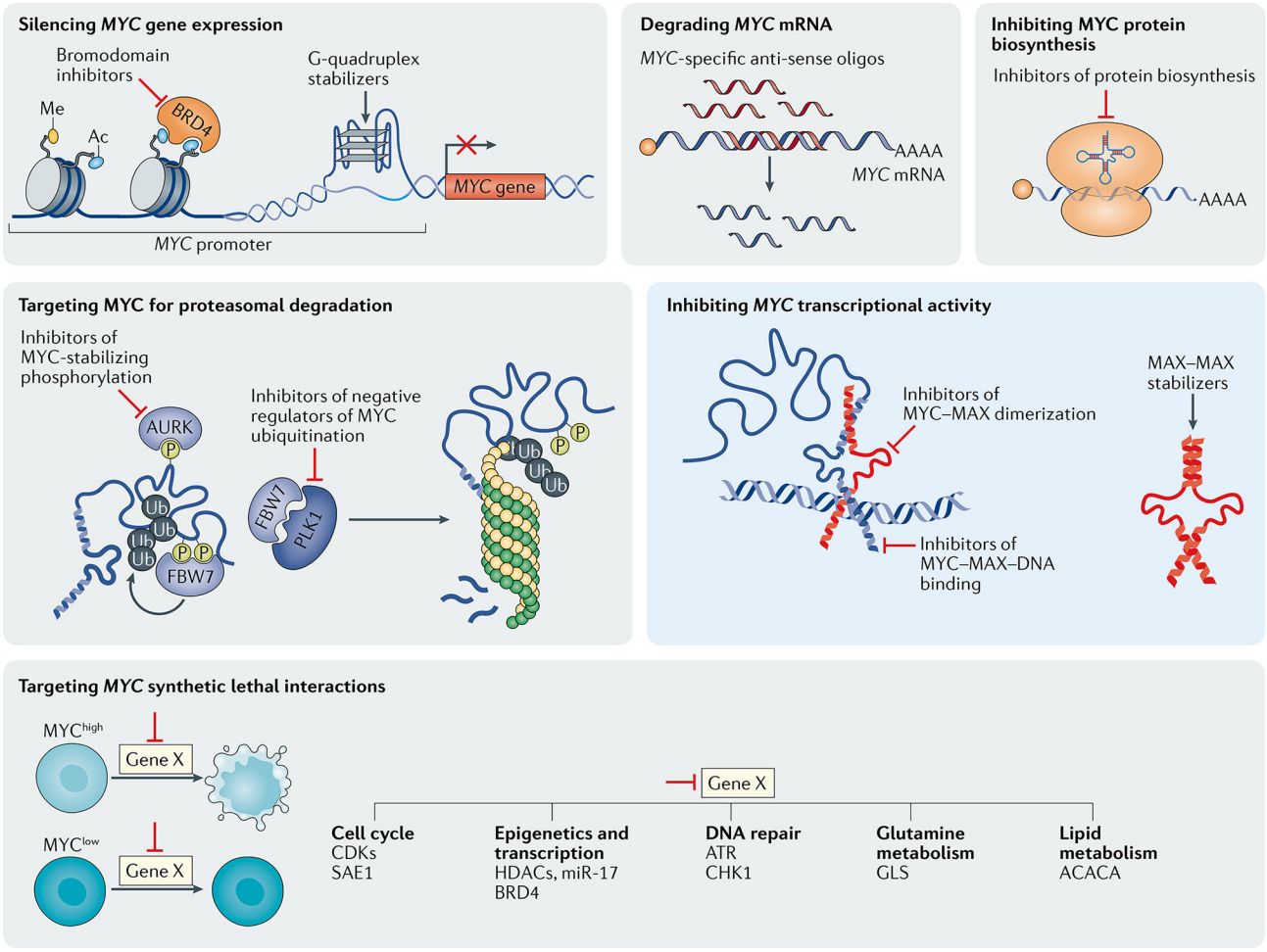

Fig. 5 |. Therapeutic strategies to target *MYC*-driven tumours.

Among the multiple strategies currently explored to target *MYC*-driven tumours, the majority use indirect approaches (grey boxes) such as those based on inhibiting *MYC* synthetic lethal genes or interfering with the expression of MYC at the DNA, RNA or protein level. Direct strategies to inhibit MYC (blue box) include approaches using small molecules, peptides or 'miniproteins' to inhibit MYC–MAX dimerization, sequester MAX via homodimer stabilization, or interfering with MYC–MAX binding to target DNA sequences. Ac, acetylation; CDKs, cyclin-dependent kinases; HDACs, histone deacetylases; Me, methylation; P, phosphorylation; Ub, ubiquitylation.

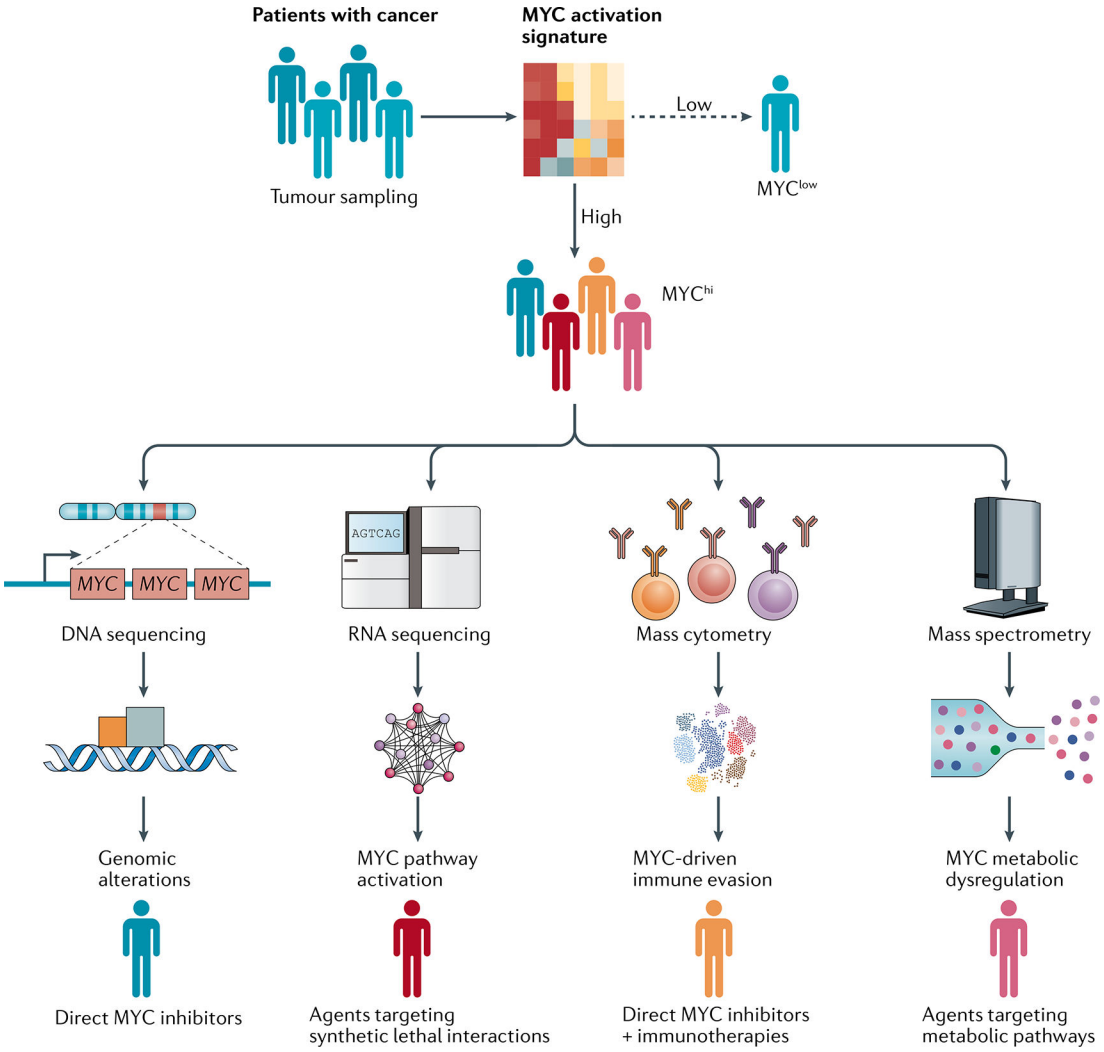

Fig. 6 |. Proposed biomarker-stratified therapeutic strategies to target *MYC*-driven cancers. Patients with cancer can be assigned to MYC^{hi} and MYC^{low} subgroups defined by enrichment of an MYC activation signature in tumour samples. Patients with *MYC*-driven tumours can potentially be further classified according to various disease phenotypes on the basis of the dominant mechanism of action of MYC, which would enable stratification to receive different treatments. For example, patients harbouring tumours with *MYC* amplifications could be treated with direct MYC inhibitors, whereas those with enrichment of synthetic lethal targets of MYC would receive agents targeting these specific gene products. By contrast, MYC-directed therapies could be used to sensitize MYC^{hi} immunologically 'cold' tumours to immunotherapies, whereas patients with tumours in which MYC prominently induces metabolic dysregulation can be treated with drugs targeting these pathways. In summary, discoveries elucidating the specific mechanisms by which MYC drives cancer are enabling the development of novel and selective therapeutic strategies to target MYC in human cancers.