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Transcription factors in autoimmune diseases

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1. ABSTRACT

Studies on the pathogenesis of autoimmune diseases have begun to delve into the molecular and cellular mechanisms, and transcription factors, as key regulators of immune effector cell development and function, have received growing attention. Their involvement has been investigated in immune cells, such as T and B lymphocytes, macrophages and neutrophils, but also end-organ tissues, such as synoviocytes, keratinocytes and epithelial cells, and has revealed particularly dominant roles for NF-kappaB, STAT and AP-1 family members. This review summarizes recent findings and current knowledge regarding the roles of transcription factors in autoimmunity, focusing on their role in pathogenesis, as evidenced by both biological and genetic studies, as well as the implications of these findings for anti-inflammatory therapies.

2. INTRODUCTION

Extensive and continuing efforts over the past several years has elucidated a multitude of information regarding the transcription factors (TFs) that regulate immune cell fate and function (Figure 1). For instance, it is now clear that members of the Ets, GATA, Ikaros and Myb families play critical roles in early hematopoietic stem cell fate determination, including the decision to form the common lymphocyte progenitor (CLP) versus the myeloid or dendritic cell (DC) lineages. Subsequent differentiation of the CLP into the NK, T and B cell lineages reflects differential activity of transcription factors of the E2, Id, Pax5, and Lef1 families, as well as Notch effector factors. Generation of mature T cells, of both the CD4 and CD8 lineages, is now known to require TFs involved in the wingless (Wnt) and Notch pathways, as well as several

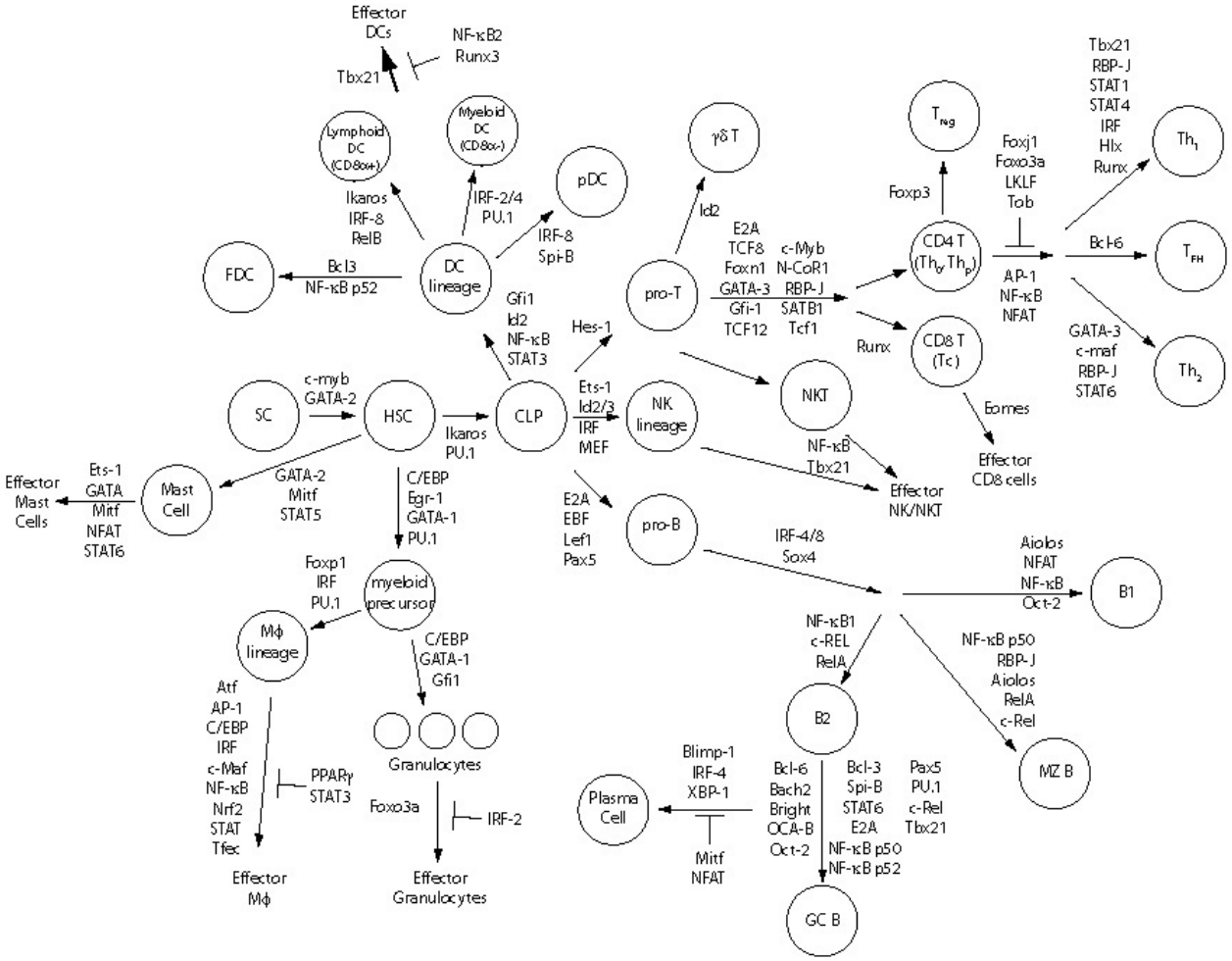

Figure 1. Transcription factors in the developmental fates of immune cell lineages. Shown are transcription factors which have been demonstrated to regulate the developmental and/or effector cell states shown. For simplicity, some assumptions have been made regarding specific lineage (e.g., derivation of T_{reg} cells from Th0 cells). AP-1, activating protein-1; Atf, activating transcription factor; Bach, BTB and CNC homology 1, basic leucine zipper transcription factor; Bcl, B cell lymphoma; Blimp-1, B lymphocyte-induced maturation protein 1; Bright, B cell regulator of Ig heavy chain transcription; C/EBP, CCAAT/enhancer binding protein; CLP, common lymphoid progenitor; c-maf, v-maf musculoaponeurotic fibrosarcoma (avian) oncogene homolog; c-myb, v-myb avian myeloblastosis viral oncogene homolog; c-rel, v-rel avian reticuloendotheliosis viral oncogene homolog; DC, dendritic cell; E2A, immunoglobulin enhancer binding factors E12/E47 (transcription factor 3, Tcf3); EBF, early B cell factor; Egr1, early growth response protein 1; Eomes, eomesodermin; Ets, v-ets erythroblastosis virus E26 oncogene homolog; FDC, follicular DC; Fox, forkhead; GATA, GATA-binding transcription factor; GC, geminal center; Gfi, growth factor independence; Hes, hairy and enhancer of split; Hlx, H2.0.-like homeobox; HSC, hematopoietic stem cell; Id, inhibitor of DNA binding; IRF, interferon regulatory factor; Lef, lymphocyte enhancer factor; LKLF, lung Kruppel-like zinc finger transcription factor (KLF2); MEF, myeloid elf-1 like factor (Elf4); Mphi, macrophage; Mitf, microphthalmia transcription factor; MZ, marginal zone; N-CoR1, nuclear receptor corepressor 1; NFAT, nuclear factor of activated T cells; NF-kappaB, nuclear factor, kappaB; NK, natural killer; NKT, NK-T cell; Nrf, nuclear factor erythroid 2-related factor; OCA-B, B-cell-specific coactivator OBF-1; Oct, octamer binding transcription factor; pDC, plasmacytoid DC; Pax5, paired-box gene 5 (BSAP); PPAR, peroxisome proliferator activated receptor; PU.1, Purine-box binding factor 1; RBP-J, recombining binding protein suppressor of hairless (Jkappa-recombination signal binding protein); RelA, v-rel avian reticuloendotheliosis viral oncogene homolog A (nuclear factor of kappalight polypeptide gene enhancer in B-cells 3 (p65); RelB, avian reticuloendotheliosis viral (v-rel) oncogene ; Runx, runt-related transcription factor; Satb1, special AT-rich sequenc-binding protein; SC, stem cell; Sox, Sry-box containing gene; Spi-B, Spi-1/PU.1-related; STAT, signal transducer and activator of transcription; Tbx21, T-box 21 (T-bet); Tcf1, T-cell factor, 1 (Tcf7); Tcf8, transcription factor 8 (dEF1); Tcf12, transcription factor 12 (HEB); Tfec, transcription factor EC; Th, helper T cell; T_{reg}, regulatory T cell; Tob, transducer of erbB2; Xbp, X-box binding protein.

members among multiple TF families, including forkhead, GATA, and Runx. Mature T cell differentiation is regulated by antagonistic effects of forkhead versus immediate-early activating (NF-kappaB, NFAT, AP-1) family members, and

the development and effector function of T cell subsets, even within the CD4 versus CD8 lineages, requires distinct TF subgroups: e.g., Foxp3 for regulatory T (Treg) cells; GATA-3, c-maf, and STAT6 for Th2 cells; T-bet, STAT1, and STAT4 for Th1 cells; Eomes for Tc1 cells; and likely Bcl-6 for follicular helper T (T_{FH}) cells. Similarly, distinct TF groups regulate the development and effector differentiation of mature B cells, including NF-kappaB and Notch-responsive family members for B1 and marginal zone (MZ) B cell subsets; Bcl-6 and several other TFs for the generation of germinal center (GC) B cells and their respective functions of isotype switching, somatic hypermutation and affinity maturation; as well as Xbp-1, IRF-4 and Blimp-1 for the generation of antibody-secreting plasma cells. Since a detailed review of these processes extends beyond the scope of this review, the reader is directed to one of several reviews for further details (1-8).

3. TRANSCRIPTION FACTORS FUNCTIONALLY DEMONSTRATED IN THE PATHOGENESIS OF AUTOIMMUNITY

3.1. NF-kappaB

Members of the nuclear factor kappaB (NF-kappaB) family, which includes RelA (p65), c-REL, RelB, p105/p50 (NF-kappaB1) and p100/p52 (NF-kappaB2), play critical roles in the induction of and response to both innate and adaptive immunity (reviewed in refs. 9-11). In general, the NF-kappaB proteins are retained in an inactive form in the cytoplasm by the inhibitor of NF-kappaB (IkappaB) proteins. Cellular stimulation, such as by the pro-inflammatory cytokines TNF-alpha or IL-1 or from stress signals, activates the inhibitor of NF-kappaB kinase (IKK) complex, which phosphorylates the IkappaBs, leading to their ubiquitination and subsequent proteosomal degradation, freeing NF-kappaB to translocate to the nucleus where it transactivates inflammatory target genes, including several NF-kappaB genes themselves as well as proinflammatory cytokines like TNF-alpha, IL-1 or IL-6. Collectively, these TFs are now known to play critical roles in the pathogenesis of multiple autoimmune diseases.

3.1.1. NF-kappaB in arthritis

NF-kappaB has been heavily implicated in the pathogenesis of inflammatory arthritides, particularly rheumatoid and psoriatic arthritis, where several studies have demonstrated that afflicted tissues contain elevated levels and/or activities of NF-kappaB family members, and multiple interventions -- including germline NF-kappaB deficiencies, dominant-negative IKK or repressor IkappaB constructs and decoy or antisense NF-kappaB oligonucleotides -- effectively treat and/or prevent the production of inflammatory cytokines in cultured synoviocytes as well as the development of arthritis in animal models (summarized in refs. 12-14). Recent work has extended these observations, suggesting that these abnormal NF-kappaB activities result not only from pro-inflammatory cytokines known to participate in RA, such as TNF-alpha and IL-1, but also IL-17, as well as the extracellular newly identified receptor for advanced glycation end products binding protein (EN-RAGE) S100A12, and DNA-binding cytokine high mobility group box chromosomal protein 1 (HMGB-1), which are highly expressed in RA and can induce arthritis via NF-kappaB and IL-1 (15-19). Furthermore, NF-kappaB likely contributes to the production of multiple chemokines in the rheumatoid synovium by monocytes/macrophages (20), as well as to the transformed-like and proliferative nature of RA synoviocytes by regulating the expression of FLIP (Fas-associated death domain-like interleukin-1beta converting enzyme (FLICE) inhibitory protein), which renders cells resistant to the otherwise apoptotic effects of TNF-alpha (21). Reinforcing the roles of both the canonical and alternative NF-kappaB pathways, the IKK inhibitor NEMO binding domain (NBD) peptide can inhibit arthritis in mice (22), and mice deficient in NF-kappaB-inducing kinase (NIK) are resistant to antigen-induced and KRN T cell receptor transgenic arthritis (23).

Interestingly, NF-kappaB expression and/or activity is most prominent at sites of joint destruction in RA (24). Here, NF-kappaB likely plays also a prominent role in osteoclast activity, probably in the response to the osteoclastogenic receptor activator of NF-kappaB ligand (RANKL, ref. 25), since a dominant-negative IkappaB protein induces the apoptosis of osteoclasts, and systemic administration of IkappaB proteins to mice undergoing arthritis prevents bone erosion (26, 27). Thus, evidence for NF-kappaB hyperactivity in inflammatory arthritis, particularly RA, continues to accumulate in both animal models and human tissues, not only in the inflammatory response that comprises synovitis, but also the osteoclast response that promotes bone erosion. This TF family therefore remains a key target in both arthritis pathogenesis and therapy (28).

3.1.2. NF-kappaB in intestinal inflammatory disorders

NF-kappaB has also been strongly implicated in the pathogenesis of inflammatory intestinal disorders (IIDs), which include Crohn's disease (CD), celiac disease and ulcerative colitis (UC). Several studies have demonstrated the increased activity of NF-kappaB family members in UC, CD and celiac disease, as well as the efficacy of IkappaB constructs and antisense NF-kappaB oligonucleotides in animal inflammatory bowel disease (IBD) models (summarized in ref. 12). Recent studies indicate that several experimental treatments for IBD inhibit NF-kappaB, at least in mice, including the IKK inhibitor BMS-345541, conjugated linoleic acid, butyrate, curcurmin, as well as anti-TNF therapies (29-33).

3.1.3. NF-kappaB in multiple sclerosis

Similarly, multiple studies have suggested the importance of NF-kappaB in multiple sclerosis, including its increased expression and/or activity in both animal models and humans, as well as the resistance of p50 and c-Rel-deficient mice to experimental autoimmune encephalomyelitis (summarized in ref. 12). Recent studies have furthered this view, demonstrating the ability of NBD peptides to inhibit EAE (34), as well as the efficacy in EAE of several relatively novel treatments which inhibit NF-kappaB, including 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, the AMP-activated protein kinase activator 5-aminoimidazole-4-carboxamide

ribonucleoside, and the major green tea constituent epigallocatechin-3-gallate (35-37).

3.1.4. NF-kappaB in type 1 diabetes mellitus

Studies primarily in rodent diabetes models have strongly implicated NF-kappaB as pathogenic in type 1 diabetes. Both diabetic mice and humans possess increased NF-kappaB activity in leukocytes (summarized in ref. 12). Mice deficient in p50 and p52 are both resistant to streptozotocin-induced diabetes (38, 39), and the anti-inflammatory cytokine IL-11 can prevent streptozotocin-induced diabetes, correlating with effective inhibition of NF-kappaB (40). Furthermore, reduction of NF-kappaB activity in dendritic cells by treatment with NF-kappaB-specific oligonucleotides resulted in reduced IL-12 expression, making them effective at preventing the development of diabetes in NOD mice (41). Thus, NF-kappaB plays a critical role in the pathogenesis of type 1 diabetes, at least in mice.

3.1.5. NF-kappaB in other autoimmune diseases

NF-kappaB has been implicated in the pathogenesis of several other autoimmune diseases, although definitive data remain somewhat lacking. In systemic lupus erythematosus (SLE), for example, seemingly paradoxical findings include the presence of high levels of c-Rel but decreased levels of RelA in T cells from patients (42, 43), and macrophages from lupus-prone (NZB x NZW)F1 mice possess increased p50, IkappaBbeta and IkappaBepsilon activity despite a reduction in the levels of IL-12 (44). Nonetheless, in the *gld* murine model of a lymphoproliferation-related lupus syndrome, a super-repressor IkappaBalpha was protective against lymphoproliferation, autoantibody production and end organ disease (45). In other autoimmune diseases, effective therapies analogously correlate with NF-kappaB inhibition, including pyrrolidine dithiocarbamate in experimental autoimmune anterior uveitis (46) and HMG-CoA reductase inhibitors in experimental autoimmune myocarditis (47), as well as TNF antagonism in human psoriasis (48). Thus NF-kappaB likely plays a broad role in the pathogenesis of multiple autoimmune syndromes which remain to be elucidated completely.

3.2. STAT

The signal transducer and activator of transcription (STAT) family, which includes STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b and STAT6, play critical roles in cellular responses to cytokines. Activation of cytokine receptors leads to phosphorylation of Janus kinases (Jaks), followed by recruitment and phosphorylation of STATs, leading to nuclear translocation and transcriptional activation. The STAT proteins exhibit a preference for specific cytokine receptors, e.g., STAT1/2 for interferons, STAT3 for IL-6, STAT4 for IFNs and/or IL-12, STAT5 for IL-2, and STAT6 for IL-4 and IL-13 (reviewed in refs. 49, 50).

3.2.1. STAT in arthritis

STAT activation is extensive in inflammatory arthritides like RA (51-53), and the importance of particularly STAT4 has been demonstrated in mutant mouse models of arthritis, including the resistance of STAT4-deficient mice to proteoglycan-induced arthritis and the correlation of arthritis resistance in the B10.Q/J strain with defective STAT4 activation (summarized in refs. 12, 13), as well as the ability of STAT4-specific antisense oligonucleotides and STAT4 deficiency to attenuate collagen-induced arthritis (54). Indeed, human *STAT4* polymorphisms have been found to confer susceptibility to RA (55, 56). Otherwise, some work has implicated STAT3 as a potentially protective member, since overexpression of the STAT3 inhibitor SOCS-3 protects against collagen-induced arthritis (57); but the Jak2-STAT3 pathway has been implicated in the pathogenesis of arthritis in IL-1RA-deficient and gp130 F759 mice (58, 59). In addition, STAT3 may contribute to an autocrine inflammatory loop in RA synoviocytes (60), and the antirheumatic drugs aurothiomalate and auranofin reduce STAT3 activity *in vitro* (61, 62). At the same time, a constitutively active STAT6 construct can inhibit NF-kappaB and JNK activation in the serum-transfer K/BxN model of arthritis, associated with protection from erosive disease (63), and in the collagen antibody-induced arthritis model, STAT4-deficient mice developed more severe arthritis than STAT6-deficient counterparts (64). Thus the STAT family members appear to exhibit varied effects in animal models of arthritis, suggesting differential activity in specific cell types.

3.2.2. STAT in type 1 diabetes

Similarly varied roles for the STATs in type 1 diabetes likely exist. Increased activity of STAT1, STAT4 and STAT5 have all been demonstrated in human and/or NOD mouse samples (12, 65). STAT4-deficient mice are protected from diabetes in several animal models, including the LCMV transgenic, streptozotocin-induced and NOD models, while STAT6-deficient mice demonstrate normal or increased susceptibility (66-70). Pathogenic involvement of other STATs have been suggested by recent studies – for instance, the presence of a dysregulated STAT5 expression and/or activity associated with the NOD *Idd4* locus (65, 71, 72), which might relate to dysregulated expression of Crkl (73), and together might contribute to diabetes via dysregulation of IL-2, Foxp3 and/or regulatory T cells (74). Indeed, expression of a dominant negative STAT5 in pancreatic beta cells increases susceptibility to streptozotocin-induced diabetes (75). Increased levels of STAT1 may account for the increased susceptibility of p53-deficient mice to streptozotocin-induced diabetes (76), and STAT1-deficient NOD mice are protected from insulitis and diabetes (77); while studies in SOCS3-deficient mice with the streptozotocin-induced diabetes model suggest that STAT3 may protect beta cells (78).

3.2.3. STAT in IIDs

Elevated levels and/or activity of several STATs have been demonstrated in both murine and human IIDs, including STAT1, STAT3, and STAT4, and several studies have demonstrated the importance of STAT4 in murine colitis via both transgenic and knockout studies (summarized in ref. 12, 79). In contrast, STAT3 has been thought to be protective against intestinal inflammation, since STAT3 deficiency leads to severe inflammatory

bowel syndromes (80, 81), perhaps relating to a need for STAT3 in antigen-presenting cells to induce peripheral tolerance (82, 83); similarly, STAT6 deficiency may increase the severity and/or susceptibility of murine colitis models, such as DSS-induced or TCRalpha-deficiency-induced (84, 85). However, recent studies indicate that STAT3 is upregulated in monocytes and T cells in IIDs, particularly at areas of gut inflammation (86), and exogenous growth hormone is capable of inhibiting murine IBD, associated with inhibition of STAT3 (87). Also, STAT3 antisense oligonucleotides block colitis in the TNBS-induced mouse model (88), and STAT3 activity, especially in response to IL-6 signaling, correlates with disease activity in SAMP1/Yit mice (89). STAT5b-deficient mice are more prone to, and STAT5b appears to be required to mediate the beneficial effects of rosiglitazone in, TNBS-induced colitis (90), but on the other hand, the exacerbated inflammatory bowel syndrome seen in sphingosine kinase 2-deficient mice correlates with enhanced STAT5 activity (91). Thus, the specific roles of the STATs in IID remain varied and likely context-dependent.

3.2.4. STAT in MS

Several STAT family members, including STAT1, STAT3 and STAT4, are upregulated in EAE and patients with multiple sclerosis, but in mice, STAT4 appears to date to have demonstrated the most consistent role in pathogenesis, while STAT6 is protective, both in knockout animals and during response to effective therapies (summarized in ref. 12, 69, 92-94). STAT1 also appears to play a predominantly protective role, since STAT1-deficient mice are potentially more susceptible to EAE, perhaps reflecting defects in the regulatory T cell lineage (95, 96). However, systemic glucocorticoid therapy in multiple sclerosis results in an attenuation of STAT1 activity (97), suggesting that here again roles of the specific STATs may vary depending on the animal model and/or disease context.

3.2.5. STAT in systemic lupus erythematosus

In SLE, abnormal STAT activity, particularly of STAT1, STAT3 and STAT4, have been described: both STAT4 and STAT6 appear to be required in murine lupus (summarized in ref. 12; 98), and *STAT4* polymorphisms confer susceptibility to human SLE (55). Recent work has suggested additional pathogenic relevance of STAT3, since its activity is increased in human SLE (99); IL-6, a cytokine which correlates with B cell activation and disease activity in SLE, induces the proposed SLE susceptibility gene Ifi202 via STAT3; and the *Sle1ab* loci in murine lupus confers increased STAT3 activation, which may account for autoantibody production via its role in the generation of T-dependent plasma cells (100-102). STAT1 activity is also high in both mice and humans with nephritis (103, 104).

3.2.6. STAT in other autoimmune diseases

Similar to observations in the preceding diseases, dysregulated STAT activity has been seen in many autoimmune diseases, but seemingly paradoxical findings are often observed. For example, STAT4-deficeint mice are more susceptible, while STAT6-deficient mice are relatively resistant, to an experimental Graves' thyroiditis model (105, 106), while STAT4-, but not STAT6-, deficient mice are resistant to experimental autoimmune myasthenia gravis (107). In psoriasis, reduced STAT1alpha responses to IFN-gamma have been described (108), while a constitutively active STAT3 confers a psorasis-like phenotype in transgenic mice (109). Also, STAT5a/b deficiency leads to multi-organ autoimmunity (110), perhaps connected to its role in the development and/or activity of regulatory T cells (111). In NOD mice, STAT6 deficiency protects against the development of Sjögren's syndrome-like sialadenitis (112). Thus, understanding of the STAT pathways in autoimmunity remains incomplete: although specific family members, such as STAT4, are emerging as key regulators in multiple autoimmune diseases, systematic investigation of the STATs in these various autoimmune syndromes is warranted to elucidate the specific mechanisms and clinical contexts of the individual family members.

3.3. AP-1

Activator protein 1 (AP-1) refers to a large basic region-leucine zipper (bZIP) family of proteins, including ATF2, LRF1/ATF3, B-ATF, JDP1, JDP2, c-Fos, FosB, Fra-1, Fra-2, c-Jun, JunB, JunD, c-Maf, MafA, MafB, MafG/F/K and Nrl, which have the ability to form homo- and heterodimers with each other and other transcription factor proteins such as nuclear factor of activated T-cells (NFAT; 113). Collectively, these proteins play key roles in many biological processes, including cell growth, differentiation, development and apoptosis (114).

3.3.1. AP-1 in arthritis

Rheumatoid synovium contains significantly elevated levels of AP-1 proteins, particularly c-Fos and c-Jun (summarized in refs. 12, 13), which likely reflect the combined activities of local IL-1beta, TNF-alpha and IL-17, among other cytokines (17, 115-117). AP-1 decoy oligonucleotides and catalytic DNAs against c-Jun effectively prevent inflammation and joint destruction in collagen-induced arthritis (118, 119), likely in part due to a role for c-Fos in osteoclastogenesis (120), and efficacy of some therapies in mice correlate in large part with reductions in AP-1 activity, such as vasoactive intestinal peptide in collagen-induced arthritis (121). The calcineurin inhibitors tacrolimus and cyclosporine A, which are effective in human RA (122, 123), appear to inhibit osteoclast formation at least in part via blockade of c-Jun (124), although the majority of osteoclast differentiation and activity has been attributed to c-Fos (120, 125). Interestingly, though, combined deficiency of c-Jun and JunB in mice leads to a spontaneous psoriatic arthritis-like syndrome (126). Thus, AP-1 appears to be an attractive target in inflammatory arthritis, although the roles of specific AP-1 family members, especially those besides c-Fos and c-Jun and their potential for intra-family antagonistic effects, remain incompletely understood.

3.3.2. AP-1 in other autoimmune diseases

In other autoimmune diseases, however, specific roles for AP-1 seem tantalizing but still largely undefined, with defective activity often associated with disease

activity. For example, T cells in humans with SLE exhibit diminished AP-1 activity, particularly of c-Fos, perhaps due to increased activity of cAMP response element modulator (CREM, 127), although increased c-Jun activity has been observed in some renal lesions (128). Psoriasis has been associated with both diminished AP-1 activity (129), and accentuated (JunB) AP-1 activity (130); yet mice deficient in JunB and c-Jun develop a syndrome highly reminiscent of psoriasis, as well as psoriatic arthritis (126). Similarly, defective c-Maf activity in non-obese diabetic (NOD) mice likely accounts for defective IL-4 expression (131), and transgenic expression of c-Maf protects at least some strains of mice from experimental diabetes (132); but treatment with the anti-inflammatory cytokine IL-11 inhibits AP-1 activity and streptozotocin-induced diabetes (40). In animal models of colitis, poly(ADP-ribose) polymerase-1 (PARP-1) deficiency results in reduced TNBS-induced colitis, correlating with reduced AP-1 activity (133), but c-Maf overexpression can prevent or augment a Th1-like colitis model involving the adoptive transfer of CD4+CD62L+ T cells into Rag-deficient mice, depending on the specific T cell population used (134). Elevated AP-1 activity has also been observed in multiple sclerosis (summarized in ref. 12) and Sjögren's syndrome (135), and has been implicated in the accentuated collagen production by scleroderma fibroblasts (136). Thus, AP-1 proteins likely play significant immunomodulatory roles in several autoimmune diseases, but the specific pro- versus anti-inflammatory roles of individual family members remains to be elucidated fully.

3.4. T-bet (Tbx21)

T-bet (Tbx21), a member of the T-box family of transcription factors, has received significant attention recently due to its critical role in establishing a Th1-like effector fates in multiple cell types, including T cells, B cells and dendritic cells (reviewed in ref. 137). Because of the substantial relationship between Th1-like responses and autoimmune diseases in general, several studies have sought evidence for a pathogenic role of T-bet in specific autoimmune states.

Not surprisingly, T-bet's importance has been most well described in the Th1-related autoimmune syndromes of multiple sclerosis and IBD, at least in mice. In EAE, both siRNA knockdown of and targeted deficiency in T-bet prevents the development of disease (95, 138, 139), and gamma-secretase inhibitors, which inhibit Notch1 activity, effectively treat EAE, correlated with inhibition of T-bet activity (140). T-bet expression is increased in multiple sclerosis patients, diminishing during glucocorticoid therapy (93, 97). Similarly, T-bet deficiency protects mice against Th1-related colitis models, but enhances Th2-related models; and several studies have demonstrated an increased expression of T-bet in CD and celiac disease, as well as in Th1 models of colitis (e.g., IL-10 knockout mice, TNBS-induced colitis), while in contrast, Th2 models of colitis (e.g., oxazolone-induced) are associated with diminished T-bet (summarized in ref. 12, 141). Interestingly, T-bet may interact with the AP-1 transcription factor c-Maf: in an experimental colitis model, c-Maf confers protection when transduced into naïve T cells, but exacerbates disease when transduced into memory T-bet-expressing cells (134). Nonetheless, in these two diseases, T-bet seems to play a strong pathogenic role.

In other autoimmune diseases, T-bet may play a less important or varied role. In the MRL/lpr mouse model of lupus, for instance, T-bet is required for autoantibody production and immune-complex end-organ disease, but its deficiency also results in an exacerbation of cellular autoimmunity, such as in the salivary gland (142). Nonetheless, T-bet expression correlates with treatment response in the 16/6-Id mouse model of lupus (143), disease activity in SLE (144), and is increased in the urinary sediment during flares of SLE nephritis (145, 146). In arthritis, Th1 cells may contribute to a significant proportion of inflammation, at least in some animal models (147), but RA demonstrates interestingly low T-bet or T-bet/GATA-3 ratios (148, 149), and T-bet-deficient mice demonstrate increased joint pathology and infection control in staphylococcal arthritis (150). In systemic sclerosis, T-bet may antagonize the fibrotic process, at least as suggested in bleomycin-induced fibrosis models in T-bet-deficient mice (151), and analogously, T-bet-deficient mice are prone to autoimmune myocarditis (152). Finally, in mouse models of type 1 diabetes, T-bet is required for LCMV-induced diabetes, likely relating to a role in the regulation of the CD8 response (153), but in an insulin-peptide induced model of diabetes, T-bet was dispensable (154). Thus, T-bet's role interestingly seems highly specific for the autoimmune processes of multiple sclerosis, with relevance to at least some aspects or forms of IBD, diabetes, and lupus, and perhaps other autoimmune pathologies.

3.5. NFAT

The nuclear factor of activated T cells (NFAT) family includes the calcium-regulated members NFATc1 (NFATc, NFAT2), NFATc2 (NFATp, NFAT1), NFATc3 (NFAT4, NFATx), and NFATc4 (NFAT3), as well as the osmotic stress-regulated NFAT5 (TonEBP, NFATL1, NFATz), all of which are structurally related to Rel (155). NFATs typically reside in a phosphorylated form in the cytoplasm. Upon receptor ligation (e.g., T cell receptor, B cell receptor, TNF superfamily receptor, etc.), calcium signaling activates protein phosphatase 2B (PP2B, calcineurin), which dephosphorylates the NFATs and allows their translocation to the nucleus, where they interact with co-activators like AP-1 to transactivate target genes.

Although NFATs have been strongly implicated in the pathogenesis of multiple autoimmune diseases due to the clinical efficacies of cyclosporin A and FK506, which inhibit NFAT activity via the inhibition of calcineurin (156, 157), these compounds can affect other cellular pathways, such as NF-kappaB, and definitive studies regarding specific NFAT isoforms have not been unreported. Some data, though, indicate that NFATs may regulate at least some aspects of arthritis (158), since NFATc2 deficiency in mice interestingly converts the symmetric arthritis of the K/BxN serum transfer model into an asymmetric, oligoarticular disease (159). In addition, NFATc1 plays a key role in the differentiation of osteoclasts (160), and

interventions which inhibit osteoclastogenesis, such as IL-4 or leflunomide and perhaps even tacrolimus and cyclosporine A treatment, appear to do so at least in part by inhibiting NFATc1 activation in response to RANKL (124, 125, 161). Also, NFATs likely participate in the regulation of intestinal inflammation, since NFATc2 deficiency confers a spontaneous inflammatory bowel syndrome on a Rag-deficient background, mediated by non-T, non-B innate immune cells (162). In human SLE, the NFATc2 isoform in particular has been implicated, where its activity appears abnormally elevated and may mediate dysregulation of CD154 and IL-2 (163, 164). Thus, some initial studies have begun to elucidate the immunomodulatory roles of specific NFAT isoforms in autoimmunity, but insufficient data exist to make more definitive conclusions.

3.6. Forkhead

Forkhead (Fox) proteins constitute a family of "winged helix" transcription factors involved in many cellular processes relevant to cancer, aging and autoimmunity (6, 165). Much investigation has focused on Foxp3 (scurfin, JM2), which is required for the generation of regulatory T (Treg) cells; mutations in human *FOXP3* account for the immunodysregulation, polyendocrinopathy, enteropathy, X linked (IPEX) syndrome, which includes intractable diarrhea, eczema, hemolytic anemia, diabetes mellitus, and/or thyroid autoimmunity (166, 167). However, more broadly, Foxp3 likely affects the pathogenesis of multiple autoimmune diseases via its role in disease-suppressive Tregs, including inflammatory arthritis (168, 169), inflammatory bowel disease (170, 171), multiple sclerosis (172, 173), lupus (174-176), pemphigus (177), pemphigoid (178), myasthenia gravis (179), autoimmune myocarditis (180), and primary biliary cirrhosis (181).

Recent work has begun to elucidate the relevance of other Fox genes in autoimmunity: Foxj1 (Fkhl13, Hfh4), Foxd1 (Fkhl8, Freac4) and Foxo3a (Fkhrl1), for example, exhibit diminished activity in murine lupus, and likely restrain spontaneous T cell activation in part collectively by inhibiting NF-kappaB and NFAT (182-185). Indeed, exogenous Foxj1 can repress the autoimmune phenotype of lupus-prone MRL/lpr mice (186), and osteopontin may promote T cell survival in EAE by inhibiting Foxo3a activity (296). Interestingly, Foxo3a deficiency specifically confers resistance to the K/BxN serum transfer arthritis model by making neutrophils susceptible to inflammation-induced apoptosis (187), and dysregulation of Foxo family members has been observed in rheumatoid arthritis and SLE (188, 189, 297). Continued work on the specific multiple Fox genes will therefore likely demonstrate their broad applicability to immunoregulation in multiple immune cell lineages (6, 165, 190).

3.7. IRF

The interferon regulatory factor (IRF) family includes several helix-turn-helix family members which play critical roles in the responses to interferons and other stimuli (191). The canonical member IRF-1 is now known to play key roles in several autoimmune syndromes, at least in mice. IRF-1-deficient animals are protected from both IL-1- and LPS-induced synovitis as well as collagen-induced arthritis (192, 193), EAE (193, 194), DSS-induced colitis (195, 196), and MRL/lpr lupus (197). Interestingly, IRF-1 deficiency also protects NOD mice from insulitis (198), but perhaps predisposes the animals to lymphocytic thyroiditis (199). The relevance of other family members have begun to be defined, as evidenced by observations of aberrant expression of IRF-2 in psoriasis (200) and IRF-7 in cutaneous lupus and psoriasis (201, 202), while IRF-2 deficiency predisposes some mouse strains to a psoriasis-like inflammatory syndrome (203). Also, RA synovia exhibit increased IRF-3 activity, perhaps related to IKK to mediate the expression of chemokines such as CCL5 (204); and *IRF5* polymorphisms have been observed in SLE and RA (256, 258). Thus, although IRF-1 appears to be a key regulator of multiple autoimmune disorders, at least in mice, other IRF family members likely further contribute to disease pathogenesis.

3.8. Ets

Several members of the Ets transcription factor family, which includes over 30 members related to the v-ets avian erythroblastosis virus E26 ongogene homolog (Ets)-1, have been found in abnormal levels in rheumatoid arthritis and lupus (summarized in ref. 12). Abnormal expression Elf-1, for instance, may contribute to the defective TCR-zeta chain expression in human SLE (205), and Fli-1 likely promotes autoimmunity in murine lupus by enhancing B cell hyperactivity (206, 207). Dysregulation of Ets-1 and other family members may contribute to neuroinflammation and demyelination in mouse models of multiple sclerosis (208, 209).

3.9. Other transcription factors

Many additional transcription factors have been implicated in autoimmune disorders, though their roles remain less well-characterized. For instance, both murine and human rheumatoid arthritis have demonstrated abnormal expression of TFs like CAAT enhancer binding protein C/EBP-beta, XBP-1, and Id proteins (summarized in ref. 12), as well as hypoxia-inducible factor (HIF)-1alpha (210). Similarly, other transcription factors have been found elevated in autoimmune diseases will still uncertain functional relevance, e.g., Id1 in psoriasis (211), Brn-3 in SLE (212), HIFs and hedgehog-related Gli transcription factors in psoriasis (213, 214), GATA-3 in cord blood from infants at risk for type 1 diabetes (215), and the recently described transcription factor lipopolysaccharide-induced TNF-alpha factor (LITAF) in inflammatory bowel disease tissues (216). Others still have been demonstrated to have functional relevance in isolated reports, such as the ability of T cell transgenic expression of GATA-3 to improve glomerulonephritis in BXSB lupus-prone mice (217), and the bHLH factor Olig1, which is required for re-myelination during recovery from EAE (218). Smad proteins may contribute to scleroderma, e.g. through their role in the signal transduction of the pro-fibrotic candidate cytokine TGF-beta (219, 220), and hc-Krox may further regulate collagen expression in this disease (221). Dysregulation of Tcf-4 may regulate the expression of defensins and therefore intestinal microbial environments in inflammatory bowel disease (222).

Table 1. Evidence for transcription factor involvement in autoimmune diseases

	Evidence[1] for pathogenic (+) versus protective (-) involvement in:					
Family/member	Arthritis	DM	IBD	MS	SLE	psoriasis
AP-1	+++	+/-	+/-	+/-	+/-	+/-
NF-kappaB[2]	++++	++++	++++[3]		++	+
RELA (p65)	++	+	++++[3]		+/-	
c-REL	+++	+++		+++	+	
NF-kappaB1 (p105/p50)	++++	+++	++	+++	+	
STAT						
STAT1	+/-	+	++	--	+/-	-
STAT3	+/-	-	+/-	+	++	+
STAT4	++++	+++	+++[3]	+++	+++	
STAT5a/b		-	+/-			
STAT6	+/-	-	--[3]	---	++	
NFAT						
NFATc1	+					
NFATc2	+		-		+	
Forkhead						
Foxp3	+/-	+/-	+/-	+/-	+/-	+/-
Foxd1					+/-	
Foxj1					+/-	
Foxo3a	+++				+/-	
Interferon (type 1)-related (non-STAT)						
Ifi202					+/-	
IRF-1	+++	+++		+++	+++	
IRF-3	+					
IRF-4	+/-					
IRF-7					+/-	+/-
T-bet	+/-	++++	++++[3]	++++	+++	
IL-4 (type 1)-related (non-STAT)						
GATA-3	+/-				--	-
c-Maf		---	+/-			
Ets						
Egr-1	+					
Elf-1					-	
Ets-1,2	+			+		
Fli-1					+	
Miscellaneous						
C/EBP-□	+					
c-Myb					+	
Olig1				-		
Runx1	+				+	+
Runx3			+			
Tcf7 (Tcf1)		+				
Xbp-1	+				+	

[1] + or +/-, supported by limited, controversial and/or conflicting studies; ++ or --, supported largely by *in vitro* or modest and/or non-definitive *in vivo* analyses; +++ or ---, supported strongly by genetic targeting in at least one animal model (via knockouts, inhibitory transgenes or oligonucleotides); ++++, strongly and consistently supported by multiple studies involving genetic targeting in animal models (via knockouts, inhibitory transgenes or oligonucleotides) and/or analogous studies in humans (e.g., genetics). Blanks indicate that insufficient knowledge is available for the transcription factor in the particular disease state. Updated from ref. (12). [2] Evaluation here reflects interventions that were not specific to individual NF-kappaB family members (e.g., decoy oligonucleotides or IkappaB super-repression). [3] In Th1 IBD models. T-bet has been shown to be protective (----) in Th2 IBD models. DM, diabetes mellitus; IBD, inflammatory bowel disease; MS, multiple sclerosis; SLE, systemic lupus erythematosus.

A growing number of still additional transcription factors has been demonstrated to regulate autoimmunity in mice, such as Aiolos and Stra13 (summarized in ref. 12), as well as E2A (223), Id3 (224) and nuclear factor erythroid 2-related factor 2 (Nrf2) (225), all of which appear to be required to prevent spontaneous inflammatory syndromes including autoantibodies and end-organ disease. Similarly, Runx3 deficiency leads to colitis in mice (226), and a critical role in organ-specific tolerance has been demonstrated for the autoimmune regulator (AIRE), mutations in which result in the autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED) syndrome, related in part to defective expression of peripheral organ autoantigens and central tolerance in the thymus (227).

These transcription factors clearly play fundamental roles in the maintenance of immune tolerance and/or homeostasis; however, solitary defects in any of these genes seem unlikely to account for the majority of autoimmune syndromes (228), in part because none of the mutant animals completely resemble any typical autoimmune disease. Still, it is tempting to speculate that loss of function in one or more of the pathways that regulate or are regulated by these genes contribute to disease incidence and/or severity, perhaps by converging upon and/or otherwise interacting with aforementioned inflammatory pathways like NF-kappaB, STAT or AP-1, or even T-bet, NFAT, Forkhead, or Ets. Table 1 summarizes the evidence for TFs in autoimmune diseases.

Table 2. Genetic evidence for transcription factor associations with human autoimmune disorders

Family/member	RA	DM	IBD	MS	Ps	SLE	Other
AP-1						*FCGRB2B*	
JunB					*JUNB*		
Foxa1, Foxa2			*AGR2*				
IRF							
IRF-2					*IRF2*		
IRF-5	*IRF5*					*IRF5*	
NF-kappaB	*TNFR2*		*NOD2*		*NOD2*	*TNFR2*	
NFKB1		*NFKB1*	*NFKB1*				
NFKBIA	*NFKBIA*		*NFKBIA*	*NFKBIA*			
NFKBIL1	*NFKBIL1*			*NFKBIL1*			*NFKBIL1*
RELA			*TNF-alpha*				
Runx1	*SLC22A4*	*PDCD1*			*SLC9A3R1*	*PDCD1*	
STAT							
STAT4	*STAT4*					*STAT4*	
STAT6			*STAT6*				
Tbx21		*TBX21*					*TBX21*
Tcf7		*TCF7*					

Listed are transcription factors, polymorphisms in which or affecting which have been associated with the autoimmune diseases indicated. For polymorphisms within the transcription factor genes, the transcription factor itself is indicated in the table. For polymorphisms which affect the binding site of the indicated transcription factor, the gene in which the polymorphism resides is indicated. For example, a Runx1 binding site polymorphism in *SLC22A4* has been identified in RA. DM, type I diabetes mellitus; IBD, inflammatory bowel disease; MS, multiple sclerosis; Ps, psoriasis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

4. GENETICS OF TRANSCRIPTION FACTORS IN AUTOIMMUNITY

A growing number of transcription factors have been linked to the pathogenesis of autoimmune diseases through genetic studies (Table 2). Although a few examples exist of monogenic polymorphisms in specific diseases, these are limited to relatively rare syndromes, such as *AIRE* and APECED (227), or *FOXP3* and IPEX (166). More relevant to the sporadic (and sometimes familial) autoimmune diseases, like RA, SLE, IBD and psoriasis, are polymorphisms within several transcription factors themselves, or in binding sites for the transcription factors in specific target genes (229).

4.1. Runx

The runt related transcription factors, which include Runx1 (AML1, Cbfa2, Pebp2a2, Pebpa2b), Runx2 (AML3, Cbf, Cbfa1, Pebp2a1, Pebpa2a) and Runx3 (AML2, Cbfa3, Pebp2a3), exhibit both tumor suppressor and oncogenic properties and play key roles in the regulation of hematopoiesis and cancer (230, 231). In the immune system, these factors are now known to play critical roles in T cell development (reviewed in ref. 4).

Recently, Runx1 has been implicated in a few autoimmune syndromes via genetic studies that have associated SNPs affecting Runx1 binding sites with specific diseases (232). The inhibitory costimulatory molecule programmed cell death 1 gene (*PDCD1, PD-1*), for instance, contains an intronic enhancer SNP which affects Runx1 binding, and has been associated with SLE, accounting for *SLEB2* (233, 234), as well as type 1 diabetes (235). Similarly, a loss-of-Runx1 binding SNP has been linked to psoriasis between *SLC9A3R1*, a PDZ domain-containing phosphoprotein which associates with members of the ezrin-radixin-moesin family, and *NAT9*, an N-acetyltransferase (PSORS2, 236). Also, one RA study has revealed in *SLC22A4*, an organic cation transporter whose expression is specific to hematological and immunological tissues and enhanced in the inflammatory joints of mice undergoing collagen-induced arthritis, but whose physiological function remains largely unknown, an intronic SNP affecting Runx1 binding and transcriptional efficiency (237-239). Thus, Runx1 has emerged as a heavily implicated transcription factor in autoimmunity; however, these genetic studies await functional biological confirmation.

4.2. NF-kappaB

Several NF-kappaB genes have been linked to autoimmunity, not only via the functional studies summarized above, but also by genetics. For instance, *NFKB1* polymorphisms have been linked to Type I diabetes susceptibility in some populations (240-242), Grave's disease (243), as well as some populations for UC (244, 245), and an *NFKBIA* polymorphism has been demonstrated in CD (246). Also, IBD-associated variants of *NOD2*, an intracellular sensor of bacterial muramyl dipeptide, accentuate NF-kappaB responses (247), and the *IBD3* susceptibility locus contains a polymorphism in the *TNF* promoter that affects the cooperative binding of Oct1 and RelA (248). In MS, polymorphisms in *NFKBIA* may protect against susceptibility, while polymorphisms in nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor-like 1 (*NFKBIL1*) may predispose (249). *NFKBIL1* polymorphisms may also contribute to susceptibility to RA and Takayasu arteritis (250). Finally, a M196R polymorphism in TNF receptor 2 (*TNFR2*), which has been associated with SLE and familial RA, results in significantly lower NF-kappaB activation (251), and *NFKBIA* may interact with *FCRL3* in RA susceptibility (252). Thus, multiple genetic studies in several autoimmune diseases have implicated genetic polymorphisms in NF-kappaB family members as contributing to disease susceptibility.

Table 3. Some current and potential therapies in autoimmune diseases and their demonstrated or potential effect upon transcription factors

Therapy	Applicable Disease(s)	Intended Target(s)	Transcription factor(s) affected	References
Antimalarials (chloroquine, hydroxychloroquine)	RA, SLE	Endosome acidification	AP-1, NF-kappaB	(270-273)
Gold compounds	RA		AP-1, NF-kappaB, STAT3	(61, 62)
Costimulatory Blockade	RA, SLE			
CTLA4-Ig	RA, SLE	CD28-B7	AP-1, NFAT, NF-kappaB	(278)
			Foxo3a	(280, 281)
CD86	RA, SLE	CD28-B7.2.	Oct-2	(282)
Cyclophosphamide	SLE	DNA akylation	NF-kappaB	(275)
Cytokine modulation				(49, 279)
Type I IFN blockade	SLE	Type I IFN	STAT1/2/4	
IFNs (IFN-alpha, -beta, etc.)	MS	IFN-I receptor	STAT1/2/4, T-bet	
IL-2 blockade	SLE, MS, IBD	IL-2	STAT5	
IL-6 blockade	RA, SLE	IL-6	STAT3	
IL-10 blockade	SLE	IL-10	STAT3	
IL-12/23 blockade	IBD, Ps, PsA, RA, SLE	IL-12/23	STAT4	
Glucocorticoids	Many	GR	NF-kappaB	(263, 264)
IL-1/TLR family	RA, SLE		NF-kappaB, IRF-3	(294, 295)
IL-1 antagonism (anakinra, etc)		IL-1		
TLR antagonism		TLRs		
Immunophilin ligands	Many		NFAT, AP-1	(124, 274)
Cyclosporin A		Cyclophilin – calcineurin		
FK506, pimecrolimus		FKBP12 - calcineurin		
Leflunomide		Pyrimidine synthesis	NF-kappaB	(269)
NSAIDs (aspirin, salicylates, traditional NSAIDs, COX-2 inhibitors)	Many	Cyclooxygenases	NF-kappaB	(266)
Sulfasalazine	IBD, PsA, RA, SLE, SpA	Adenosine metabolism? NSAID-like?	NF-kappaB	(265)
TNF superfamily members			NF-kappaB	(277)
TNF antagonists (adalimumab, etanercept, infliximab, etc)	IBD, Ps, PsA, RA	TNF-alpha		(48)
BLyS family blockade (anti-BLyS, TACI-Ig)	RA, SLE	BLyS/APRIL TACI/BCMA/BAFF-R		
CD40 blockade	RA, SLE	CD40 – CD40L		
OX40 blockade	RA, SLE	OX40 – OX40L		

Shown are current therapies in autoimmune diseases that regulate or likely regulate transcription factor activity. COX, cyclo-oxygenase; GR, glucocorticoid receptor; IBD, inflammatory bowel disease; IFN, interferon; MS, multiple sclerosis; NSAID, non-steroidal anti-inflammatory drug; Ps, psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; SpA, spondyloarthropathy; SLE, systemic lupus erythematosus.

4.3. Other transcription factors

Other studies have found association between additional transcription factors and disease. For instance, diabetes has been associated with polymorphisms in *TBX21* (253), as well as *T cell-specific transcription factor (TCF) 7* (254). A 3' UTR SNP in *STAT6* is associated with Crohn's (255), and SLE susceptibility polymorphisms have been found in *IRF5* (256) as well as in an AP-1 binding site in the *FCGR2B* promoter (257). *STAT4* polymorphisms have been found to confer susceptibility to RA and SLE (55, 56), and *IRF5* mutations have also been observed in RA (258). The psoriasis susceptibility locus *PSORS6* contains *JUNB* (126, 259), and polymorphisms in *IRF-2* has been proposed as *PSORS3* (260). Also, promoter polymorphisms in the goblet cell protein anterior gradient protein 2 (AGR2) have been linked to inflammatory bowel disease, correlating with differential regulation by the forkhead family members Foxa1 and Foxa2 (261). Thus, polymorphisms in several transcription factors may underlie the susceptibility to specific autoimmune syndromes.

5. TREATMENTS OF AUTOIMMUNE DISEASE AND INTERPLAY WITH TRANSCRIPTION FACTORS

Although several drugs which target transcription factors are in wide therapeutic use, they were all initially developed based upon their ability to modulate specific biological processes, with the effect upon TFs discovered later (Table 3) (262). For instance, aspirin and salicylates, sulfasalazine, and glucocorticoids -- which are all used for diverse indications, including IBD, MS, RA, Ps, PsA, SLE, and SpA -- all strongly inhibit NF-kappaB activities (263-266), and given the dominant role for NF-kappaB in each of these diseases, it is not surprising that efficacy has been demonstrated. Similarly, leflunomide (HWA-486), an inhibitor of de novo pyrimidine synthesis developed primarily for arthritis and/or lupus indications, inhibits NF-kappaB (267-269). Antimalarials such as chloroquine and hydroxychloroquine exhibit multiple cellular effects, including inhibition of endosomal acidification and acidic sphingomyelinase, which are required for the cellular response to several mitogenic signals, such as toll-like receptors (TLR, especially TLR-9) or costimulatory

molecules that activate AP-1 and NF-kappaB (270-273). Common immunusuppressants include the immunophilin ligands, such as cyclosporine A and FK506, also applicable to all such autoimmune diseases, which inhibit NFAT transcription factors by, in conjunction with the immunophilins cyclophilin or FK506-binding protein (FKBP) 12, binding to and inhibiting the activity of calcineurin (274). Antimalarials, often used in inflammatory arthritides and SLE, have been demonstrated to inhibit AP-1 and NF-kappaB activities (270-273), and cyclophosphamide may inhibit NF-kappaB activity by altering DNA binding (275). Thus many anti-inflammatory and immunosuppressive medications likely act at least in part via TF inhibition, predominantly members of the NF-kappaB, NFAT and/or AP-1 families.

Recently introduced and upcoming therapies are similarly likely to regulate TF activity. The TNF-alpha antagonists, for instance, which have been extensively employed for inflammatory arthritides and IBD, all inhibit NF-kappaB, a major TF target of the TNF receptor pathway (276). Indeed, NF-kappaB activation is a common pathway of the TNF superfamily in general, such that inhibitors of other TNF superfamily pathways would be expected to inhibit NF-kappaB as well: BLyS (BAFF, TALL-1, THANK, zTNF4)-APRIL (TALL-2)-BCMA (B cell maturation factor)-TACI (transmembrane activator and CAML interactor)-BAFF-R (BAFF receptor), CD40-CD40L (CD154), RANK/OPG (osteoprotegerin)- RANKL, OX40 (CD134)-OX40L, etc (277). Analogously, IL-1 antagonists, such as anakinra, are expected to modulate NF-kappaB and/or IRF-3 (263, 264); costimulatory modulators like CTLA4-Ig would be expected to modulate NF-kappaB, NFAT and AP-1 activities (278); and cytokines and/or their antagonists would be expected to modulate their respective STAT family members (49) and/or T cell differentiation TFs, such as T-bet for IFN-gamma or IL-12 (279). However, effects upon other TFs seem highly likely to explain the diverse biological roles of these receptors. For instance, CTLA4 ligation may also affect T cell survival via Foxo3a (280, 281); CD86 signaling can also activate Oct-2 (282); and TNF antagonism can affect synovial Treg activity, suggesting that Foxp3 may be affected as well (283). Thus, as novel drugs are developed, an increasing relevance and diversity of transcription factors to the mechanisms of action of therapy is highly likely.

6. SUMMARY AND PERSPECTIVE

Transcription factors play important roles in the development, differentiation and function of immune effector cells, and therefore also critical roles in the pathogenesis of autoimmune disorders (Table 1). The most abundant data emphasize the importance of the NF-kappaB, STAT and AP-1 families in the pathogenesis of multiple autoimmune diseases, but exciting data is accumulating for additional TFs and their families, such as T-bet, NFAT, IRF, Forkhead, and Ets proteins. Interestingly, but perhaps not surprisingly, the relative importance of each of these TF families in specific autoimmune diseases remains is varied and remains still relatively poorly understood.

Nonetheless, continuing progress in the understanding of the roles of TFs in disease pathogeneses offers hope for a new generation of therapeutic strategies targeted at the modulation of transcription factor activity, e.g. by altering their synthesis, their activity via post-translational modifications and/or their protein-DNA or protein-protein interactions (262, 284). Indeed, progress has been made at targeting specific members within a known pathway, such as inhibitors of IKK for NF-kappaB (285), as well as AP-1 (286). Other strategies involve library screens via cell-based assays for transcription factor activities, such as the identification of small molecule or peptide inhibitors for NFAT (287-289), decoy oligonucleotides for NF-kappaB (290, 291), or siRNAs targeting novel components of the STAT pathway (292, 293). Disease-targeted investigations continue to be needed to yield not only a further understanding of these critical pathways in disease pathogenesis, but also additional disease-relevant pathways and targets for therapeutic intervention.

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Abbreviations: CD: Crohn's disease, CLP: common lymphocyte progenitor, COX: cyclooxygenase, DC: dendritic cell, DM: type I diabetes mellitus GC: germinal center, GR: glucocorticoid receptor, IBD: inflammatory bowel diseases, IID: inflammatory intestinal disorders, IFN: interferon, IkappaB: inhibitor of NF-kappaB, IKK: inhibitor of NF-kappaB kinase, Jak: Janus kinase, MS: multiple sclerosis, MZ: marginal zone, NBD: NEMO binding domain, NFAT: nuclear factor of activated T cells, NF-kappaB: nuclear factor kappaB, NOD, non-obese diabetic, NSAID: non-steroidal anti-inflammatory drug, Ps: psoriasis, PsA: psoriatic arthritis, RA: rheumatoid arthritis, RANKL: receptor activator of NF-kappaB ligand, SLE: systemic lupus erythematosus, SpA: spondyloarthropathy, STAT: signal transducer and activator of transcription, TNF: tumor necrosis factor, Treg: regulatory T cell, UC: ulcerative colitis, Wnt: wingless

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