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Transcription Factors and Cancer: Approaches to Targeting

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Abstract

Cancer is defined by the presence of uncontrollable cell growth, whereby improper proliferative signaling has overcome regulation by cellular mechanisms. Transcription factors are uniquely situated at the helm of signaling, merging extracellular stimuli with intracellular responses. Therefore, this class of proteins plays a pivotal role in coordinating the correct gene expression levels for maintaining normal cellular functions. Dysregulation of transcription factor activity unsurprisingly drives tumorigenesis and oncogenic transformation. While this imparts considerable therapeutic potential to targeting transcription factors, their lack of enzymatic activity renders intervention challenging and has contributed to a sense that transcription factors are "undruggable". Yet, enduring efforts to elucidate strategies for targeting transcription factors as well as a deeper understanding of their interactions with binding partners have led to advancements that are emerging to counter this narrative. Here, we highlight some of these approaches, focusing primarily on therapeutics that have advanced to the clinic.

Keywords

transcription factors; cancer; therapeutics

Introduction

As one step of a larger signaling cascade, transcription factors bind to specific DNA sequences to modulate transcription of target genes.[1] By regulating gene expression, transcription factors play an integral role in governing important cellular processes including cell growth and proliferation, differentiation, apoptosis, and metabolic and immune homeostasis.[2–5] Thus, dysregulation of transcription factor activity resulting in aberrant gene expression has been implicated in numerous cancers.[6,7] Chromosomal translocation, mutation, amplification, or deletion of transcription factor genes have been directly linked

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Competing interests

D.E.J. and J.R.G. are co-inventors of cyclic STAT3 decoy and have financial interests in Bluedot Bio. Bluedot Bio holds an interest in cyclic STAT3 decoy.

to cancer development and progression.[8] As gain-of-function oncogenes, for which they comprise around 20% of those currently identified, transcription factors drive constitutive signaling of proliferation pathways, while as tumor suppressors their loss of function or deletion contributes to evasion of cell death mechanisms, both of which are quintessential hallmarks of cancer.[9,10] These factors implicate transcription factors as plausible therapeutic targets. Yet, targeting transcription factor activity has come with its own set of particular challenges, in that transcription factors lack enzymatic activity that has conventionally enabled the design of small-molecule inhibitors, rendering them elusive to direct targeting.[2] Sustained efforts, however, have brought forth new developments in the targeting of transcription factors and these approaches and novel agents are beginning to enter or complete investigational clinical trials.

Challenges of Targeting Transcription Factors

A lack of enzymatic activity precludes transcription factors from having an active site amenable to small-molecule inhibition. Rather, the activation of transcription factors and their subsequent mechanism of action may involve phosphorylation, dimerization, binding to specific DNA motifs, and heterologous interaction with various regulators/cofactors.[1,11] Hence, interference with any of these events has the potential to inhibit the activation or activity of the transcription factor (Figure 1). However, the obstacles accompanying targeting these events and interactions are multiple. For example, the ability to target protein-DNA interactions is limited by the difficulty of generating inhibitor selectivity considering the restrictions on diversity that could confer specificity given only four DNA bases.[12] Targeting of intracellular protein-protein interactions is limited by the fact that these interfaces are large (1500–3000 $Å^2$), hydrophobic in nature, and often lacking in pronounced binding grooves or pockets, none of which are characteristics conducive to the design of small-molecule drugs.[13] Furthermore, the dynamic flexibility of a large number of transcription factors results in a binding domain that may remain unstructured until its binding partner, whether a specific DNA motif or a protein, is present.[2,12] The notable challenges presented by targeting transcription factors have fueled substantial endeavors resulting in a myriad of strategies designed to overcome these hurdles. A survey of these approaches is detailed below, with a focus on therapeutics in clinical development.

Indirect Targeting of Transcription Factors

Given the challenges of targeting transcription factors directly, many studies have focused alternatively on suppressing activity through indirect means. Increased understanding of the mechanisms driving transcription factor activation has allowed for more “druggable” proteins involved in the activation process to be targeted for the purpose of indirectly decreasing transcription factor activity.[14,15] A major caveat to this approach is reduced specificity and increased potential for undesirable off-target effects.[16] Nevertheless, indirect targeting of transcription factors remains a viable therapeutic avenue, particularly for those transcription factors for which inhibition by a direct mode of action has not yet been developed.

Targeting Upstream Kinases

Extracellular signaling molecules such as cytokines and growth factors bind to receptors on the surface of target cells to initiate cascades of gene expression that effect critical cellular responses.[17] These receptors typically contain kinase sequences in their intracellular domain. As kinase enzymes, the receptors possess a natural ligand and binding pocket after which inhibitors can be structurally modeled.[18] In some cases, ligand-activated receptors have the capacity to directly phosphorylate and activate transcription factors. In other cases, activated receptors phosphorylate and activate receptor-associated cytosolic kinases, such as members of the Janus kinase (JAK) protein family, which subsequently are responsible for phosphorylation of transcription factors.[19] Thus, targeting upstream kinases can potentially reduce aberrant transcription factor signaling in lieu of direct targeting.[20]

This approach has been used to inhibit the activation of signal transducer and activator of transcription 3 (STAT3), an oncogenic transcription factor that has been associated with cell proliferation, invasion, metastasis, and angiogenesis. STAT3 is activated by the JAK/STAT pathway in response to interleukin-6 (IL-6), which is elevated in many forms of cancer and leads to upregulation of cell proliferative and survival as well as immunosuppressive genes.[4] Several JAK-selective inhibitors have been investigated in clinical trials in cancer patients, including ruxolitinib, a small-molecule inhibitor approved by the Food and Drug Administration (FDA) for the treatment of myelofibrosis, polycythemia vera, graft-versus-host disease, and most recently, nonsegmental vitiligo.[21–24] In patients with non-small cell lung cancer (NSCLC), a Phase Ib study of ruxolitinib in combination with the EGFR inhibitor afatinib demonstrated activity with a partial response of 23.3% and overall disease control rate of 93.3% (NCT02145637), while in a Phase I/II study of ruxolitinib in patients with chronic myelomonocytic leukemia (CMML) the overall response rate was 46% (NCT01776723).[25,26] In head and neck squamous cell carcinoma (HNSCC), treatment with ruxolitinib in patient-derived xenograft models from patients participating in a window-of-opportunity trial suggested that baseline levels of activated STAT3 may operate as an indicator of clinical response.[27] However, various clinical trials studying ruxolitinib in lung adenocarcinoma (in addition to EGFR inhibitor erlotinib) (NCT02155465) and triple negative breast cancer (NCT01562873), among others, have been terminated due to lack of efficacy despite evidence of tolerability.[28–30]

Tofacitinib, a JAK1/3-selective inhibitor, is FDA approved for the treatment of rheumatoid arthritis as well as ulcerative colitis.[31,32] In preclinical studies in breast cancer cell lines, treatment with tofacitnib inhibited *in vivo* peritumoral angiogenesis, and a Phase I study of tofacitinib in combination with LMB-100 in patients with pancreatic adenocarcinoma and cholangiocarcinoma is currently ongoing (NCT04034238).[33,34] In 2019, the JAK2 inhibitor fedratinib was approved for the treatment of myelofibrosis and is presently under investigation in a Phase II study in patients with myeloproliferative neoplasms and chronic neutrophilic leukemia (NCT05177211).[35]

Targeting Epigenetic Regulation

Epigenetic modulation refers to heritable changes in the chromatin structure that are independent of alterations to the DNA sequence.[36] These modifications can include

post-translational modifications of histones (acetylation, methylation, phosphorylation, and sumolyation), DNA methylation, and nucleosome positioning.[37,38] By influencing how tightly folded chromatin is, epigenetic patterns regulate its accessibility to transcriptional complexes which in turn impacts gene expression.[39] Dysregulation of these processes can lead to aberrant levels of transcription and has consequently been implicated in cancer; targeting regulators of epigenetic mechanisms and associated enzymes thus presents an additional strategy for countering elevated transcription factor activity.[40,41]

The bromodomain and extraterminal domain (BET) family of proteins is one such candidate that has garnered considerable interest as a potential target for curbing epigenetic-related hyperactivation of oncogenes.[42] As epigenetic readers, the BET protein members consisting of BRD2, BRD3, BRD4, and BRDT bind to acetylated histones, which leads to recruitment of components of the transcriptional machinery, thereby aiding in enhanced expression of genes.[43] The discovery of a rare and highly aggressive subtype of squamous cell cancer, NUT midline carcinoma (NMC), derived from the fusion of the *NUT* gene to the *BRD4* gene by chromosomal translocation t(15;19) directly linked BET proteins to oncogenic transformation.[43,44] Moreover, overexpression of BRD4, the most well-characterized BET protein, has been associated with heightened cell proliferation and survival in various malignancies. For example, shRNA screens in acute myeloid leukemia and ovarian carcinoma both identified BRD4 as a vital driver of disease, where suppression of BRD4 elicited cell cycle arrest, inhibition of proliferation, and induction of apoptosis.[40,45,46] Notably, these oncogenic phenotypes may be attributed to BRD4's preferential association at super-enhancer regions of important genes such as *MYC*, *BCL2*, and *CDK4*.[43,47] c-Myc, which belongs to the MYC family, has been comprehensively studied and established as a major oncogenic transcription factor, owing to its critical role in upregulating target genes involved in cell cycle progression, metabolism, protein translation, and ribosome biogenesis.[48,49] c-Myc is thought to target roughly 15% of the genome, meaning that the scope of its regulatory control is vast and the ramifications of dysregulation are accordingly impactful. Expression of c-Myc is found to be altered in greater than 70% of human cancers and chromosomal rearrangement of c-Myc is habitually present in Burkitt lymphoma, multiple myeloma, and diffuse large B-cell lymphoma (DLBCL).[9,50] Collectively, these findings substantiate BET inhibitors as candidates for indirectly targeting a network of aberrant cancer-associated transcription including c-Myc (Figure 2).

JQ1 is a small-molecule BET inhibitor that competitively binds to the bromodomain and displaces BRD4 from super-enhancer regions. This leads to suppression of c-Myc transcription and its subsequent downstream effectors. Treatment with JQ1 triggered cell cycle arrest and cellular senescence in multiple myeloma cells *in vitro* as well as induced tumor regression in Burkitt lymphoma and acute myeloid leukemia *in vivo*.[42,51,52] However, due to its short half-life and poor oral bioavailability JQ1 was not an ideal candidate for treatment in humans.[40,53] With improvement of pharmacokinetic properties in mind, other BET inhibitors have been developed and some have advanced to clinical trials. OTX-015, a BRD2/3/4-selective inhibitor, was the first BET inhibitor for which clinical findings were published.[43] In a Phase I study in 45 patients with lymphoma or multiple myeloma, OTX-015 was found to be generally well-tolerated and yielded two complete responses and one partial response in patients with DLBCL.[54] In a parallel study in 41 patients with

acute leukemia, treatment with OTX-015 resulted in complete remission for two patients, complete remission with incomplete platelet recovery for an additional patient, and partial blast clearance in two patients (NCT01713582).[55]

These clinical reports of BET inhibitors indicate that further investigation in the clinic is warranted.[56] However, the clinical activity observed has generally been modest, such as a 38% best response rate of stable disease in a Phase I study of BET inhibitor ODM-207 in patients with solid tumors (NCT03035591). More preclinical studies are needed to investigate the biology of BET protein functions, especially when considering that many BET inhibitors are non-selective. In addition, BET proteins are involved in several pathways, which can vary and are not redundant between individual BET family members. [57,58] This last consideration also raises concern for potential off-target effects that may produce adverse toxicities, as were observed with BET inhibitor BAY 1238097, resulting in early termination of its Phase I trial in patients with solid tumors (NCT02369029).[59] It is possible that concerns of toxicity as well as the development of resistance may be ameliorated with combination therapy, and a Phase III study of BET inhibitor CPI-0610 in combination with ruxolitinib in patients with myelofibrosis is currently ongoing (NCT04603495).[60]

Targeting Protein-Protein Interactions

Despite the challenges posed by the fundamental nature of protein-protein interaction surfaces, efforts to design inhibitors that disrupt these interactions have advanced the field. For instance, while it is true that PPI surfaces are generally large, studies have shown that binding affinity is chiefly determined by a small number of essential amino acid residues, and these regions are known as “hotspots”.[13,61] Concentrating efforts to targeting hotspot regions, which have been found to be conserved, improves the feasibility of PPI drug discovery, though challenges remain. Progress in methodology ranging from high-throughput screening, structure-based design, and fragment-based drug discovery to computational screening approaches is yielding greater success and inhibitors targeting PPIs of transcription factors are in clinical development.[13,62]

Transcription Factor Dimerization

It is not uncommon for transcription factors to undergo dimerization, whether as homodimers or heterodimers, which mediates functional activity and binding to target genes.[63] Thus, preventing this mechanism by inhibiting or disrupting dimer interactions provides a strategy for repressing activation of oncogenic transcription factors. c-Myc dimerizes with the MYC-associated protein X (Max) in its primary activity, where this association induces a conformational change that facilitates binding to its target DNA motifs and induction of gene transcription. Targeting c-Myc directly to inhibit this interaction has proven especially difficult, hence the aforementioned efforts to suppress c-Myc indirectly with BET inhibitors. This may be attributed to the intrinsically disordered nature of c-Myc’s functional domains, which fold only once it is in dimeric form.[64–66]

A breakthrough on this front, however, is the development of Omomyc, a 90 amino acid miniprotein comprising a mutant form of the basic helix-loop-helix leucine zipper (bHLH-LZ) domain of c-Myc.[67,68] As the bHLH-LZ domain is responsible for oligomerization

and binding to specific DNA sequences, this enables Omomyc to form heterodimers with both Max and c-Myc and modulate their activity.[66,69] Omomyc/Max dimers bind and act to displace c-Myc/Max from promoter regions while Omomyc/c-Myc dimers are incapable of binding to DNA. Omomyc thus interferes with the interaction between c-Myc and Max, inhibiting dimerization with its obligate partner and sequestering c-Myc to repress transcriptional activation of its target genes. Studies suggest that Omomyc can also form homodimers which act similarly to Omomyc/Max heterodimers in competitively occupying E-box DNA response elements.[65,70,71] Despite its large molecular size, which would suggest unfavorable physicochemical properties, Omomyc was found to possess cell-penetrating activity by acting as a protein transduction domain (PTD), a characteristic observed of many proteins with bHLH-LZ domains. Omomyc was shown to inhibit tumor growth in lung adenocarcinoma *in vivo*. When administered in combination with the chemotherapeutic paclitaxel, Omomyc demonstrated anti-tumor activity and increased survival of mice in a lung adenocarcinoma xenograft model.[72] As OMO-103, Omomyc entered a Phase I/II study in 2021 to evaluate its safety, pharmacokinetics, and biological activity in solid tumors (NCT04808362).[69]

Regulators of Transcription Factor Activity

Other transcription factors may associate with specific proteins that modulate their activity, such as the transcription factor p53. In contrast to other transcription factors described thus far, p53 is best characterized as a tumor suppressor and is involved in initiating cell cycle arrest and apoptosis in response to cellular stress, most notably DNA damage.[73,74] This makes p53 essential for maintaining the integrity of the human genome and consequently, loss or mutation of p53 occurs in over 50% of human cancers.[75] Additionally, p53 is negatively regulated by MDM2 (the human homolog is HDM2), an E3 ubiquitin ligase, wherein binding of MDM2 to p53 promotes ubiquitination of p53 and subsequent nuclear export and/or proteasomal degradation.[76,77] MDM2 has been shown to be overexpressed or amplified in human cancers, contributing to oncogenic transformation due to inhibition of p53 transcriptional activity and function.[77] Targeting the p53/MDM2 interaction is correspondingly enticing and investment in the development of such therapeutics has translated into nine inhibitors currently under investigation in clinical trials. These inhibitors generally target the deep hydrophobic cavity where three p53 amino acid residues, Phe19, Trp23, and Leu26 interact with MDM2.[78]

RG7112 was the first MDM2 inhibitor to reach the clinic.[77] Derived from a family of *cis*-imidazoline-based compounds known as nutlins, RG7112 exhibited activity in a Phase I study in patients with MDM2-amplified liposarcoma, where treatment in 20 patients resulted in one confirmed partial response and 14 stable disease responses. However, at least one adverse event occurred per patient and 12 serious adverse events, mainly neutropenia and thrombocytopenia, were reported (2009-015522-10).[79,80] In another Phase I study in patients with hematologic malignancies, treatment with RG7112 resulted in three complete responses, two partial responses, and nine stable disease responses in a cohort of 30 patients with acute myeloid leukemia (NCT00623870).[81] AMG 232 is a piperidinone-containing MDM2 inhibitor investigated with or without trametinib in a Phase Ib study in patients with acute myeloid leukemia; in a group of 30 patients, one complete remission, four

morphologic leukemia-free states, and one partial remission responses were observed, although gastrointestinal adverse events occurred at higher doses (NCT02016729).[82,83] In a Phase I study of NVP-CGM097, a dihydroisoquinolinone derivative, in patients with wild-type p53 solid tumors, partial responses and stable disease were seen in 2.1% and 43.8% of patients, respectively (NCT01760525).[84,85] Other p53/MDM2 inhibitors currently under study in the clinic include RG7388, SAR405838, MK-8242, RAIN-32 (formerly DS-3032b), HDM201, and APG-115 (Table 1).[78]

While inhibiting MDM2 is a viable therapeutic strategy for cancers with wild-type p53, the remaining 50% of cancers are hindered by p53 mutations; this illustrates a prominent limitation of this approach.[78] Moreover, MDMX, a homolog of MDM2, has been shown to stabilize MDM2 and formations of MDM2/MDMX dimers augment p53 ubiquitination.[76,86–88] As studies suggest that MDMX too is overexpressed in a number of cancers, dual inhibition of MDM2 and MDMX may be necessary for efficacious liberation of p53.[89] ALRN-6924, an α-helical peptide that inhibits both MDM2 and MDMX, was investigated in a Phase I study in patients with solid tumors or lymphomas; evidence of tolerability and activity were demonstrated, resulting in 4.9% complete response, 4.9% partial response, and 48.8% stable disease.[90]

Transcription Factor Co-factors

Co-activators of transcription factors also constitute compelling targets for therapeutic discovery, as their association with transcription factors are required for transcription initiation. Thus, inhibiting these types of PPIs can suppress aberrant gene expression.[91] Mixed Lineage Leukemia 1 (MLL) is a transcription factor that frequently undergoes chromosomal translocation, and the resulting MLL fusion protein has been implicated in acute myeloid (AML) and acute lymphoblastic leukemias (ALL). As prognosis for patients with MLL translocations is quite poor, strategies for developing treatments for this malignancy are being explored. One approach has focused on targeting the co-activator protein menin, which studies have indicated to be important for recruiting the oncogenic MLL fusion protein to its target genes.[92,93] Small-molecule inhibitors targeting the menin-MLL interaction were developed from a class of thienopyrimidine compounds and licensed to Kura Oncology.[8,93] One candidate, KO-539, is currently under investigation in a Phase I/IIa study in patients with AML, and promising preliminary clinical data reported by the company suggests tolerability and presence of biological activity (NCT04067336).[94]

Targeting the DNA-Binding Domain

The DNA-binding domain of transcription factors confers to this class of proteins the unique ability to bind to specific DNA sequences in the enhancer or promoter regions of genes and modulate transcriptional activity.[95] In the case of oncogenic transcription factors, targeting the DNA-binding domain holds attractive therapeutic potential. Transcription factor decoys that mimic the binding motifs of their respective transcription factors leverage this feature by competitively inhibiting binding of the transcription factor to the normal genomic binding site.[96,97] In doing so, transcription factor decoys act as a sink, preventing transcription factor-DNA interactions. These decoys are typically double-stranded DNA oligonucleotides

and are often chemically modified to enhance stability and resistance to degradation by cellular nucleases, such as with the use of phosphorothioate linkages.[96]

The number of transcription factor decoys that have advanced to clinical trials in cancer is few. An exception to this is a STAT3 decoy derived from the STAT3 response element in the c-*FOS* promoter. This first-generation linear STAT3 decoy preferentially bound to activated STAT3, suppressed proliferation of HNSCC cells, and downregulated expression of the STAT3 target genes *in vitro* (Figure 3a).[98,99] The decoy further promoted tumor growth inhibition and reduced activated STAT3 *in vivo*.[4,100] In a first-in-human Phase 0 study in patients with HNSCC, intratumoral administration of the STAT3 decoy was found to exhibit pharmacodynamic activity by downregulating expression of the STAT3 target genes *cyclin D1* and *Bcl-xL* following intratumoral delivery (NCT00696176).[4] A second-generation decoy, referred to as cyclic STAT3 decoy, cyclized the decoy to reinforce resistance to denaturation by heat and nuclease degradation (Figure 3b).[98] This second iteration of the decoy exhibited greater stability in human serum and inhibited the growth of HNSCC and NSCLC tumors in preclinical models following tail vein delivery.[101,102]

Transcription factor decoys face a challenge in the task of efficiently delivering oligonucleotides to target sites of residing tumor.[96] Some successes on this front have included utilizing glycopolymer and nanoparticle carriers as well as an ultrasound-targeted microbubble destruction (UTMD) technology to locally deliver oligonucleotides.[97]

Targeting Transcription Factors for Degradation

In recent years, the emergence of proteolysis targeting chimeras (PROTACs) has revealed a novel avenue for targeting transcription factors. PROTACs harness the cellular ubiquitin-proteasome system, employing a heterobifunctional molecule that comprises two ligands joined by a linker. One ligand recruits the protein of interest (POI) and the other an E3 ubiquitin ligase. This enables the formation of a ternary complex and ubiquitination of the POI, facilitating targeted proteasomal degradation.[103,104] The promise of PROTACs lies in their unorthodox mode of action, which is distinct from traditional inhibitors that have customarily constituted small molecules. For example, whereas small-molecule inhibitors rely on occupancy-driven inhibition to fulfill their function, a mechanism that necessitates high affinity, PROTACs engage in catalytic-driven degradation.[105] Accordingly, PROTACs can modulate degradation with less than consummate POI binders, binders that are absolved of the requisite to target function, and with lower doses, reducing prospective toxicity.[95,105,106] Therefore, PROTACs may be less susceptible to compensatory mechanisms of resistance and as they operate through protein degradation, permit elimination of all functions of the target.[103,107]

There is appreciable interest in the potential of applying PROTACs to transcription factors given how historically difficult they have been to target. Significant momentum has been achieved by Arvinas in targeting the androgen receptor (AR) and estrogen receptor (ER) nuclear hormone transcription factors.[108] Mutation or amplification of the AR is widely recognized as critical for prostate cancer progression.[109,110] Similarly, the ER is acknowledged for its crucial role in breast cancer where virtually 80% of all breast

cancers are ER-positive.[111,112] ARV-110, an AR-targeting PROTAC, advanced to Phase I/II clinical trials in 2019 in patients with metastatic castration-resistant prostate cancer (mCRPC) (NCT03888612). Data from the ongoing trial demonstrated suitable tolerability and decreased prostate specific antigen (PSA) levels; in a group of seven patients with T878 or H875 AR mutations evaluable by RECIST, six displayed tumor size reduction.[113] ARV-110 has since entered a Phase Ib study in combination with the anti-androgen therapy abiraterone in patients with mCRPC (NCT05177042). Promisingly, the ER degrader ARV-471 also produced encouraging results in an ongoing Phase I/II study in patients with ER+/HER2- or metastatic breast cancer, with or without addition of CDK4/6 inhibitor palbociclib (NCT04072952). Monotherapy of ARV-471 was well-tolerated and resulted in a clinical benefit rate of 40% in the Phase Ia portion of the study, with three out of 38 patients achieving partial responses. Additionally, on-target activity was confirmed by observation of ER degradation.[114]

Unlike other transcription factors, ARs and ERs have undergone extensive investigation as targets for small-molecule inhibition due to their “druggability” as receptors whose natural ligands, androgen and estrogen hormones, are themselves small molecules. However, these approaches have frequently been plagued by development of resistance.[115–117] It is also remarkable to note that the patient population of the two aforementioned studies included those heavily pretreated by other therapies; the encouraging findings of ARV-110 and ARV-471 in these patients allude to the potential capacity of PROTACs to surmount these limitations. A few other transcription factor-targeting PROTACs currently under study in the clinic include KT-333 (STAT3, Phase I; NCT05225584), AC682 (ER, Phase I; NCT05080842), and CC-94676 (AR, Phase I; NCT04428788).[106,118–120]

Of particular interest to transcription factor targeting is the development of PROTACs with oligonucleotide warheads.[121] In developing TF-PROTACs, the Wei group linked azide-modified NF-κB or E2F oligonucleotide decoys to VHL ligands to create NF-κB and E2F PROTACs, respectively (Figure 4). In HeLa cells, NF-κB-PROTACs degraded NF-κB p65 while E2F-PROTACs degraded E2F, and both TF-PROTACs inhibited colony formation. By contrast, their respective oligonucleotides alone did not.[122] The Huang group has also introduced oligonucleotide-based PROTACs (O’PROTACs) targeting LEF1 and ERG. These O’PROTACs efficaciously degraded their targets *in vitro* and the LEF1 O’PROTAC further inhibited tumor growth *in vivo* in a prostate cancer mouse model.[123]

The outlook for PROTACs appears promising. Yet, it is important to consider and anticipate challenges. For instance, studies have shown that PROTACs may suffer from on-target toxicities and the total elimination of certain targets involved in multiple functions may lead to detrimental repercussions, raising concerns of safety.[107,124] Moreover, though the human genome encompasses over 600 E3 ligases, only a small minority are routinely implemented; this currently limits the potential of this technology given that some cell-type and tissue-specific ligases exist and could be harnessed by PROTACs to great benefit.[105,124] Poor pharmacokinetic properties due to the large molecular weight of PROTACs are also of concern; conversely, the promising early clinical results of ARV-110 and ARV-471 suggest that this may not significantly hinder the potency of PROTACs.[113,114] Furthermore, the ability to use oligonucleotides as the POI ligand and even more expansively, ligands that

bind to domains other than those that are important for PPIs or DNA binding highlights the powerful potential of PROTACs to target a large number of transcription factors that have until recently been considered “undruggable”.[95,121]

Conclusion

Clinical strategies for targeting transcription factors in cancer have been challenging to develop. This is aptly reflected in the numerous approaches that have been explored in the pursuit of therapeutic intervention, including indirect targeting, targeting protein-protein interactions, targeting the DNA-binding domain, and proteasomal degradation. Some of these approaches have encountered limitations: small-molecule inhibition of upstream kinases is prone to developing resistance while insufficient selectivity of BET inhibitors may induce off-target effects. Others, such as Omomyc and PROTACs, are being tested in ongoing clinical studies and as such, their safety and efficacy in patients remains to be determined. Nevertheless, the progress as of late following years of work is evident in the number of transcription factor-targeting therapeutics beginning to reach the clinic. Investigating the scope of their therapeutic potential will be exciting to follow.

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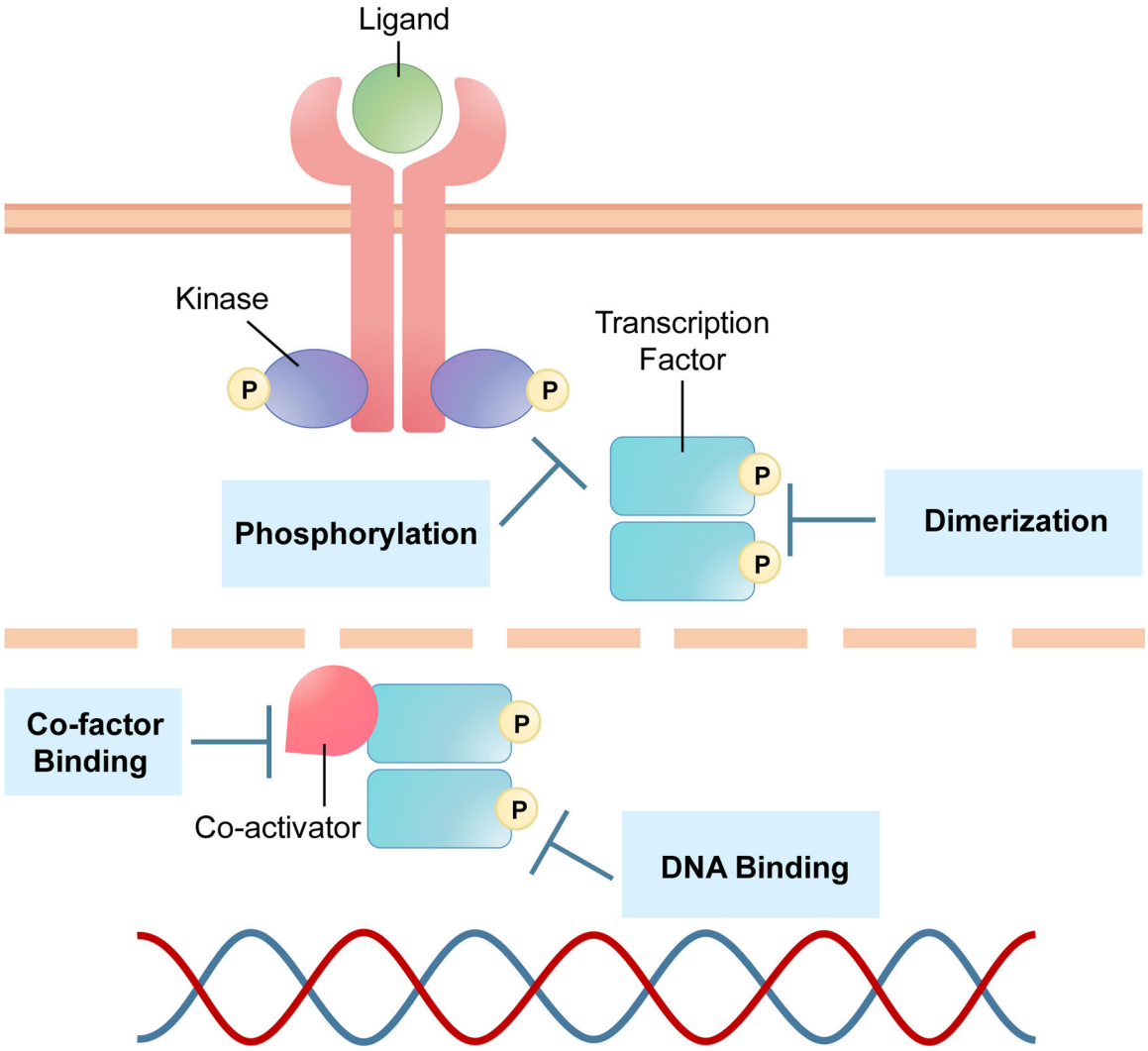

Figure 1. Transcription factor activation and mechanism

Transcription factors may be activated by various mechanisms (as shown in this representative example) including phosphorylation by upstream kinases, homotypic or heterotypic dimerization, and interaction with co-factor regulators such as co-activators or co-repressors. Once activated, transcription factors bind to specific DNA motifs in the enhancer or promoter regions of target genes and induce transcription. Inhibiting or preventing these interactions are viable therapeutic approaches for targeting oncogenic transcription factor activity.

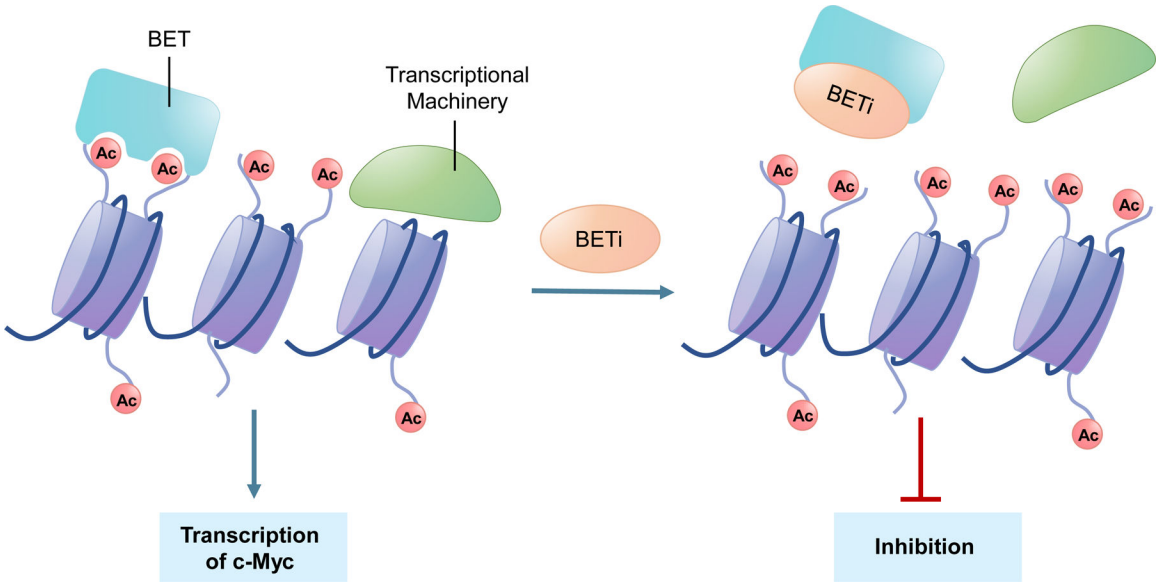

Figure 2. Indirect targeting of transcription factor activity by BET inhibition

BET proteins bind to acetylated lysine residues on histone tails and recruit co-activators of the transcription preinitiation complex, leading to activation of transcription by RNA Polymerase II. BET family member BRD4 is found in high concentrations at super-enhancer regions of genes, including those associated with the oncogenic transcription factor c-Myc. Inhibiting BET proteins with BET inhibitors prevents interaction of BRD4 with DNA super-enhancer regions. In the absence of BRD4, transcriptional machinery is not recruited, and this serves to indirectly downregulate c-Myc expression.

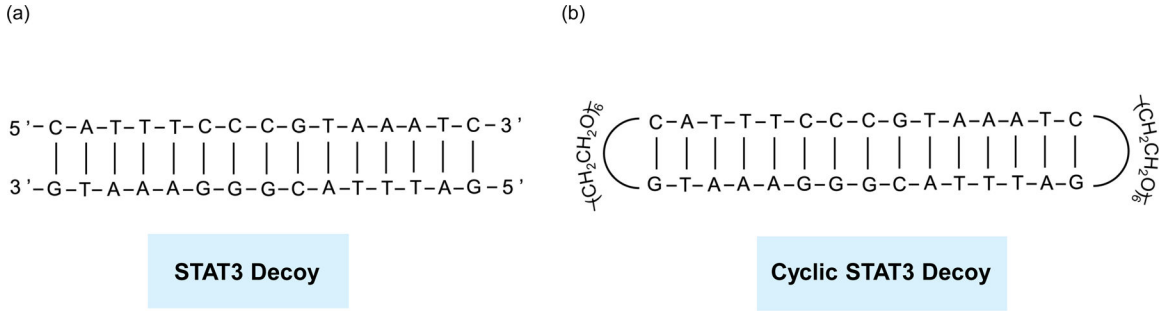

Figure 3. Structures of STAT3 decoy and cyclic STAT3 decoy

(a) Structure of the first-generation STAT3 decoy. The STAT3 decoy is a double-stranded, 15-bp linear oligonucleotide with modified phosphorothioate nucleotides at the 5' and 3' ends to confer resistance to degradation. (b) Structure of the second-generation cyclic STAT3 decoy. The cyclic STAT3 decoy has been modified to contain hexaethylene glycol linkages at either end. This creates a fully cyclic decoy that further increases stability. Figure adapted from Sen *et al.*[98]

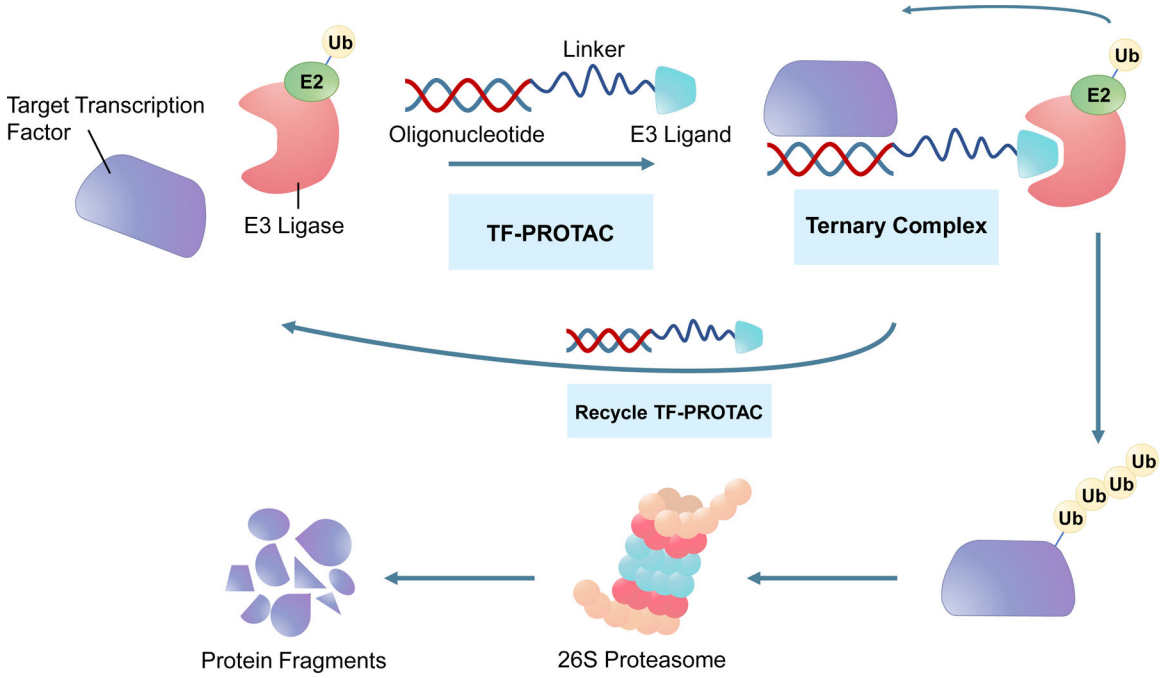

Figure 4. TF-PROTAC mechanism of action

TF-PROTACs utilize oligonucleotides as the protein of interest ligand. The oligonucleotide used corresponds to a target transcription factor's DNA response element, enabling recruitment and subsequent degradation of the transcription factor. The TF-PROTAC simultaneously recruits the target transcription factor and E3 ligase, forming a ternary complex that leads to polyubiquitination of the target transcription factor which is then degraded by the 26S proteasome. The TF-PROTAC is recycled and can participate in successive reactions. This distinguishing feature of PROTAC mechanism of action results in sub-stoichiometric degradation of target proteins.

Table 1.

MDM2 inhibitors in clinical development for cancer

Inhibitor	Development Phase	Indication
RG7112 (Roche)	Phase I	Advanced solid tumors, hematologic neoplasms
RG7388 (Roche)	Phase I, II, III	ET, PV, AML, solid tumors, ALL, NB, MM, NHL, breast cancer, CRC, glioblastoma
SAR405838 (Sanofi)	Phase I	Neoplasm malignant
MK-8242 (Merck)	Phase I	AML, solid tumors
AMG232 (Amgen)	Phase I	Advanced solid tumors, MM, AML, melanoma, glioblastoma, STS
RAIN-32 (formerly DS-3032b) (Rain)	Phase I, II, III	MM, AML, advanced solid tumors, lymphoma, MDS, liposarcoma
HDM201 (Novartis)	Phase I, II	STS, AML, CRC, liposarcoma, advanced solid and hematological TP53wt tumors, UM, AML, MF
NVP-CGM097 (Novartis)	Phase I	TP53wt solid tumors
APG-115 (Ascentage Pharma)	Phase I, II	T-PLL, advanced solid tumors, lymphoma, liposarcoma, AML, CMML, MDS, melanoma, salivary gland cancer

This table summarizes the nine MDM2 inhibitors currently under investigation in clinical trials in patients with cancer.

ET: essential thrombocythaemia; PV: polycythemia vera; AML: acute myeloid leukemia; ALL: acute lymphocytic leukemia; NB: neuroblastoma; MM: multiple myeloma; NHL: non-Hodgkin lymphoma; CRC: colorectal cancer; STS: soft-tissue sarcoma; MDS: myelodysplastic syndrome; UM: uveal melanoma; MF: myelofibrosis; T-PLL: T-cell prolymphocytic leukemia; CMML: chronic myelomonocytic leukemia