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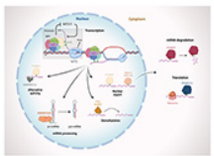

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Samantha D. Patalano, Paula Fuxman Bass & Juan I. Fuxman Bass

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REVIEW

Transcription factors in the development and treatment of immune disorders

Samantha D. Patalano[a,b], Paula Fuxman Bass[c], and Juan I. Fuxman Bass[a,b,d]

[a]Biology Department, Boston University, Boston, MA, USA; [b]Molecular Biology, Cellular Biology and Biochemistry Program, Boston University, Boston, MA, USA; [c]Facultad de Medicina, Universidad de Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina; [d]Bioinformatics Program, Boston University, Boston, MA, USA

ABSTRACT

Immune function is highly controlled at the transcriptional level by the binding of transcription factors (TFs) to promoter and enhancer elements. Several TF families play major roles in immune gene expression, including NF-κB, STAT, IRF, AP-1, NRs, and NFAT, which trigger anti-pathogen responses, promote cell differentiation, and maintain immune system homeostasis. Aberrant expression, activation, or sequence of isoforms and variants of these TFs can result in autoimmune and inflammatory diseases as well as hematological and solid tumor cancers. For this reason, TFs have become attractive drug targets, even though most were previously deemed "undruggable" due to their lack of small molecule binding pockets and the presence of intrinsically disordered regions. However, several aspects of TF structure and function can be targeted for therapeutic intervention, such as ligand-binding domains, protein–protein interactions between TFs and with cofactors, TF-DNA binding, TF stability, upstream signaling pathways, and TF expression. In this review, we provide an overview of each of the important TF families, how they function in immunity, and some related diseases they are involved in. Additionally, we discuss the ways of targeting TFs with drugs along with recent research developments in these areas and their clinical applications, followed by the advantages and disadvantages of targeting TFs for the treatment of immune disorders.

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Introduction

The immune system requires many layers of positive and negative regulation to elicit effective responses against pathogens, while preventing autoimmunity and damage associated with extended inflammation [1]. This regulation is controlled at multiple levels including transcription, mRNA processing and stability, protein stability, and post-translational modification [2]. Transcription is one of the main levels of this regulation and controls the expression of cytokines, inflammatory mediators, and immune response genes, some of which are upregulated hundreds of fold. Transcription factors (TFs) play a critical role in regulating the expression of immune genes due to their ability to activate or repress transcription in response to both intracellular and extracellular signals, potentially allowing for their activity to be modulated for the treatment of immune-related diseases [3].

TFs play several roles in the regulation of gene expression in immune cells, including lineage specification and commitment, differentiation, migration, activation, cytokine production, survival and homeostasis, and environmental sensing and response [4–11]. Aberrant TF expression, expression of specific TF isoforms, or presence of TF variants can lead to dysregulation of immune signaling pathways and the development of immune-related diseases (Figure 1) [12,13]. For instance, humans are known to express two distinct isoforms of FOXP3 due to alternative splicing, the principal isoform containing all coding exons and a shorter isoform that omits exon 2 during splicing. Patients expressing only the shorter isoform have been found to develop autoimmunity due to regulatory T cell instability [14]. Similarly, the IRF5 rs2004640 T allele is a genetic risk factor for the development of systemic lupus erythematosus (SLE) because it promotes the expression of different isoforms of IRF5 [15]. Persistent activation or silencing of signaling pathways that impinge on TFs can also lead to autoinflammation, autoimmunity, or susceptibility to infections. For

CONTACT Juan I. Fuxman Bass fuxman@bu.edu Biology Department, Boston University, 5 Cummington Mall, Boston, MA 02215, USA
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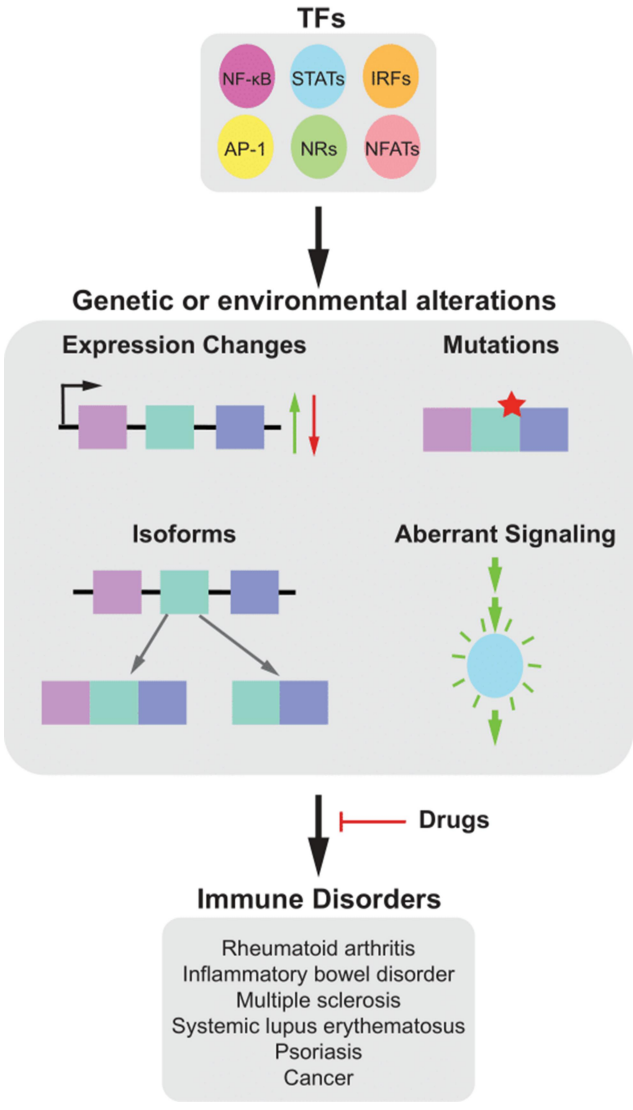

Figure 1. Roles played by transcription factors in the development of immune disorders.

The transcription factor (TF) families NF-κB, STAT, IRF, AP-1, NR, and NFAT are important transcriptional regulators in the immune system. Alterations in these TFs such as increased or decreased expression, SNPs and other mutations, isoforms caused by alternative splicing, starts or termination, and aberrant signaling through the pathways these TFs are involved in can all contribute to the development of autoimmune, inflammatory, and other immune-related disorders. Drug development efforts are underway to target TFs in these families for the treatment of such disorders.

example, TFs within the Nuclear factor-κB (NF-κB) family are major regulators of pro-inflammatory gene expression in both innate and adaptive immune cell types and it has been demonstrated that constitutive activation of NF-κB or genetic alterations in the *NFKB1* gene can lead to inflammatory bowel disease [16]. Furthermore, the Signal Transducer and Activator of Transcription (STAT) family of TFs also plays many roles in immune regulation. Overactivation of the JAK/STAT pathway by the proinflammatory cytokines IL-1, IL-17, IL-12, IL-23, IL-6, TNF-α, and IFN-γ causes rheumatoid arthritis by inducing inflammation in the synovium [17].

Currently, over 300 of the approximately ~ 1,600 TFs encoded by the human genome have been linked to at least one disease phenotype [18,19]. However, drugs are not available for most of these TFs as TFs have typically been deemed "undruggable" due to their intrinsically disordered structure and lack of binding pockets for small molecules [19,20]. Recent advances in the field have shown that many aspects of TF function can potentially be targeted for disease treatment, such as ligand binding, DNA binding, dimerization, protein–protein interactions, stability, cofactors, expression, activity and signaling pathways involving the TF [21,22]. The purpose of this review is to provide an overview of the TF families involved in immune regulation, emphasizing the major players, and the different strategies of targeting TFs for the treatment of immune-related disorders. Additionally, we will discuss the advantages and disadvantages of using drugs to modulate TF expression and function. Finally, we will provide examples of current drugs used to treat immune diseases by targeting TFs.

TFs families and their role in the immune response

There are several major TF families that are known to be heavily involved in the regulation of immune gene expression, including NF-κB, STAT, Interferon Regulatory Factor (IRF), Activating Protein-1 (AP-1), Nuclear (NRs), and Nuclear Factor of Activated T cells (NFAT), among others (Figure 1). Members from these TF families regulate both distinct and overlapping target genes, which allows for crosstalk between immune signaling pathways [23,24]. For example, TFs from all of these families have been found to regulate the expression of the pro-inflammatory

cytokines IL17A, IL1B, and TNF [9,24]. In this section, we will provide an overview of the notable roles each TF family plays in the immune response, including their functions, mechanisms of action, the signaling pathways, and disease associations.

NF-κB

NF-κB is a family of inducible TFs, consisting of the proteins p50, p52, c-Rel, p65 (RelA), and RelB, that play major roles in both the innate and adaptive immune responses [25]. A key feature of the NF-κB family members is that they homo- and heterodimerize to form transcriptionally active complexes, with 15 possible dimers, all with somewhat different DNA specificities and transcriptional activities [25,26]. In unstimulated cells, NF-κB dimers are sequestered in the cytoplasm by IκB proteins. Upon stimulation by pathogen ligands such as bacterial and viral components (i.e., lipopolysaccharide and dsRNA) and pro-inflammatory cytokines, signaling to NF-κB dimers occurs through either the canonical or non-canonical pathway [27–29]. In the canonical pathway, the IκBs are phosphorylated by IKKβ, leading to their degradation via ubiquitination, allowing p50-p65 dimers to translocate to the nucleus. In the non-canonical pathway, IKKα phosphorylates the NF-κB subunit p100, resulting in its proteasomal processing to p52 and activation of p52-RelB dimers. Both pathways lead to the binding of NF-κB dimers to κB sites in enhancer and promoters to induce transcription of specific target genes which ultimately affect immune responses associated with the different immune cell types.

Dysregulation of NF-κB and its signaling pathways can lead to a multitude of immune-related diseases including IBD, rheumatoid arthritis (RA), multiple sclerosis (MS), and a variety of different cancers [16,30]. Overactivation of both the canonical and noncanonical NF-κB signaling pathways in myeloid cells, T cells, and B cells in synovial tissue contributes to the development of RA and such overactivation in the central nervous system contributes to MS progression [16,29]. The treatment for RA has mainly involved reducing immune system activity as a whole with drugs like Methotrexate or blocking production of the pro-inflammatory cytokine tumor necrosis factor (TNF), a known activator of NF-κB, with a class of drugs known as TNF inhibitors, both of which have significant side effects [31]. Current research has moved toward developing drugs that target NF-κB directly by inhibiting the phosphorylation of NF-κB proteins, such as Tetrandrine, or their translocation to the nucleus, like Iguratimod, both of which are currently in clinical trials [32,33]. Iguratimod is also being investigated for the treatment of MS using an animal model of a similar disease known as experimental autoimmune encephalomyelitis, where NF-κB pathways have also been found to be overactivated in astrocytes and microglia [34,35]. In addition to pathway overactivation, GWAS studies have identified some NF-κB protein and pathway participants as candidates for susceptibility to MS [36]. Present treatment for MS mainly involves immunosuppression using glucocorticoids or drugs that either prevent the migration of T cells to the central nervous system or deplete specific immune cell types, such as B cells, all of which come with a number of unwanted side effects [37]. Research in MS treatment is moving toward targeting NF-κB inhibitors in a cell-specific manner to avoid systemic side effects [34,38,39]. Overall, NF-κB has been widely studied for the treatment of immune-related diseases, but is difficult to target due to its essential function in many cell types.

STATs

The STAT family of TFs consists of seven members: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6, all of which play essential roles in immune regulation [40,41]. STAT1 and STAT2 are involved in the protection against viral and bacterial infection through signaling from interferon (IFN) receptors [42,43]. STAT3 helps regulate innate immunity, inflammation, stem cell maintenance, and cell metabolism by signaling downstream of growth factor, cytokine, and pathogen ligand receptors [44]. STAT4 functions in the development of both innate and adaptive immune cells by signaling through cytokine and interferon receptors [45,46]. STAT5A and

STAT5B contribute to the development of blood and immune cell lineages by signaling downstream of growth factor and cytokine receptors [47,48]. Finally, STAT6 assists in the regulation of innate immune and antibody production from B cells after being activated through the IL-4 and IL-13 receptors [49,50]. Like NF-κB, STATs also reside in the cytoplasm and require phosphorylation to be activated. However, in the case of STATs this is mediated by the non-receptor tyrosine protein Janus kinases (JAKs) [40,41,51]. The JAK-STAT signaling pathway is activated when cytokines or growth factors bind to their receptors on a target immune cell, resulting in receptor dimerization and the recruitment of JAKs to the intracellular portion of the receptor. These JAKs phosphorylate the receptors, creating docking sites for the STATs, where they are recruited and, subsequently, phosphorylated by the JAKs. The phosphorylated STATs then dissociate from the receptors, homo- or heterodimerize via interactions between their SH2 domains, and translocate to the nucleus to regulate target genes.

Mutations or polymorphisms in the STAT TFs, aberrations in their production, or dysregulation of the JAK-STAT signaling pathways results in a number of immune-related diseases, such as RA, atopic dermatitis, Parkinson's disease, and cancers like acute myeloid leukemia, lymphoma, and hepatocellular carcinoma [40,41,51]. One example is a disease known as STAT3 gain-of-function syndrome, an autosomal dominant disorder in which mutations within the STAT3 protein result in prolonged activation of STAT3 signaling due to a delay in dephosphorylation [52,53]. Patients with this syndrome can develop many autoimmune disorders, including hemolytic anemia, neutropenia, thrombocytopenia, type I diabetes, scleroderma, arthritis, and lung disease [54]. Current treatments mainly consist of immunosuppressants. However, research is being done to develop more targeted therapies to block signaling upstream of STAT3 using JAK inhibitors [55]. In cancer, constitutive activation of STATs occurs as a result of overactive or aberrantly expressed cytokine and growth factor receptors, causing excessive signaling through the JAK/STAT pathway [41,56,57]. This causes tumor cell proliferation, inhibition of apoptosis, and immunosuppression. Small molecule STAT inhibitors have been continually developed over the past two decades, and research is aiming at targeting the endogenous inhibitors of STATs, the suppressors of cytokine signaling (SOCS) and protein inhibitor of activated STAT (PIAS) protein families [41,56,58,59].

IRFs

The IRF TF family members are essential in antiviral and antibacterial immune responses as they act downstream of pathogen ligands and cytokines, as well as in immune cell differentiation [51,60]. Humans express nine of the known IRF family homologs, IRF1–9, all of which are involved in innate immunity and some also have roles in adaptive immunity [61,62]. The major role of several IRFs is the production of type I IFNs (IFNα and IFNβ) and, subsequently, the transcription of IFN-stimulated genes. This occurs when pattern recognition receptors on innate immune cells detect the presence of foreign nucleic acids, or in some cases self nucleic acids in the cytosol or endosomal compartment [51,63,64]. Upon recognition, the pattern recognition receptors signal through adapter molecules to induce the phosphorylation of TANK binding kinase 1 (TBK1), which then phosphorylates IRF3 and IRF7 waiting in the cytosol. IRF3 and IRF7 can then homodimerize and translocate to the nucleus, leading to the transcription of type I IFNs. These type I IFNs can then bind to their target receptor on adjacent cells, IFNα/β receptor 2 (IFNAR2), which recruits IFNAR1 and forms a complex with the ability to activate JAK1 and tyrosine kinase 2 (TYK2). JAK1 and TYK2 phosphorylate STAT1 and STAT2, which form a heterotrimeric complex with IRF9 called the IFN-stimulated gene factor 3 complex that binds to IFN-stimulated regulatory elements in DNA to promote transcription of ISGs.

Dysregulation of IRFs or IRF-dependent pathways or mutations in IRF genes can contribute to sepsis, autoimmune diseases such as SLE, IBD, scleroderma, Herpes simplex encephalitis, and severe influenza, with IRF5 being the IRF most well-known for disease involvement due to its association with autoimmunity [60,65]. SLE is an

autoimmune disease characterized by elevated IFNα serum levels [66]. IRF5 regulates IFNα expression via signaling through TLRs 7,8 and 9 [67]. The T allele of rs2004640 in the IRF5 gene increases the risk for the development of SLE because it introduces a new donor splice site in exon 1, permitting alternative splicing of this exon [15,68]. Another nearby SNP, the T allele of rs2280714, is strongly associated with increased expression of IRF5 and is also linked to SLE, establishing a SLE risk haplotype [15,69]. Additionally, IRF5 has been found to be constitutively active in the monocytes of SLE patients, leading to increased expression of IL-6, TNFα, and IFNα [60,70]. Current treatment for SLE involves immunosuppressants, glucocorticosteroids, and antimalarial drugs to control the inflammation, but relying on them can leave patients more susceptible to infection and cause long-term organ damage [71]. Recently, the drug anifrolumab, a monoclonal antibody against type I interferon receptor subunit I (IFNAR1) that blocks signaling through the receptor, was approved by the FDA for the treatment of SLE and has shown to decrease SLE-like symptoms, but the relapse rate was still high [72]. For these reasons, targeting IRF5 for SLE treatment is of great interest and recent studies in mice have shown that partial IRF5 inhibition is superior in suppressing SLE-like disease development [73].

AP-1

AP-1 is a family of basic leucine zipper TFs consisting of four subfamilies, JUN (c-Jun, JunB, JunD), FOS (c-Fos, Fra1, Fra2, and FosB), ATF (ATF2, ATF3, ATF4, BATF, and BATF3), and MAF (c-Maf, MafA, MafB, MafG, MafK, MafF, and NRL) that form homo- and heterodimers [74–76]. Jun proteins can homodimerize or heterodimerize with Fos and ATF family members, while Fos proteins can only heterodimerize with Jun family members [76,77]. Mafs are only known to homodimerize in humans *in vivo*, but studies have shown that they can heterodimerize with other AP-1 family members *in vitro* [78,79]. AP-1 dimers are expressed in multiple cell types and regulate different sets of target genes depending on the subunit composition. In addition, different AP-1 dimers are activated by various cellular stimuli, including cytokines and growth factors, viral and bacterial infections, as well as UV radiation, and other cellular stresses [74,80]. These signals activate mitogen-activated protein kinase (MAPK) signaling cascades, which result in either the phosphorylation of Jun proteins and ATF2 by jun amino-terminal kinases (JNK1/2/3) and FOS by ERK2 [81–84]. In immunity, AP-1 TFs are involved in numerous processes such as cytokine gene expression (TNFα, IL-1, IL-2, IFNγ, and GM-CSF), T-cell and B-cell development, and T-cell differentiation [85–87].

Aberrant expression of AP-1 TFs, particularly c-Jun and c-Fos, contributes to several immune-related diseases such as RA, SLE, asthma and psoriasis, as well as a variety of different cancers [88,89]. Overexpression of c-Jun and c-Fos in synovial tissues have been identified as promoters of disease severity in patients with RA by contributing to osteoclast-mediated bone erosion and the dysregulation of soluble mediators of bone erosion from synovial fibroblasts [86,88,90]. Interestingly, JunB is found to be downregulated in some inflammatory diseases and hematological malignancies [88,91]. In psoriasis, downregulation of JunB in keratinocytes causes initiation of the disease by inducing pro-inflammatory cytokine and chemokine expression and, in turn, recruiting macrophages and neutrophils to the epidermis, causing the characteristic skin rashes [92,93]. In chronic myeloid leukemia, JunB is downregulated due to CpG methylation at the promoter, a deviation from what is observed in healthy patients, which results in the GM-CSF mediated myeloproliferation contributing to disease progression [94,95].

Nuclear receptors

NRs are a superfamily of 48 ligand-dependent TFs containing four subfamilies based on their ligand-binding properties: steroid receptors, RXR heterodimers, homodimeric orphan receptors, and monomeric orphan receptors [96,97]. Steroid receptors (type I receptors), such as glucocorticoid receptor (GR), estrogen receptor, and androgen receptor, bind steroidal ligands which is required for their activation and interact with DNA mostly as homodimers [97,98]. In the absence of a ligand, the TF homodimer is bound by heat-shock protein

complexes via their ligand-binding domains in the cytoplasm or the nucleus to prevent DNA binding [99,100]. Upon ligand-binding, the steroid-hormone receptor homodimer dissociates from the heat-shock protein complexes and binds to two closely spaced, palindromic DNA half sites via the individual DNA-binding domains on each monomer of the homodimer to activate transcription of target genes [101]. Retinoic X receptor homodimers or heterodimers (type II receptors) are constitutively bound to DNA, even in the absence of a ligand, and activate target gene expression upon ligand binding [97,98]. Members of this subgroup include thyroid receptor, retinoic acid receptor, vitamin D receptor, and peroxisome proliferator activated receptor-γ [102–104]. Orphan receptors do not have any known endogenous ligands, but are still able to regulate transcription in the absence of a bound ligand via changes in their expression levels or post-translational modifications [98,102,105,106]. Dimeric orphan receptors (type III receptors) can only bind to DNA as dimers, examples being HNF4A, NR2F1, and NR2F2, while monomeric orphan receptors (type IV) can bind to DNA as monomers or dimers, such as estrogen-related receptors and the retinoic acid receptor-related orphan receptors [102,107]. Despite the lack of known endogenous ligands for these receptors, they can still be targeted with synthetic ligands. For example, the activity of the estrogen-related receptors is inhibited by diethylstilbestrol and 4-hydroxytamoxifen [108].

NRs have been found to activate or repress immune gene transcription in both innate and adaptive immunity [9,109,110]. Due to their dependence on ligand binding for activation, they have become desirable drug targets for the treatment of immune-related disease because their activity can be easily modulated using small molecules. GR has the ability to affect transcription of immune related genes in both DNA binding-dependent and DNA binding-independent manners, leading to repression of the inflammatory response [111,112]. Upon direct DNA binding, GR activates the transcription of anti-inflammatory genes and represses the transcription of pro-inflammatory genes [111,112]. GR can also inhibit pro-inflammatory gene expression in a DNA-binding independent manner by interfering with the activities of other immune-related TF families like NF-κB and AP-1 [109,111–113]. Specifically, GR blocks interactions between these TFs and their co-activators and mediates the recruitment of co-repressors, a mechanism known as transrepression [109,113]. Because GR has the ability to inhibit the expression of pro-inflammatory genes, synthetic glucocorticoids have been used to treat a number of inflammatory diseases such as RA, SLE, IBD, and psoriasis [114–117]. As another example, peroxisome proliferator activated receptor-γ (PPARγ) is a major player in the inflammatory response in macrophages, specifically following bacterial, viral, and fungal infections. Upon activation, PPARγ promotes anti-inflammatory macrophage polarization to reduce inflammation-induced tissue damage [118,119]. For this reason, small molecule agonists have been designed against PPARγ to treat autoimmune and inflammatory diseases, including Graves' disease, MS, RA, scleroderma, and SLE, and PPARγ has been investigated as a potential target to treat severe COVID-19-related cytokine storm [120–125]. Additionally, recent studies have shown that partial agonists for PPARγ can be designed to favor specific coactivators, allowing fine-tuning of PPARγ function [126]. Isoforms of NRs can also play specific roles in immunity and immune-related disorders. RORγt, an isoform of retinoic acid receptor-related orphan receptor-γ, is essential for the differentiation of IL-17$^+$ T helper cells and, when dysregulated, can contribute to the development of autoimmune diseases such as type 1 diabetes and spondyloarthritis [127,128]. Inverse agonists and antagonists against RORγt have shown potential in inhibiting the development of such immune-related disorders by suppressing IL-17$^+$ T helper cell differentiation [128,129].

Nuclear factor of activated T-cells (NFAT)

NFAT is a TF family expressed in most immune cells that plays a key role in immune regulation, particularly in adaptive immunity [130–132]. The family consists of five members: NFATc1, NFATc2, NFATc3, NFATc4, and NFAT5, all of which, except for NFAT5, respond to calcium signaling [131,133,134]. This calcium-dependent activation is mediated by calmodulin, which, upon binding calcium, activates the serine/

threonine phosphatase calcineurin that dephosphorylates the N-terminus of the NFATC1–4 [133,135]. This leads to a conformational change that exposes a nuclear localization signal promoting nuclear translocation, and depending on the cell type, the formation of complexes with other TFs such AP-1, TBX21, GATA3, SMAD3, and RORγ, which lead to cell-type specific transcriptional responses [135–137].

NFAT plays a key role in different autoimmune and inflammatory diseases [132,136]. For example, LRRK2, which encodes for a negative regulator of NFATc2, has been associated with inflammatory bowel disease and neuroinflammation in synucleinopathies like Parkinson's disease [138,139]. NFAT also plays a role in RA by activating macrophage inflammatory function in response to TNF [140]. Due to the critical role of NFAT in regulating the T-cell proliferative cytokine IL-2, NFAT is considered an important immunosuppressive pharmacological target [141,142]. Calcineurin inhibitors, such as tacrolimus (FK506) and CsA, are used inhibit NFAT activation in the treatment of autoimmune diseases such as MS, Crohn's disease, RA, and ulcerative colitis [143–145]. However, given the central role of calcineurin in signaling across cell types, these drugs have widespread side effects [146,147]. More specific drugs that target NFAT directly are under development which may retain immunosuppressive activity with limited toxicity [136,148,149].

Drug targeting of TFs for immune regulation

TFs are considered desirable drug targets because they frequently regulate the expression of sets of functionally related genes and are often more specific to the regulation of target genes compared to signaling molecules and transcriptional cofactors, which are typically more broadly expressed and are involved in numerous signaling pathways across different cellular contexts [22]. However, TFs have generally been considered "undruggable" due to their intrinsically disordered structure and lack of small molecule binding pockets, with the exception of NRs that have ligand-binding domains for small molecules [19,20,97]. Multiple studies in the past two decades have shown that there are a number of ways TFs can potentially be targeted for disease treatment, including using small molecules that bind to ligand-binding domains, inhibiting TF dimerization or protein–protein interactions with cofactors, preventing DNA binding, modulating TF stability, and targeting signaling pathways that activate or repress TF function (Figure 2). In this section, we will describe each targeting method and provide examples of drugs, FDA-approved or experimental, using these methods for the treatment of immune-related diseases.

Ligand-mediated activation and repression

The most successful method of targeting TFs for therapeutics to date is targeting their ligand-binding domains (LBDs) (Figure 2a). Currently, the only TFs known to have effector domains that bind small molecules are the NRs and the transcriptional enhanced associate domain family, the latter of which has no major known role in immune gene regulation. Many small molecule agonists, antagonists, and inverse agonists have been designed to target NR function in disease [150]. Agonist binding leads to activation of NRs, while antagonist binding blocks activation of NR activity. Inverse agonist binding to the LBD downregulates the activity of constitutively or highly active NRs by recruiting corepressors [151].

Most NRs, with the exception of the steroid hormone receptors, are bound by transcriptional corepressors, either NCoR1 or SMRT, in their unliganded state that recruit histone deacetylases to repress gene expression [152,153]. Upon binding of an agonist, the hydrophobic groove in the LBD bound by the corepressors undergoes a conformational change, releasing the corepressors and allowing recruitment of coactivators for the initiation of target gene expression [152,154,155] (Figure 2a). In the case of antagonist binding, the LBD adopts a conformation that blocks agonist binding, preventing the release of corepressor complexes, and coactivator binding by preventing the formation of a coactivator interface (Figure 2a) [155].

The development of these agonists, antagonists, and inverse agonists allows for the specific regulation of NR activity in disease, depending on the context. For example, in the context of

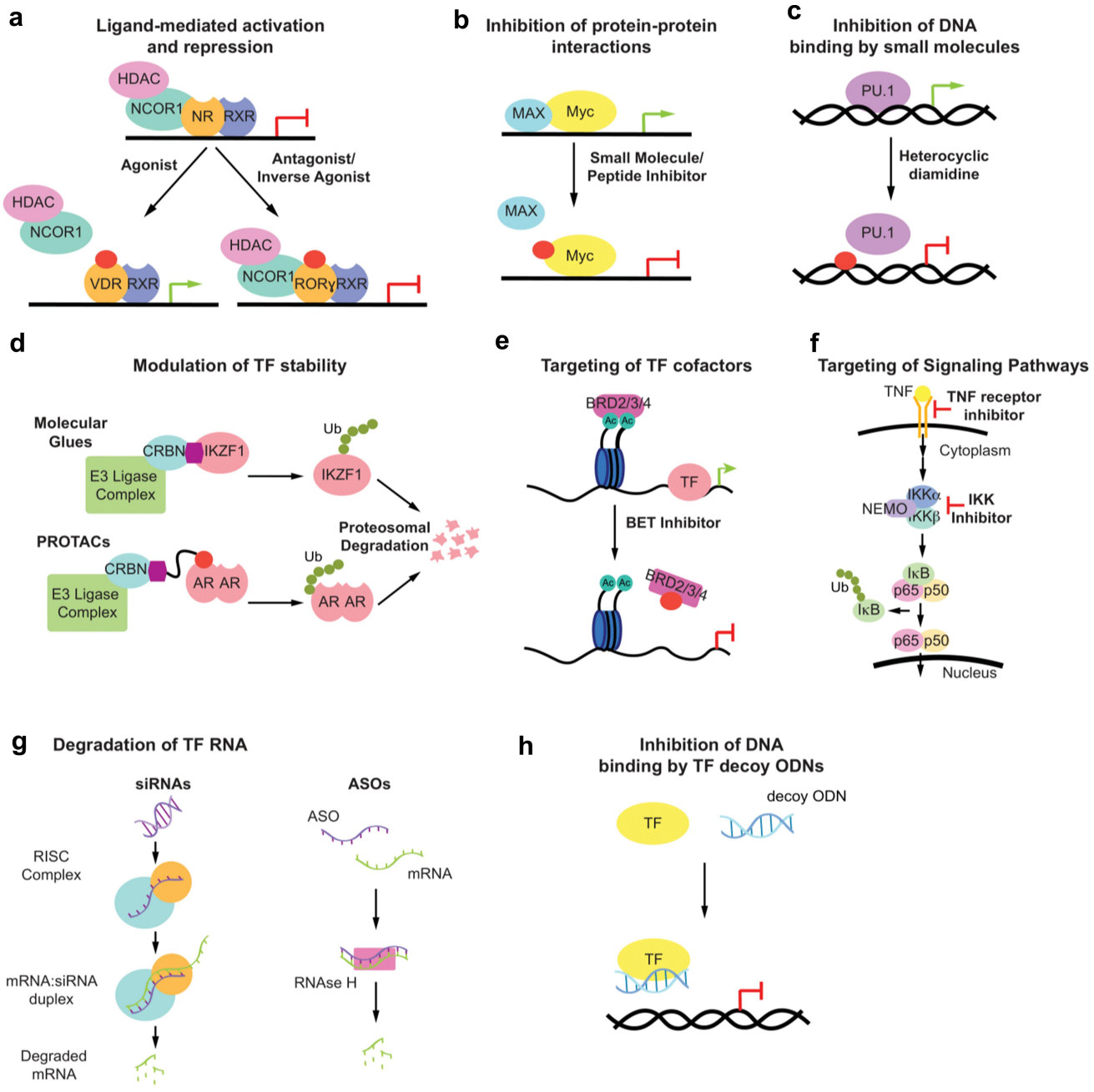

Figure 2. Methods for targeting TFs with drugs to treat diseases.

Several methods are being used in research to develop drugs targeting TFs for disease treatment, including (a) ligand-mediated activation and repression, (b) inhibition of protein–protein interactions, (c) inhibition of DNA binding by small molecules, (d) modulation of TF stability, (e) targeting of TF cofactors, (f) targeting of signaling pathways, (g) degradation of target RNA, and (h) inhibition of DNA binding by TF decoys. (a) Ligand-mediated activation and repression requires the TF target to have a ligand binding domain for small molecule agonists and antagonists to bind to. Agonists will activate the targeted TF, while antagonists and inverse agonists will inhibit its action. (b) Inhibition of protein–protein interactions (PPIs) involves targeting a small molecule or peptide inhibitor to a ligandable surface on one TF to block its interaction with another TF, cofactor, or signaling protein to prevent transcription of its target genes. (c) Inhibition of DNA binding can be achieved using small molecules that bind to a specific DNA sequence to block the TF of interest from binding to DNA. This can also be achieved by targeting a small molecule to the DNA-binding domain of the TF. (d) Modulation of TF stability mainly utilizes E3 ligases to target the TF of interest for degradation. Molecular glues bind to two different proteins and force a non-native PPI between them. In this case, between a TF of interest and an E3 ligase substrate adapter to mark the TF for degradation. PROTACs function by tethering a ligand that binds to a TF of interest to another ligand that binds an E3 ligase substrate adapter to mark the TF for degradation. (e) Cofactors such as chromatin remodelers can be targeted to repress chromatin opening, thereby preventing TF binding and recruitment of RNA polymerase II. (f) Targeting of signaling pathways involves using small molecule drugs to prevent or promote the activation of signaling proteins such

autoimmune and inflammatory diseases, agonists are used to decrease inflammation by promoting the anti-inflammatory actions of NRs, like PPARγ, GR and VDR [111,118,156]. Alternatively, antagonists or inverse agonists can be used to dampen the immune response by blocking the activity of NRs that regulate pro-inflammatory gene expression, such as RORγ in T-cells [157]. In the context of infection, antagonists against RXRα can be used to bolster the host antiviral response because RXRα activation has been shown to inhibit antiviral gene expression [158]. The development of small molecule drugs to modulate NR activity has proved an effective avenue for the treatment of immune diseases.

Inhibition of protein–protein interactions

Inhibiting interactions between TFs and their corresponding coactivators or corepressors or between cooperative TFs is another effective way of perturbing their ability to modulate gene expression (Figure 2b). Several methods have been used to drug protein–protein interactions (PPIs), including monoclonal antibodies, small molecules, and peptides or peptidomimetics. Therapeutic monoclonal antibodies are highly efficient and have strong target specificity, but their very high molecular weight limits them to mostly regulating cell surface targets, making them insufficient for therapeutically targeting intracellular TFs [159,160]. Small molecules are well-suited for drug treatment because they are generally cell-permeable, can often be delivered orally, and are cost-effective [161,162]. However, drugging PPIs with small molecules involves overcoming a few challenges: 1) the interfaces between proteins are usually smooth without grooves to bind to small molecules and are highly hydrophobic; 2) contact surfaces involved in PPIs are much larger than those for protein-small molecule interactions, making it difficult to block high-affinity PPIs 3) proteins tend to use the same interface to bind to several protein partners; and 4) characterizing the site where the drug binds to the protein is difficult [161,162]. Despite these challenges, a number of successful small molecule PPI inhibitors have been designed. For example, several compounds have shown promise in inhibiting the heterodimerization between the proto-oncogene MYC and its binding partner MAX by selectively binding to their bHLH domains (Figure 2b) [163,164]. Additionally, the small molecule inhibitor AI-10-49 was found to disrupt the PPI between RUNX1 and CBFβ-SMMHC, a TF fusion that normally outcompetes normal CBFβ for binding with RUNX1 and dysregulates the transcription of CBFβ-RUNX1 heterodimer target genes, by selectively binding to CBFβ-SMMHC for the treatment of acute myeloid leukemia [165,166]. Therefore, small molecule PPI inhibitors could still potentially be used for the treatment of immune-related diseases as well.

Peptides or peptidomimetics, synthetic peptides designed to mimic natural peptides, may also be well suited to inhibit TF PPIs because they can be specifically designed to mask the critical surfaces mediating PPIs on proteins, acting as competitive inhibitors [167,168]. Even though peptides are normally flexible and unstructured, they can be chemically modified to mimic the secondary structure motifs found on target proteins [168]. One of the most well-known examples of this is ALRN-6924 and ATSP-7041, which inhibit the PPIs between the tumor suppressor gene p53 and its negative regulators, MDM2, and MDMX, to activate p53 signaling for the treatment of cancer patients with wild-type p53 tumors [167,169–171]. ALRN-6924 and ATSP-7041 are cell-permeating macrocyclic α-helical peptides, also known as stapled peptides, that function by mimicking the N-terminal domain of p53, the surface of p53 that would normally bind to MDM2 and MDMX. Binding of these peptides to MDM2 and MDMX prevents p53 degradation and allows it to activate transcription of its target genes [170–

as kinases and phosphatases that act upstream of TFs. (g) Degradation of RNA encoding the TF can be achieved using small interfering RNAs (siRNAs) and antisense oligonucleotides (ASOs), which bind to the RNA molecule and cleave it using endogenous cellular mechanisms such as the RISC complex (siRNA) and RNase H1 or ribozymes (ASOs). (h) TF decoys function by binding to the DNA binding motif of a TF and blocking the TF from binding to target regulatory regions, thereby blocking downstream gene expression regulated by the TF.

172]. Although these peptides have yet to advance through phase I clinical trials, they exemplify that such therapeutic peptides can potentially be used for cancer treatment and hopefully for the treatment of immune disorders as well [169].

Inhibition of DNA binding

Since a major feature of TFs is their ability to bind to DNA and influence gene expression, inhibition of TF-DNA binding interactions is a logical area of research for targeted disease treatment (Figure 2c). TFs interact with DNA in several ways: 1) via non-sequence specific interactions with the DNA backbone; 2) via sequence-specific hydrogen bonding with the DNA bases, mostly within the major groove; and 3) via the DNA minor groove, which has the ability to confer additional sequence specificity [173,174]. Due to the dimensions of the major and minor grooves, small molecules favor binding in the minor groove and, upon binding, can disrupt these TF-DNA contacts [175]. A recent study exemplified this by targeting the DNA minor grooves flanking PU.1 TF binding sites with small molecule inhibitors of the heterocyclic diamidine family for the treatment of acute myeloid leukemia (Figure 2c) [176]. These molecules are highly potent and selective for AT-rich DNA sequences, which flank the core PU.1 consensus sequence of 5'-GGAA-3' [177]. Binding of these inhibitors to the minor groove induces conformational changes of the PU.1 binding site in the major groove, preventing the TF-DNA contact [176,177]. DB2313 was shown in this study to increase survival and decrease tumor burden *in vivo* in cells from acute myeloid leukemia patients, while maintaining normal transcriptional levels of ETS family TFs other than PU.1 [176]. Another way of disrupting TF-DNA binding is to target the DNA-binding domain of the TF, rather than the DNA sequences it binds to. The small molecule inhibitor InS3-54A18 has shown this to be a potential strategy for breaching the protein–DNA interaction between STAT3 and its target genes in cancer cells [178]. STAT3 is constitutively active in many cancer types and InS3-54A18, upon binding to the DNA-binding domain of STAT3, exhibited anti-tumoral effects such as inducing cancer cell apoptosis and inhibiting metastasis via hindering the expression of STAT3 downstream targets [178]. This demonstrates that blocking TF-DNA interactions is another potential approach for the treatment of immune-related diseases, such as cancer.

Modulation of TF stability

One crucial way the activity and abundance of TFs can be regulated is by modulating their stability, mostly by controlling ubiquitin-mediated proteolysis (Figure 2d) [179]. Methods of modulating TF stability and targeting TFs for degradation include molecular glues, monomeric degraders, and proteolysis targeting chimeras (PROTACs) [21,22]. Molecular glues are natural or synthetic small molecules which function by inducing PPIs between proteins that would not normally bind (Figure 2D) [22,145]. The effectiveness of molecular glues for immune-related diseases has been demonstrated for decades, and includes as hallmark examples CsA and FK506, both FDA-approved small molecule immunosuppressive drugs used to prevent organ rejection after transplant [145,180]. CsA and FK506 form complexes with the immunophilins cyclophilin and FKBP12, respectively, and these complexes were both found to bind calcineurin, a serine/threonine protein phosphatase involved in activating T-cells via dephosphorylation of the TF cytoplasmic NFAT [143,144]. The non-native PPIs between CsA-cyclophilin-calcineurin and FK506-FKBP12-calcineurin inhibit the activation of T cells by preventing the interaction between calcineurin and NFAT, resulting in immunosuppression [143–145]. More recently, molecular glues targeting TFs for degradation have been identified, such as the FDA-approved thalidomide-based anticancer immunomodulatory imide drugs, which function by inducing non-native PPIs between the Ikaros zinc finger (IkZF) TFs IKZF1 and IKZF3 and CRBN, a ubiquitin E3 ligase substrate adapter, which results in degradation of the IkZF TFs by the proteasome (Figure 2d) [181,182]. Taken together, these examples illustrate the therapeutic potential of molecular glues to target TFs for the treatment of immune-related diseases.

Monomeric degraders are small molecules which bind directly to a protein and promote its degradation via a variety of mechanisms, such as proteolysis and ubiquitination [183]. Due to the direct-binding aspect of monomeric degraders, their design has mostly been focused on targeting TFs with small molecule binding pockets, such as the NRs [22]. For example, fulvestrant, an FDA-approved estrogen receptor antagonist functions by binding to the estrogen receptor LBD, decreasing estrogen receptor stability and accelerating its degradation [184]. This strategy can potentially be extended to other immune-relevant TFs, such as other NRs, and could add to the toolkit of protein-degradation methods for disease treatment. In contrast to monomeric degraders, PROTACs offer a more modular way of targeting TFs for degradation. PROTACs function by linking a ligand targeting the protein of interest to a ligand that binds an E3 ligase, inducing proteasomal degradation of the target protein via ubiquitination (Figure 2d) [185,186]. One of the first examples of this was designed against androgen receptor (AR) for the treatment of cancers with increased AR levels, such as prostate cancer [185]. In this case, the non-steroidal androgen receptor ligand (SARM) and nutlin, a ligand of the E3 ubiquitin ligase MDM2, were linked together. When the SARM arm of this bifunctional protein binds to AR, the nutlin arm targets AR to MDM2 to be ubiquitinated for proteasomal degradation (Figure 2d) [185]. This construct, designed by the company Arvinas, is now named Bavdegalutamide (ARV-110) and is currently in Phase 1/2 clinical trials [187]. Like monomeric degraders, PROTACs are mostly limited to TFs with LBDs, such as the NRs. However, the modular design eliminates the need for the ligand targeting the TF to have inherent degradative properties [22,182]. Indeed, the development of PROTACs provides another promising way of targeting TFs for the treatment of immune-related diseases.

Targeting of TF cofactors

Modulating TF activity indirectly via targeting their cofactors is another promising avenue for drug research and, despite their broad expression patterns, have been shown to be highly specific drug targets, especially at super-enhancers (Figure 2e) [22,188]. Chromatin remodeling factors, such as bromo- and extra-terminal (BET) proteins, histone deacetylases, histone acetyltransferases, DNA methyltransferases, enhancer of zeste homolog 2 proteins, and protein arginine N-methyltransferases, are of particular interest as they are highly recruited to enhancers and because they regulate gene expression at enhancers in a cell type-specific manner [22,189]. Of these, targeting of the BET protein family has been shown to be an effective way of modulating immune gene expression controlled by super-enhancers in a variety of immune cell types, including macrophages, T-cells, B-cells, and dendritic cells [190–193]. BET proteins BRD2, BRD3, and BRD4 act as chromatin readers of acetylated lysines on histones and TFs in many cell types via their two bromodomains, allowing them to recruit other transcriptional regulatory proteins to activate transcription [194,195]. Blocking the recognition of acetylated lysines by BET proteins using BET inhibitors disrupts chromatin complexes and inhibits transcription (Figure 2e) [188,190,196]. Specifically, in macrophages, the pan-BET inhibitor I-BET762 was identified to suppress expression of LPS-stimulated secondary response genes, which require chromatin remodeling to be expressed, while not affecting the expression of housekeeping genes or LPS-stimulated primary response genes, which are controlled by constitutively active promoters and enhancers [188,190,197]. In T-cells, another pan-BET inhibitor, JQ1, was shown to downregulate immune gene expression at enhancers and super-enhancers associated with the autoimmune disease juvenile idiopathic arthritis [198]. No BET inhibitors have achieved FDA approval to date, but a number of them are in phase I/II clinical trials for hematological malignancies as well as other cancers and some are also being investigated for their potential to work synergistically with other FDA-approved treatments [199,200].

Targeting of signaling pathways

TFs generally act downstream in various signaling pathways that result in activation or repression of target gene expression. When directly targeting a TF for disease treatment proves difficult, an alternative approach involves targeting the

upstream signaling pathways that modulate TF activity (Figure 2f). One such example is the targeting of JAKs upstream of STAT TFs to block excessive signaling through this pathway [40,41,51]. The NF-κB signaling pathway can be blocked by inhibiting the IKKs, the kinases upstream of the NF-κB proteins (Figure 2f) [27,28,201]. Several types of IKK inhibitors have been discovered such as ATP analogs, compounds that affect the structure of the IKK protein, and compounds that interact with Cys-179 in the IKKβ activation loop [202]. These inhibitors ultimately interfere with the essential phosphorylation event that allows the translocation of NF-κB dimers to the nucleus [201,202]. Further upstream of the IKKs, the receptors binding extracellular signals that activate the NF-κB pathways can also be targeted for disease treatment, such as TNF receptor 1 and TNF receptor 2, which would prevent IKK activation and, subsequently NF-κB activation (Figure 2f) [202,203]. Similarly, overactivation of type I interferon signaling can be blocked by inhibiting signaling through IFNAR1 and IFNAR2 upstream of STATs [51,204]. Overall, targeting of the upstream or downstream signaling pathway of a TF opens up a plethora of options for drug targeting for immune-related diseases when the TF itself is not easily druggable.

Targeting TF activity with nucleic acids

In addition to small molecule drugs, nucleic acid-based therapeutics are also being investigated to target TF expression and activity for the treatment of immune disorders. This includes antisense oligonucleotides (ASOs), small interfering RNAs (siRNAs), and transcription factor decoy oligodeoxynucleotides (TFD ODNs) (Figures 2g, h). ASOs and siRNAs are both types of short RNAs with the ability to degrade target mRNAs using the endogenous cellular mechanisms, thus preventing the production of target proteins [205,206] (Figure 2g). Initially, major concerns with using ASOs and siRNAs for drug treatment were their propensity for degradation by endogenous nucleases and the potential to activate the immune system through nucleic acid recognition receptors [207]. However, advances made in chemically modifying these RNAs to improve their stability and in delivery methods to target different cell types more specifically have made them viable candidates for drug development [206–208]. There are 14 AASOs/siRNAs that are FDA approved, many of which target mutated forms of dystrophin that lead to the development of Duchenne muscular dystrophy [209]. However, there are no such drugs approved by the FDA for targeting TFs or for treating immune disorders, although initial studies have shown promising results [210,211]. For example, siRNA-targeting of p53 was shown to reduce inflammation quickly and effectively in a mouse model of RA by inhibiting inflammatory cytokine production [210]. Interestingly, short activating RNAs (saRNAs) are starting to emerge as potential therapeutics for increasing the expression of target genes by initiating transcription using the RNA-induced transcriptional activation complex [212,213]. A saRNA targeting the TF CEBPA is currently being tested as a supplemental treatment to standard cancer drugs, which most likely functions by inactivating immune-suppressive myeloid cells via upregulation of CEBPA [213–215].

TFD ODNs are short double-stranded DNA molecules with similar sequences to the DNA motifs bound by a TF, therefore blocking TF binding to target regulatory regions [216] (Figure 2h). The structures of these TFD ODNs as well as their delivery into mammalian cells have been enhanced over the past two decades to prevent degradation by nucleases, avoid premature renal elimination, and achieve optimal therapeutic effects [217,218]. TFD ODN drugs have not achieved FDA approval to date, but ones targeting NF-κB and STAT3 have been tested in clinical trials for the treatment of atopic dermatitis and head and neck squamous cell carcinoma, respectively [216,219,220]. Research is underway to potentially use TFD ODNs for the treatment of several other immune disorders, including targeting AP-1 for IBD treatment, targeting STAT3 for sepsis treatment, and targeting NF-κB and STAT6 simultaneously as a chimera for the treatment of asthma, RA, osteoarthritis, and Crohn's disease [221–223]. Overall, there is a considerable body of research that demonstrates the potential of nucleic acid-based therapeutics for the treatment of immune disorders.

Clinical applications of TF drug targeting

Multiple TF-targeting drugs are currently on the market to treat immune-related diseases [224] (Supplementary Table S1). Most of these drugs target NRs by binding their LBDs and acting mostly as agonists. For example, several drugs have been developed to target nuclear retinoic acid receptors such as RXRA, RXRB, RXRG, RARA, RARB, and RARG. These drugs include Acitretin, Alitretinoin, Adapalene, and Tazarotene, which share structural resemblances with retinoic acid, the natural ligand of these NRs [225,226]. While the exact mechanisms of action of these drugs and relative specificity remain partly unknown, it is expected that they act as agonists by binding to the LBD of retinoic acid receptors due to this structural similarity. These drugs are commonly used to treat immune-related conditions like psoriasis and eczema, where there is an accumulation of skin cells leading to scale formation, because retinoic acid receptors regulate the expression of genes controlling skin cell differentiation and proliferation.

Another major group of drugs to treat immune-related diseases target the GR NR3C1 [224,227]. Although these drugs generally act as agonists, suppressing immune responses, they elicit different pharmacological responses due differences in formulations, administration routes, potency, and pharmacokinetics. Some of these drugs, such as fluticasone, betamethasone, hydrocortisone, prednisolone, dexamethasone, cortisone, and triamcinolone are available in multiple formulations for different administration routes (e.g., oral, intramuscular, intravenous, topical, etc.) and therefore can be used to treat systemic (e.g., SLE and MS), respiratory (e.g., asthma and COPD), and skin conditions (psoriasis and eczema). Other drugs instead have specific administration routes and are used for more narrow ranges of diseases. For example, mometazone, clobetasol, and fluocinolone are for dermatological use to treat skin inflammatory conditions such as psoriasis, atopic dermatitis, and eczema. Flunisolide and budesonide are used to treat asthma and allergic rhinitis to dampen the immune response and ameliorate respiratory symptoms. Fluorometholone and rimexolone have ophthalmologic use to treat allergic conjunctivitis. Most of these drugs differ in their pharmacokinetic characteristics determining variable absorption, distribution, metabolism, and excretion mechanisms and have different potencies, requiring different effective concentrations. In addition to the drugs mentioned above, other TF-targeting drugs have been developed. For example, obeticholic acid, a ligand for the farnesoid X receptor NR1H4, is used to treat primary biliary cholangitis, an auto-immune inflammatory liver disease which can lead to cirrhosis [228], while tapinarof, an aryl hydrocarbon receptor agonist, is used topically to treat plaque psoriasis [229]. Other TFs which do not have a LBD, such as NF-kB, have been targeted indirectly by interfering with different steps in their activation pathway such as receptor activation phosphorylation, proteasome degradation, and nuclear translocation [202]. However, although there have been significant advances in recent years developing novel approaches to target TFs from families other than the NRs, these drugs are still experimental or undergoing clinical trials (Supplementary Table S2).

Limitations, future perspectives & conclusions

There are many advantages of targeting TFs for the treatment of immune-related diseases, but research in this area has not come without its challenges and limitations. One major disadvantage is that most TFs are not easily druggable. Only TFs with small molecule binding pockets, such as the NRs, are readily suitable for drug targeting and several current methods of doing so are dependent on binding pockets, including PPI inhibition, ligand-mediated activation or repression, monomeric degraders, and PROTACs. However, as illustrated throughout this review, research in this area has expanded to target other aspects of TF structure and function, such as drugging cofactors and upstream signaling pathways, which expands the repertoire of TFs that can be targeted. Methods that require ligand binding may benefit from identifying small molecules that target intrinsically disordered regions rather than binding pockets. Although intrinsically disordered regions have contributed to the challenge of drugging TFs, recent research has shown that these intrinsically disordered regions can become more structured upon interactions with binding partners

and can form potential small molecule binding cavities [230,231]. Binding-focused screening methods, such as small-molecule microarrays and covalent ligand screening have seen success in identifying potential ligandable sites on TFs that are currently undruggable, exemplifying that targeting of a TF directly does not have to be limited to a ligand binding domain [232,233].

Another limitation of targeting TFs for drug treatment is their lack of specificity in cell type expression of the gene targets and signaling pathways they regulate. Indeed, most TFs involved in immune gene regulation are also expressed in non-immune cells and targeting them could result in off-target effects in other systems due to influencing the expression of unrelated genes. For instance, targeting certain members of the AP-1 family, such as c-Jun and c-Fos, could affect cellular proliferation and apoptosis pathways, in addition to immune pathways [234]. Similarly, many immune-related TFs have roles in several immune signaling pathways and regulate many target genes associated with a variety of biological processes. As a result, targeting these TFs could wreak havoc in other areas of the immune system. For example, targeting NF-κB family members for anti-inflammatory purposes has been shown to actually promote inflammation in some cases by potentiating the activation of the NLRP3 inflammasome, due to its role as a negative regulator in this signaling pathway [30,235]. Therefore, TFs to be targeted must be chosen carefully based on the roles they play in all cell types and processes, beyond those of interest.

With this in mind, strategies to mitigate such off-target effects have been developed, including varying routes of administration and ligand-mediated drug delivery. Drugs can enter the human body enterally, parenterally, topically, transdermally, via inhalation, among other ways, and one delivery system may be more advantageous than the others depending on the disease [236]. For infectious diseases that affect the lungs, such as SARS-CoV-2 and tuberculosis, delivery of drugs directly to the pulmonary system via inhalation increases bioavailability, as opposed to taking a medication orally that might be metabolized by the liver or gut before it reaches the site of infection, and prevents drug exposure to other systems [237]. Similarly, applying a medication topically to treat inflammatory skin diseases, including psoriasis and eczema, provides the same benefits [238].

Ligand-mediated drug delivery involves targeting drugs to specific cell types in areas of the body that are not easily reached by the above different routes of administration using small molecule, aptamer, peptide, antibody, and cell-based strategies [239,240]. With this method, a ligand targeting the pathological cell-type is tethered to the drug cargo via a spacer and a cleavable linker [240]. Small molecules, aptamers, peptides, and antibodies take advantage of the various aspects of cell-type specific receptors to deliver therapeutics, while cell-based strategies utilize native or genetically engineered cells loaded with the drug treatment to bring the drug to pathological cells of the same type and secret it in a controlled manner [239]. For example, red blood cells have been leveraged using this strategy to carry the glucocorticoid dexamethasone for the treatment of chronic inflammatory diseases such as ulcerative colitis [241]. When not packaged into cells, the drugs are typically transported via lipid-based, polymeric, or inorganic nanoparticles [218].

Even after a successful drug target against a TF has been identified, a concern that arises is the potential development of resistance and compensatory mechanisms during treatment, reducing the effectiveness of the drug. Some TFs exhibit functional redundancy, meaning they regulate the same target genes or signaling pathway in a similar manner [19,75]. Therefore, if one of these TFs is inhibited, the other one could compensate so transcription of their shared gene targets can still occur. In some cases, these compensatory effects can be reduced using drugs that target multiple potentially redundant TFs, such as drugs that target all or most paralogs of retinoic acid receptors.

Despite these challenges, TFs are still attractive targets for the treatment of immune disorders for a number of reasons: 1) their direct role in the regulation of gene expression, 2) the broad therapeutic potential that comes with targeting those TFs which play roles in a variety of immune-related diseases, 3) their flexibility in the various approaches that can be used to target them with drugs, and 4) their specificity and precision, when

the drugs targeting them are properly designed. With many TF-targeting drugs currently under experimental investigation or in clinical trials, we anticipate a new generation of drugs with lower side-effects and a broader range of immune diseases that can be treated.

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