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Research Progress on Targeted Degradation of Transcription Factors Based on PROTAC Technology

Menglin Han

College of Wine and Horticulture, Ningxia University, Yinchuan, China
2287389473@qq.com

Abstract. For transcription factors (TFs), biological importance has not always translated into pharmacological tractability. These proteins coordinate gene expression programs involved in proliferation, differentiation, immune homeostasis, and development, yet many disease-relevant TFs lack the compact binding pockets that make enzymes or receptors easier to target. Their extended protein-DNA and protein-protein interfaces, together with frequent intrinsic disorder, further complicate ligand discovery. PROTAC technology offers a different route: instead of requiring continuous functional blockade, a degrader recruits an E3 ubiquitin ligase to the TF and lowers the cellular amount of the target through ubiquitin-proteasome-dependent degradation. In this review, TF-directed degraders are considered according to how the target is recognized. Four representative modes are discussed: ligand-binding-domain-directed PROTACs for nuclear receptors, small-molecule degraders that use noncanonical binding surfaces, nucleic-acid-recognition-element-mediated degraders, and biological PROTACs (bioPROTACs). Examples centered on ERα, AR, STAT3, and c-Myc are used to compare where each approach works well and where it remains limited. Particular attention is paid to the scarcity of selective binders, the narrow E3-ligase repertoire currently used, ternary-complex geometry, intracellular and nuclear delivery, and the distinct developability problems of different degrader formats. The review also considers how broader E3-ligase recruitment, structure-guided optimization, improved delivery, and AI-assisted discovery may extend targeted degradation to TFs that remain difficult to modulate by conventional pharmacology.

Keywords: PROTAC, transcription factor, targeted protein degradation, nuclear receptor, biological PROTAC

1. Introduction

Transcription factors (TFs) translate regulatory signals into changes in gene expression by recognizing cis-regulatory DNA elements and controlling downstream transcription. Through this activity, they participate in proliferation, differentiation, apoptosis, immune responses, and development. Disease can arise when TF expression, activity, or sequence is altered; such abnormalities have been linked to malignant, inflammatory, autoimmune, and neurodegenerative disorders. Their importance as disease drivers, however, contrasts with their poor tractability as drug targets [1]. Many TFs do not contain the deep catalytic pockets typical of enzymes. Instead, they

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often act through broad protein-DNA or protein-protein interfaces, and intrinsically disordered or conformationally flexible regions are common. These features make selective ligand discovery difficult. Small-molecule inhibitors are available for a subset of TFs, but their use is largely confined to proteins that offer a suitable binding site and can be controlled through sustained occupancy. Finding ways to modulate TFs outside this relatively small group therefore remains a central problem in drug discovery.

Where a ligandable site is present, conventional inhibitors can suppress TF activity by occupying ligand-binding or regulatory regions and disturbing DNA binding, cofactor recruitment, or receptor activation. This approach is well established, but its effect usually falls as drug concentration and target occupancy decline. It also leaves the target protein in the cell, allowing altered expression, compensatory signaling, or mutations in the binding region to weaken the response [2]. Targeted degradation addresses the problem from a different angle. A PROTAC brings the TF into proximity with an E3 ubiquitin ligase, promotes ubiquitination, and directs the protein to proteasomal degradation. The pharmacological objective is therefore not simply to block a functional site, but to reduce the abundance of the TF itself.

The growing number of TF-directed degraders shows that this concept is feasible, but the design route is not the same for every TF. Some targets already have high-affinity ligands, whereas others offer only shallow surface sites, sequence-specific nucleic-acid recognition, or protein epitopes that can be captured by engineered binders. E3-ligase compatibility and the geometry of target recognition also vary from one TF to another. Rather than organizing the field target by target, this review compares four recognition-based strategies: nuclear-receptor-binding PROTACs, PROTACs that use noncanonical small-molecule binding sites, nucleic-acid-recognition-element-mediated degraders, and biological PROTACs. ERα, AR, STAT3, and c-Myc are discussed as representative examples. This framework is used to examine not only degradation activity, but also the practical limits of each format and the design issues that will matter when extending targeted degradation to TFs for which conventional ligands are scarce.

2. PROTAC technology

Successful PROTAC action requires several events to occur in sequence. The degrader must first engage the TF and an E3 ligase, place them in a productive ternary complex, allow ubiquitin transfer to accessible lysine residues, and ultimately direct the modified target to the proteasome. This sequence explains why binding affinity alone is an incomplete predictor of degradation. E3-ligase choice, linker architecture, ternary-complex cooperativity, lysine accessibility, cellular uptake, and entry into the compartment in which the TF resides can each become rate-limiting [3]. For transcription factors, these variables are especially relevant because many targets are nuclear and because recognition modules range from small molecules to nucleic acids and proteins.

2.1. Composition and mechanism of PROTAC-mediated degradation

A conventional PROTAC contains a target-recognition ligand and an E3-ligase-recruiting ligand joined by a linker. The two binding elements do more than tether separate proteins: together with the linker, they determine whether the target and ligase can adopt a geometry that supports ubiquitination. One end of the molecule engages the TF, or an accessible site associated with it, while the other binds an endogenous E3 ubiquitin ligase. Linker length and attachment point are therefore important, but so are rigidity and conformational freedom, since these features influence the orientation and stability of the target-PROTAC-E3 complex.

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Once a productive ternary complex is formed, ubiquitin can be transferred through the E2/E3 machinery to lysine residues on the target. Accumulation of a polyubiquitin signal allows recognition by the 26S proteasome and leads to degradation of the TF [1]. This differs from classical occupancy-based inhibition in an important way. Continuous occupation of a functional site is not necessarily required after degradation has been initiated, because the target protein itself is removed. The resulting loss of TF abundance can suppress several functions of the same protein at once. Even so, degradation is not automatic: the quality of the target ligand, the recruited E3 ligase, the ternary-complex conformation, and intracellular delivery all remain decisive.

2.2. Mechanistic differences among PROTACs, conventional inhibitors and molecular glues

Conventional inhibitors and PROTACs differ most clearly in what they require from target engagement. For an occupancy-driven inhibitor, pharmacological activity generally tracks the fraction of target that remains bound; when in-vivo drug levels fall, inhibition commonly falls as well. Mutations in the ligand-binding region can further weaken affinity and contribute to resistance. A PROTAC is instead described as event driven because a transient encounter can be sufficient if it produces a ternary complex that initiates ubiquitination. Target function then returns only after new protein is synthesized, so the biological effect may outlast degrader exposure. This distinction does not eliminate resistance, but it means that some variants that remain bindable and recruitable to an E3 ligase may still be susceptible to degradation [1].

Molecular glues use the same cellular degradation machinery but reach the target-ligase complex in another way. Rather than carrying two ligands connected by a linker, a glue is usually a single small molecule that creates or stabilizes an interaction between an E3 ligase and a protein that would otherwise interact only weakly, if at all, with that ligase. The newly recruited protein is treated as a neo-substrate and can then be ubiquitinated and degraded [4]. Their smaller molecular size can give molecular glues physicochemical and pharmacokinetic advantages over heterobifunctional PROTACs. The trade-off is discoverability. Many glues were identified through phenotypic screening or unexpected observations, and the structural rules that govern glue-induced protein-protein recognition are still incomplete. Rationally extending this modality to new targets is therefore less straightforward than its compact architecture might suggest.

2.3. Major challenges and design considerations for TF-targeting PROTACs

Several constraints repeatedly appear when PROTACs are designed for TFs. The most obvious is target recognition: many TFs still lack a selective small-molecule ligand that can serve as a useful warhead. E3-ligase recruitment creates a second bottleneck because present designs are dominated by a small group of ligases, especially CRBN and VHL, whose abundance and subcellular distribution differ across tissues [2]. Even when both ligands are available, linker design remains difficult. Length, flexibility, rigidity, polarity, and attachment position can all reshape the ternary complex, yet no general linker rule reliably predicts a productive geometry [3]. The developability problem also depends on modality. Heterobifunctional small molecules can be large and may show poor solubility, membrane permeability, oral bioavailability, or metabolic stability [2]. Nucleic-acid and biological PROTACs face a different set of barriers, notably cellular and nuclear delivery and vulnerability to nuclease or protease degradation [4].

These limitations make TF properties the natural starting point for degrader design. A nuclear receptor with a defined ligand-binding domain and a validated high-affinity ligand can often be approached with a conventional small-molecule PROTAC. A TF that lacks such a pocket may still

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expose a groove or allosteric surface that accepts a weaker ligand; in that setting, attachment chemistry and ternary-complex geometry become particularly influential [3]. When small-molecule recognition is not practical but sequence-specific DNA binding is retained, DNA decoys, oligonucleotides, artificial nucleic acids, or aptamers can provide the recognition element. Engineered protein binders such as nanobodies or DARPins offer yet another route when neither small molecules nor nucleic-acid elements are suitable. In other words, the recognition module is not a fixed component of TF degradation but a design variable that should be matched to the molecular features of the target.

3. Target-recognition strategies for PROTAC-mediated degradation of transcription factors

The strategies discussed below are separated by the way in which the transcription factor is captured. This distinction is useful because recognition determines much of the downstream design problem. Established ligands allow a relatively conventional heterobifunctional PROTAC architecture, whereas shallow or noncanonical sites may require weaker small-molecule binders whose value emerges only in the ternary complex. Sequence-specific DNA binding can be exploited with decoys or aptamers, and engineered protein binders can recognize targets that remain inaccessible to the other formats. The four categories therefore overlap in purpose but differ substantially in molecular size, delivery requirements, target coverage, and the amount of optimization needed before efficient degradation is obtained.

3.1. Ligand-binding-domain-directed PROTACs for nuclear receptors

Nuclear receptors are among the most tractable TFs for targeted degradation because their ligand-binding domains (LBDs) are well characterized and high-affinity antagonists or modulators are already available. Such compounds can be repurposed as the target-binding arm of a PROTAC and linked to a CRBN- or VHL-recruiting ligand. This avoids starting target-ligand discovery from scratch. The remaining challenge is to place the two proteins in a productive arrangement: linker structure and the exit vector from the receptor ligand can markedly alter ternary-complex formation. Careful optimization of this geometry may also preserve degradation of receptor variants that have become less responsive to conventional endocrine or antiandrogen therapy.

ERα provides a well-developed example. In ER-positive breast cancer, continued ERα signaling supports tumor growth, while ESR1 LBD substitutions such as Y537S and D538G promote ligand-independent activation and can reduce sensitivity to endocrine therapy. ERD-308, reported by the Crews group, joined a fulvestrant-derived ER ligand to a VHL-recruiting group through an aliphatic linker [5]. In MCF-7 cells, its DC_{50} was 0.17 $nmol \cdot L^{-1}$, and more than 95% ERα degradation was observed at 5 $nmol \cdot L^{-1}$; degradation was retained against both wild-type and mutant receptors. ARV-471 (vepdegestrant), which recruits CRBN, subsequently advanced into late-stage clinical development [6]. The same general logic has been used for androgen receptor (AR) degradation. ARV-110 (bavdegalutamide) couples an AR-binding scaffold to a VHL-recruiting moiety and has been studied in metastatic castration-resistant prostate cancer. It produced marked AR degradation in 22Rv1 xenografts, and a Phase I/II study (NCT03888612) reported a PSA50 response in 46% of patients with AR T878X or H875Y mutations [7].

The strength of ligand-directed receptor degradation is also its main restriction: it works best when a validated receptor ligand already exists. TFs without an equivalent LBD or ligand set cannot be transferred directly into this design scheme. Resistance can also reappear if an LBD mutation weakens warhead binding or changes the orientation of the ternary complex enough to reduce

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ubiquitination. Another concern is the repeated use of CRBN and VHL. Because these ligases are not expressed or accessible to the same extent in every tissue, identical degraders may behave differently across biological contexts. For targets that are also present in normal tissue, this raises a safety question that cannot be answered by degradation potency alone.

3.2. Small-molecule PROTAC strategies targeting non-canonical binding sites

Many TFs sit outside the nuclear-receptor paradigm because they do not offer a deep pocket with a high-affinity ligand. That does not necessarily mean that small-molecule recruitment is impossible. Shallow grooves, allosteric surfaces, or transient pockets may still bind compounds strongly enough to support degradation. In a PROTAC, such a ligand does not need to behave as an excellent inhibitor on its own. What matters is whether the ligand, its attachment point, and the linker allow the target and E3 ligase to form a productive complex. For this reason, a parent compound with only moderate affinity or weak functional inhibition can become useful after conversion into a degrader.

Pregnane X receptor (PXR) illustrates this point. PXR controls xenobiotic metabolism and contains a large, flexible ligand-binding domain that accepts chemically diverse ligands, a property that complicates the search for selective antagonists or inverse agonists. Kamaraj and co-workers converted the PXR antagonist SPA70 into the PROTAC MI1013 by linking it to the CRBN ligand pomalidomide through a polyethylene glycol spacer. In HepaRG cells, MI1013 produced a DC_{50} of 89 $nmol \cdot L^{-1}$ and a Dmax of 82%. MG132 blocked the loss of PXR, consistent with proteasome-dependent degradation. MI1013 also reduced rifampicin-induced expression of downstream drug-metabolizing genes, including CYP3A4. The result is instructive because SPA70 did not need exceptional intrinsic inhibitory potency to function as a useful recognition element; its value emerged in the context of a degrader that could assemble a productive ternary complex.

Noncanonical-site targeting therefore expands small-molecule PROTAC design, but only as far as a chemically usable surface can be found. Moderate-affinity warheads place greater pressure on linker selection and attachment geometry, and flexible or shallow surfaces can make both affinity and selectivity difficult to optimize. Off-target binding becomes a practical concern when the recognition site is poorly defined. Structure-guided work can narrow the search, but empirical testing is still common because linker behavior is highly context dependent. TFs that provide no exploitable small-molecule surface remain beyond the reach of this approach and require a different recognition modality.

3.3. Nucleic-acid-recognition-element-mediated PROTAC strategies

For some TFs, the most reliable recognition feature is not a protein pocket but the DNA sequence that the factor normally binds. A sequence-specific DNA element can be repurposed as a decoy, attached to an E3-ligase-recruiting group, and used to bring the TF into a degradation pathway. This concept avoids the need to identify a conventional small-molecule warhead. It can also be extended beyond natural DNA sequences: TNA-based constructs and aptamers provide additional ways to recognize TFs through nucleic-acid chemistry. The resulting degraders are therefore attractive for chemically difficult targets, although their larger and highly charged recognition elements introduce delivery problems that small-molecule PROTACs do not share.

STAT3 is a representative target because persistent STAT3 activation occurs in several solid and hematological malignancies, while direct small-molecule inhibition has been limited by ligandability and selectivity. Liu's group exploited STAT3 DNA recognition to construct a D-PROTAC in which a DNA decoy was linked to an E3-ligase-recruiting moiety. In HeLa cells, the degrader showed a DC_{50}

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of 0.46 μmol·L^{-1} and removed more than 80% of STAT3. STAT1 and STAT5 were not degraded to a comparable extent, supporting sequence-dependent selectivity. Loss of STAT3 was accompanied by lower expression of BCL-2, Survivin, and MMP-9 and by reduced tumor-cell proliferation and invasion. In a cervical-cancer xenograft model, tumor growth was inhibited by 64%, with no obvious liver or kidney toxicity reported [8]. The same recognition principle has been applied to NF-κB p65 using an NF-κB-specific DNA element [8]. TNA/DNA chimeric degraders and aptamer-based PROTACs directed at c-Myc further show that nucleic-acid recognition need not be limited to a single chemical format.

The practical difficulty is getting these nucleic-acid-containing degraders to the place where they must act. Their size and dense negative charge hinder passive membrane passage and can make nuclear entry inefficient [9]. They are also exposed to nuclease degradation in biological fluids, which can shorten systemic persistence before sufficient intracellular concentrations are reached. Some sequences or delivery vehicles may stimulate innate immune sensing, adding an immunological safety issue. As a result, degradation potency measured after successful cellular entry may overstate how readily the modality will work in vivo. Delivery vehicles, chemical stabilization, and the route of administration are therefore integral parts of nucleic-acid-mediated PROTAC development rather than secondary formulation considerations.

3.4. BioPROTACs and protein-recognition strategies

Engineered protein binders provide a third recognition solution when neither a useful small molecule nor a nucleic-acid element is available [10]. In a bioPROTAC, a selective binder such as a nanobody or DARPin recognizes the target protein and is fused to a full-length E3 ligase or to a functional ligase domain. The construct therefore creates target-ligase proximity through protein-protein recognition rather than through a heterobifunctional small molecule. This gives bioPROTACs access to epitopes that would be difficult to address with a conventional warhead.

FOXO1 illustrates both the opportunity and the selectivity challenge. FOXO-family TFs regulate cell-cycle progression, apoptosis, and senescence, but conventional PROTAC development is hampered by the shortage of suitable small-molecule ligands and by the high sequence and structural similarity among FOXO proteins [11]. In one study, FOXO1-binding nanobodies isolated by phage display were fused to the E3 ligase Parkin. After intracellular expression, the resulting bioPROTAC reduced FOXO1 protein levels by more than 70%. Changes in apoptosis- and cell-cycle-related gene expression were observed together with reduced tumor-cell survival. The experiment established proof of concept for selective protein-binder-mediated TF degradation, although it did not yet provide a systematic in-vivo pharmacodynamic or safety assessment.

That proof of concept also highlights the main translational barrier: bioPROTACs are macromolecules and generally do not cross cell membranes efficiently on their own. Effective use may therefore require viral delivery, mRNA, or another strategy that produces the degrader inside the cell. These solutions bring their own constraints, including control of expression, in-vivo stability, and potential immunogenicity. Upstream discovery can also be labor intensive because a nanobody or DARPin must be both high affinity and sufficiently selective, often after substantial library screening. For these reasons, TF-directed bioPROTACs remain largely preclinical. Progress will depend as much on delivery and control of intracellular expression as on the degradation machinery itself, and longer-term pharmacokinetic and safety studies are still needed.

Taken together, the four recognition modes occupy different parts of the TF target space rather than forming a simple hierarchy. Validated small-molecule ligands make conventional PROTAC construction relatively direct; noncanonical surfaces can extend that approach to weaker or

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unconventional binders; nucleic-acid elements exploit sequence recognition; and engineered proteins can reach epitopes inaccessible to the other formats [12]. Their weaknesses are equally different. Small-molecule designs are constrained by ligandability and ternary-complex geometry, whereas nucleic-acid and protein formats carry a heavier delivery burden. Choosing among them should therefore begin with the molecular biology of the TF and the intended therapeutic setting, not with a preference for one degrader architecture.

4. Challenges and future perspectives

TF degradation has moved beyond a small set of proof-of-principle examples, but clinical maturity remains uneven [13]. Nuclear-receptor degraders benefit from established ligands and have progressed furthest, whereas many nucleic-acid and biological formats are still supported mainly by cell studies or early animal data. Several obstacles are shared across the field. Many TFs still lack selective recognition ligands; CRBN and VHL dominate E3 recruitment even though ligase abundance and localization vary with tissue and cell state [2]; and small changes in linker geometry can turn a potentially productive ternary complex into an ineffective one. The concentration response can also be non-linear, with a hook effect at high degrader concentrations when binary complexes outcompete productive ternary-complex formation [1]. For small-molecule PROTACs, high molecular weight, limited aqueous solubility, weak oral exposure, and metabolic instability further restrict in-vivo use [2]. Nucleic-acid and biological degraders face the separate problem of reaching the cytosol or nucleus in an intact form.

Future development will therefore need to improve several components in parallel rather than optimizing the warhead alone [14]. New recognition elements may come from computational chemistry, AI-assisted screening, high-throughput experimental campaigns, phage display, or aptamer selection, depending on the target. Expanding the E3-ligase toolbox is equally important. Ligases with useful tissue-expression or subcellular-localization profiles could offer selectivity that CRBN or VHL cannot provide, provided that suitable recruiting ligands can be identified [15]. Structural analysis and molecular simulation can then be used to test linker length, rigidity, polarity, and attachment position against ternary-complex geometry. For degraders whose exposure or localization remains limiting, delivery systems, prodrug approaches, and light- or stimulus-responsive designs may provide additional control over when and where degradation occurs [16].

Technical optimization is only part of the remaining work. Long-term suppression of a TF could trigger compensatory signaling or select for new resistance mechanisms, questions that cannot be answered from short degradation assays alone [17]. Nucleic-acid-based degraders also need systematic evaluation of immunogenicity [18]. At the same time, broader E3-ligase recruitment raises the possibility of tissue- or compartment-selective degradation, but this has to be demonstrated rather than assumed [19]. A useful translational assessment should therefore connect molecular degradation with function and exposure: degradation potency and selectivity in vitro, cellular consequences, pharmacokinetics in vivo, and safety after relevant durations of treatment all need to be considered together.

PROTACs have changed the practical question around transcription factors from whether a functional pocket can be continuously inhibited to whether the protein can be recognized and productively presented to the ubiquitin-proteasome system [20]. That shift has opened several design routes, ranging from ligand-based degraders for nuclear receptors to nucleic-acid and protein-recognition formats for less conventional TF targets. The field is unlikely to advance through a single universal architecture. Instead, progress will depend on matching recognition chemistry, E3-ligase choice, ternary-complex geometry, and intracellular delivery to the biology of each target,

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while evaluating selectivity, pharmacokinetics, safety, and developability early enough to influence design.

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