Tyrosine kinases in inflammatory dermatologic disease

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Tyrosine kinases (TKs) are enzymes that catalyze the phosphorylation of tyrosine residues on protein substrates. They are key components of signaling pathways that drive an array of cellular responses including proliferation, differentiation, migration, and survival. Specific TKs have recently been identified as critical to the pathogenesis of several autoimmune and inflammatory diseases. Small-molecule inhibitors of TKs are emerging as a novel class of therapy that may provide benefit in certain patient subsets. In this review, we highlight TK signaling implicated in inflammatory dermatologic diseases, evaluate strategies aimed at inhibiting these aberrant signaling pathways, and discuss prospects for future drug development. (J Am Acad Dermatol 2011;65:389-403.)

Key words: autoimmune; dermatology; dermatomyositis; fibrosis; inflammatory; pemphigus; phosphorylation; psoriasis; tyrosine kinase.

I n recent years, the number of studies on tyrosine kinases (TKs) in autoimmune or inflammatory disease has exponentially increased. The use of TK inhibitors have been proposed as potential therapies for rheumatoid arthritis, pulmonary arterial hypertension (PAH), Crohn disease, and type 1 diabetes.[1-7] Here, we present experimental evidence that highlights TKs as key players in the etiology and pathogenesis of inflammatory dermatologic diseases, and discuss the potential of TK inhibition for the treatment of these diseases.

TYROSINE KINASES

Reversible phosphorylation is a posttranslational mechanism that controls an array of fundamental

Abbreviations used:

Abl:	Abelson
DM:	dermatomyositis
Dsg:	desmoglein
EGF:	epidermal growth factor
EGFR:	epidermal growth factor receptor
FDA:	Food and Drug Administration
FLT3:	Fms-like tyrosine kinase 3
GVHD:	graft-versus-host disease
HCT:	hematopoietic cell transplantation
IFN:	interferon
JAK:	janus kinase
MAPK:	mitogen-activated protein kinase
NSF:	nephrogenic systemic fibrosis
PDGF:	platelet-derived growth factor
PDGFR:	platelet-derived growth factor receptor
PV:	pemphigus vulgaris
SLE:	systemic lupus erythematosus
Src:	sarcoma
SSc:	systemic sclerosis
TGF:	transforming growth factor
TK:	tyrosine kinase
TLR:	Toll-like receptor
VEGF:	vascular endothelial growth factor
VEGFR:	vascular endothelial growth factor receptor

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cellular events. TKs contribute to phosphorylation-mediated regulation by catalyzing the transfer of a phosphate group from adenosine triphosphate or guanosine triphosphate to tyrosine residues on protein substrates. The human genome encodes 90 TKs, which can be divided into two main classes: receptor and nonreceptor TKs.[8] Receptor TKs are transmembrane proteins composed of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain containing the catalytic

components. The 58 receptor TKs are grouped into 20 families that include the platelet-derived growth factor (PDGF) receptor (PDGFR), vascular endothelial growth factor (VEGF) receptor (VEGFR), epidermal growth factor (EGF) receptor (EGFR), fibroblast growth factor receptor, and the rearranged during transfection (RET) kinase.[9] In the absence of ligand binding, all receptor TKs (with the exception of the insulin receptor family) exist in the cell membrane in a monomeric and nonphosphorylated form. Ligand binding to the extracellular domain of receptor TKs induces oligomerization through conformational changes, in addition to stabilizing the active oligomeric form of receptor TKs[10] (Fig 1). Oligomerization of receptor TKs classically leads to their activation via autophosphorylation of tyrosine residues in the activation loop of the intracellular domain, which leads to an increase in intrinsic catalytic activity and the formation of additional binding sites for substrate proteins.[11] Active receptor TKs can then catalyze the transfer of phosphate groups to tyrosine residues on substrate proteins, thus propagating the signal from the cell surface to the cell cytoplasm and nucleus.

Nonreceptor, or cytosolic, TKs lack extracellular and transmembrane domains and are activated by signals that cause either their dissociation from inhibitors or the phosphorylation of tyrosine residues within the TK complex.[12] The 32 nonreceptor TKs can be grouped into 10 families including Abelson (Abl), sarcoma (Src), and janus kinase (JAK).[9] As with receptor TKs, nonreceptor TKs exist in an inactive conformation under basal conditions, and phosphorylation stabilizes the active kinase conformation, enabling the catalytic transfer of phosphate groups to the bound substrate protein (Fig 2). Excellent insights into TK structure-function relationships are reviewed elsewhere.[11,13-15]

Systemic sclerosis

Systemic sclerosis (SSc), a chronic connective tissue disease of unknown etiology, is characterized by extensive fibrosis of the skin and internal organs, production of autoantibodies, and widespread vasculopathy.[16] SSc remains an incurable disease with a median of 11 years of survival from the time of diagnosis.[17] Although the pathogenesis of SSc is unclear, current evidence implicates profibrotic pathways initiated by the cytokines PDGF and transforming growth factor (TGF)-β.

Members of the PDGFR family are PDGFR-α, PDGFR-β, c-Fms (colony-stimulating factor 1R), c-Kit, and Fms-like TK 3 (FLT3). PDGF ligands bind and activate PDGFR-α and PDGFR-β, macrophage colony-stimulating factor (also known as colony-stimulating factor 1) binds c-Fms, stem-cell factor binds c-Kit, and FLT3 ligand binds FLT3.[18] The PDGF isoforms, PDGF-A, PDGF-B, PDGF-C, and PDGF-D, combine to form either homodimers (PDGF-AA, PDGF-BB, PDGF-CC, and PDGF-DD) or heterodimers (PDGF-AB only) that are biologically active.[19] PDGFs are produced by discrete cell populations including macrophages and endothelial cells. They bind to either PDGFR-α or PDGFR-β found primarily on mesenchymal cells such as fibroblasts, smooth muscle cells, and glial cells, thereby driving local cellular responses including proliferation, migration, and survival.

Up-regulation of the PDGF ligands PDGF-AA, PDGF-AB, and PDGF-BB is detected in bronchoalveolar lavage fluid, blood, endothelial cells, and infiltrating macrophages in patients with SSc.[20-22] Locally captured platelets, endothelial cells, monocyte lineage cells, and fibroblasts are all potential sources of PDGF ligands, however, the exact cellular origin of these PDGF ligands in patients with SSc remains to be elucidated. Expression of PDGFRs is high in skin biopsy specimens and cultured fibroblasts from patients with SSc; in contrast, PDGFR expression is low or absent in tissue or fibroblasts from healthy control subjects.[23-26] In a recent study, autoantibodies against the inactive monomers of PDGFR were detected exclusively in patients with SSc, and these PDGFR-specific autoantibodies could induce mitogen-activated protein kinase (MAPK) signaling and type I collagen gene expression in fibroblasts.[27] Although follow-up studies by other research groups have been unable to confirm the presence of stimulatory PDGFR-specific autoantibodies in patients with SSc,[28-30] the up-regulation of both PDGFRs and their ligands in patients with SSc suggests that PDGFR signaling is involved in SSc fibrosis. In theory, autoantibodies against receptor TKs, such as PDGFR, have the potential to either act

CAPSULE SUMMARY

- Tyrosine kinase regulation of phosphorylation controls an array of fundamental cellular events.

- Tyrosine kinases play critical roles in the etiopathogenesis of several inflammatory dermatologic diseases.

- Tyrosine kinase inhibition represents a novel and promising treatment strategy for certain inflammatory dermatologic diseases.

- It will be essential to perform rigorous clinical trials to guide treatment decisions.
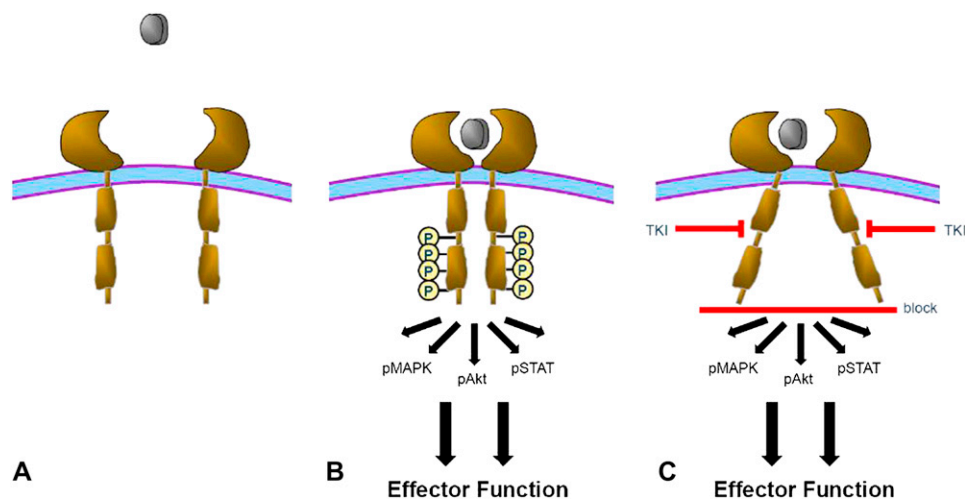
Fig 1. Receptor tyrosine kinase (TK) activation. **A**, In absence of ligand binding, receptor TKs usually exist in cell membrane in monomeric and nonphosphorylated form. **B**, Ligand binding to extracellular domain causes conformational changes that induce and stabilize oligomerization of receptor TKs, leading to autophosphorylation of their cytoplasmic domains. Active kinase catalyzes transfer of phosphate groups (*P*) to substrate molecules, thereby promoting signal transduction, including through mitogen-activated protein kinases (*MAPKs*), Akt, and STATs, and downstream effector functions. Conformational changes involved in receptor TK activation may also promote signal transduction by releasing inhibitory constraints on substrate molecules. **C**, In presence of TK inhibitor (*TKI*), cytosolic components of receptor TK fail to effectively oligomerize and autophosphorylate, which prevents signal transduction and effector function. *p*, Phosphorylated.
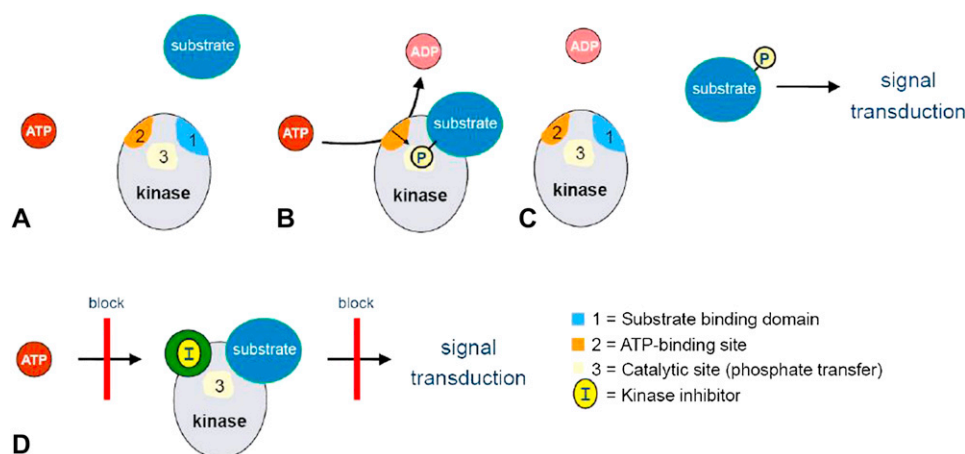
Fig 2. Activation of tyrosine kinases (TKs). **A**, TKs contain substrate-binding domain, adenosine triphosphate (*ATP*)-binding site, and catalytic site where phosphate group (*P*) will be transferred. Substrate is molecule to which phosphate will be transferred. Under basal conditions, TKs exist in inactive ("closed") conformation (not shown), and phosphorylation of TKs stabilizes active ("open") kinase conformation that permits catalytic transfer of P to substrate molecules. **B**, Activated TK transfers P from ATP (or guanosine triphosphate) to tyrosine residue on substrate molecule. **C**, Phosphorylation of substrates by TKs is important cellular mechanism by which signal is propagated from one part of cell to another and leads to various effector functions. **D**, TK inhibitors usually bind kinase at ATP-binding site, thus preventing ATP from binding and transferring P to substrate, and consequently preventing active substrate from signaling to other parts of cell. Selectivity of TK inhibitors is made possible by generating inhibitors that bind to specific chemical pockets adjacent to ATP-binding site. *ADP*, Adenosine diphosphate.

as agonists (stimulating signaling through the receptor) or antagonists (by preventing the binding of ligand).

In addition to PDGF, TGF-β is a critical cytokine in SSc, promoting fibroblast growth, differentiation, and extracellular matrix synthesis.[31] In animal models, constitutive TGF-β signaling in fibroblasts induces fibrotic features that are similar to those of human SSc.[32] A TGF-β signature is found in skin biopsies in a subset of patients with diffuse systemic sclerosis. TGF-β is secreted by several cell types including monocytes, macrophages, fibroblasts, and T cells, in a latent form; activation of TGF-β occurs via several distinct mechanisms including catalysis by thrombospondin, plasmin, and cell-surface integrins. Binding of TGF-β to oligomeric TGF-β receptor complexes, which are serine/threonine receptor kinases and not TKs, activates both Smad (mothers against decapentaplegic homolog)-dependent and -independent signaling pathways.[33] TGF-β induces Smad2- and Smad3-independent activation of the TK c-Abl in fibroblasts[34,35]; thus, TGF-β signaling could potentially be dampened with a TK inhibitor that targets c-Abl.

Interestingly, c-Abl and Abl-related gene, both members of the Abl TK family, are also activated, as part of a feed-forward loop, by the PDGFR and EGFR signaling cascades.[36-38] Furthermore, TGF-β stimulation up-regulates PDGFR-α expression in SSc fibroblasts,[25] suggesting that synergy exists between TGF-β and PDGFR signaling. Indeed, we showed that costimulation of SSc fibroblasts with PDGF and TGF-β, by activation of c-Abl, induced a greater and synergistic proliferative response than would be expected compared with stimulation with PDGF or TGF-β alone.[39] This evidence suggests that there are a multitude of opportunities to negate synergistic stimuli to fibroplasia, such as c-Abl and PDGFR, and further suggests that blocking multiple TK pathways may produce better efficacy outcomes compared with inhibition of a single TK.

In preclinical models of SSc, small-molecule inhibitors of PDGFR and c-Abl have shown efficacy in the treatment of skin fibrosis. For instance, the small-molecule inhibitor imatinib mesylate (imatinib), which inhibits PDGFR, Abl, c-Fms, and c-Kit at clinically relevant concentrations, has been shown to provide significant efficacy in several animal models of fibrosis.[34,35,40] Imatinib reduced dermal thickening in both the bleomycin-induced acute model of dermal fibrosis and the tight-skin-1 mouse late-fibrotic model of SSc.[41,42] Nilotinib, which inhibits PDGFR, Abl, and c-Kit, and dasatinib, which inhibits PDGFR, Abl, c-Kit, and Src, have also been shown to decrease TGF-β- and PDGF-driven production of extracellular matrix proteins by dermal fibroblasts and to block bleomycin-induced dermal fibrosis.[43]

Case reports on the effects of imatinib on SSc-related disease are conflicting. Recent case reports describe patients with refractory SSc whose symptoms, particularly cutaneous sclerosis, improved after treatment with imatinib.[39,44,45] Case reports have also described improvement in cardiopulmonary hemodynamics in patients with refractory SSc-associated PAH treated with imatinib.[46] However, in another case series that explored the addition of imatinib to cyclophosphamide therapy in patients with SSc-related interstitial lung disease, only one patient exhibited improvement in pulmonary status after 12 months of treatment with imatinib.[47] Similarly, there was no statistical improvement in skin score (6-month delta modified Rodnan skin score [MRSS] change from baseline = −2.0), inflammatory markers, or global assessments in 4 patients who completed 6 months of imatinib in a group of patients with diffuse cutaneous SSc.[48] Five patients in this open-label study withdrew because of intolerable side effects.[48] In sharp contrast, a larger phase II study that followed up patients with diffuse cutaneous SSc for 12 months found a benefit with imatinib therapy.[49] In this latter study, improvements did not start to emerge until the imatinib treatment period reached 6 months (3-month delta MRSS change from baseline = −0.4, 6-month delta MRSS change = −4.9), and improvements continued to increase through the 12-month end point (12-month delta MRSS change −7.3).[49] This study also found statistical improvements in mean forced vital capacity and diffusing capacity of carbon monoxide from 84% and 80% at baseline to 90% and 88% at 12 months, respectively.[49]

The reasons for the discrepancies in these case reports and open-label trials may be multifold. The current data suggest that at least 6 to 9 months of consistent imatinib therapy are required until benefits are first observed. Perhaps at least part of the conflicting reports stems from insufficient time on imatinib therapy. Also, clearly imatinib tolerability is an issue in these reports. Our unpublished observations on the use of imatinib in SSc suggest that lower doses of imatinib (eg, 100-200 mg/d) are equally effective and better tolerated than the higher doses used in the aforementioned studies ($\geq$ 400 mg/d). Unlike cancers, the fibroplasia seen in SSc is driven by wild-type kinases (eg, PDGFR and c-Abl) in which low doses of TK inhibitors may be more appropriate. Lower doses of imatinib, with a corresponding reduced side effect profile, would increase the likelihood that patients with SSc would safely reach the 6- to 9-month mark that appears to be required for benefits. Further, we

found that the abnormal expression of group of genes (that characterizes most diffuse scleroderma patients) was reversed in two patients that were treated successfully with imatinib.[39] We speculate that there are several patient population subsets that currently fall under the umbrella category of SSc, and that at least one subset may be responsive to imatinib therapy whereas other subsets may not be responsive. Molecular biomarkers could prove useful in guiding therapeutic decision-making, an approach that must be validated by rigorous clinical trials, which are currently underway.

Graft-versus-host-disease

Graft-versus-host disease (GVHD) is a potentially lethal complication of allogeneic hematopoietic cell transplantation (HCT).[50] HCT is of significant value for patients with leukemia or other diseases that stem from aberrations in hematopoiesis.[51] Acute GVHD generally occurs 20 to 40 days after HCT and is caused by activation of host antigen-presenting cells, activation of donor T cells in response to the activated host antigen-presenting cells, and finally secondary activation of host effector cells, resulting in further inflammation, local tissue injury, and organ attack.[52] Skin manifestations of acute GVHD include lichenoid macules and papules that may blister or ulcerate in severe cases.[52] Chronic GVHD is less well understood but recent insights suggest that B cells may be involved.[53] Skin lesions in chronic GVHD are classically divided into lichenoid and sclerodermoid categories, and recently an eczematoid form has been described.[54,55]

Patients with extensive sclerodermoid chronic GVHD frequently have cutaneous manifestations similar to those of patients with SSc. Similar to SSc, GVHD may be associated with the development of autoantibodies against PDGFR. In a study on a small number of patients with HCT, those patients with extensive chronic GVHD possessed stimulatory autoantibodies against PDGFR, whose levels correlated with fibrosis severity; in contrast, patients with HCT without chronic GVHD and healthy individuals did not possess anti-PDGFR antibodies.[56] In a recent study on the use of low-dose imatinib in the treatment of chronic GVHD, imatinib was well tolerated overall, and the rate of response to treatment with imatinib was 86% after 8 months, which included a reduction in the sclerodermal disease and in chronic bronchiolitis and osteomyalgia.[57] Targeting B-cell activity and PDGFR autoantibodies holds promise for the treatment of chronic GVHD, and studies assessing the efficacy of small-molecule TK inhibitors of PDGFR, such as imatinib, in the treatment of chronic GVHD are ongoing.

Nephrogenic systemic fibrosis

Less than 10 years have elapsed since the first published description of nephrogenic systemic fibrosis (NSF) (formerly nephrogenic fibrosing dermopathy) in patients with severe renal disease.[58] The number of cases has been increasing, and more than 200 patients are currently described in the International Center for Nephrogenic Fibrosing Dermopathy Research.[59] The major risk factor for developing NSF is the use of gadolinium-containing magnetic resonance contrast agents by patients with impaired renal function.[59] Cutaneous changes are the most prominent sign, occurring in all patients, and include skin tightening and thickening, induration, contractures, and hyperpigmentation.[60] Systemic involvement may also be observed and includes fibrosis of internal organs such as lungs, myocardium, and pericardium.[61] NSF skin biopsy specimens show an increase in collagen levels and in proliferation of fibrocytes thought to be derived from the bone marrow.[62,63]

Levels of the profibrotic cytokine TGF-β are increased in affected skin, fascia, and muscle of patients with NSF,[64] suggesting that TGF-β plays a role in the development of fibrosis in NSF. Because TGF-β stimulates extracellular matrix production in fibroblasts by Smad-independent activation of the c-Abl TK, inhibitors of c-Abl could potentially provide therapeutic benefit in NSF. In addition, PDGFR may also be involved in the pathogenesis of NSF, as in other fibrotic disorders such as SSc and GVHD. Two recent case reports describe the use of imatinib—which inhibits both c-Abl and PDGFR—in the treatment of 3 patients with NSF.[65,66] Administration of imatinib at 400 to 600 mg per day significantly improved NSF in two men (a 65-year-old and a 75-year-old) with stage-5 kidney disease.[65] In another study, imatinib at 400 mg per day or 300 mg twice a day provided significant therapeutic benefit in a 57-year-old woman with end-stage renal disease and biopsy-proven NSF.[66] In a recent open-label clinical trial, the therapeutic efficacy of imatinib was assessed in 6 patients with biopsy-proven NSF after 4 months of treatment.[67] The patients' cutaneous symptoms improved by 24% within 2 months of therapy, but worsened in 4 of 6 patients after the discontinuation of imatinib treatment.[67] Additional studies using larger numbers of patients with NSF to determine the clinical efficacy of imatinib or other c-Abl/PDGFR inhibitors are warranted.

Psoriasis

Psoriasis is a common inflammatory autoimmune disease with a strong genetic component. It is characterized by epidermal hyperproliferation and a

diverse infiltration of leukocytes, which classically leads to the development of well-demarcated erythematous plaques with white scales.[68,69] Evidence to date underscores the importance of angiogenic factors, keratinocytes, and T cells in the pathophysiology of psoriasis.[70-72]

VEGF ligands are growth factors important in angiogenesis and signal through the TK VEGFR family members VEGFR1 (aka Fms-related TK 1 [FLT1] or fetal liver kinase 2 [FLK2]), VEGFR2 (aka kinase domain receptor [KDR] or fetal liver kinase 1 [FLK1]), and VEGFR3 (aka Fms-related TK 4 [FLT4]). Induction of inflammation with oxazolone in transgenic mice that heterozygously overexpress VEGF-A in the epidermis induces features that resemble those of human psoriasis, including epidermal hyperplasia, hyperkeratosis, and T-cell infiltration.[73] Homozygous overexpression of VEGF-A in transgenic mice resulted in the spontaneous development of a psoriasiform phenotype that mirrored human psoriasis.[74] Although VEGFRs are expressed by vascular endothelial cells and epidermal keratinocytes,[75,76] aberrations in VEGFR signaling in psoriasis appear to occur primarily in epidermal keratinocytes. Compared with skin sections from healthy patients, skin sections from patients with psoriasis exhibit markedly higher expression of VEGF, VEGFR1, VEGFR2, and VEGFR3, all of which localize to epidermal keratinocytes.[77-79]

Compared with keratinocytes from normal-appearing skin, VEGFR1 and VEGFR2 on keratinocytes from both involved psoriatic and normal-appearing uninvolved psoriatic skin are significantly up-regulated.[78] In contrast, tissue levels of VEGF ligands are significantly elevated only in involved psoriatic skin and are low in both uninvolved psoriatic skin and normal-appearing skin.[80] This raises the possibility that VEGFR1 and VEGFR2 signaling may be aberrantly up-regulated in both involved and uninvolved psoriatic skin independent of the presence of VEGF ligands.

Thus VEGF/VEGFR signaling may be important in psoriasis, and blocking this pathway may have potential as a therapeutic strategy in psoriasis. NVP-BAW2881, a TK inhibitor that potently inhibits VEGFR1 to VEGFR3 at 1.0- to 4.3-nmol concentrations and inhibits PDGFR-β, c-Kit, and RET at 45- to 72-nmol concentrations reduced psoriasis-like symptoms in heterozygous VEGF-A transgenic mice challenged with oxazolone.[72] Interestingly, topical administration of NVP-BAW2881 was almost as efficacious as oral administration. Because topical administration will reduce systemic toxicities associated with TK inhibition, these studies may represent an important step toward the use of topical TK inhibitors for the treatment of skin lesions.

Like VEGF/VEGFR signaling, EGF/EGFR signaling has been implicated in keratinocyte dysregulation in psoriasis. The EGFR family is composed of 4 members: EGFR (also known as erythroblastic leukemia oncogene homolog 1 [ErbB1]), ErbB2, ErbB3, and ErbB4. EGFR, ErbB2, and ErbB3 are expressed in epithelial tissues and promote cell survival, migration, and proliferation.[81] The EGF ligands are produced largely by keratinocytes and include TGF-α, amphiregulin, EGF, and epiregulin.[82] Levels of TGF-α,[83,84] amphiregulin,[85,86] heparin-binding EGF,[87] and epiregulin[88] are increased in psoriatic keratinocytes and psoriatic skin biopsy specimens. Furthermore, transgenic mice that overexpress EGF ligands in basal keratinocytes develop psoriasis-like skin lesions.[89] EGFR expression is also significantly increased in psoriatic skin, and even in normal-appearing skin adjacent to psoriatic lesions, compared with normal-appearing skin.[83,84] Psoriatic skin biopsy specimens were shown to maintain histologic features of psoriasis while in tissue culture, a phenotype that partially reverted to normal in the presence of neutralizing EGFR antibodies[90] or the EGFR inhibitor PD169540.[91]

T cells play a major role in the autoimmune response in psoriasis, and both Th1 and Th17 cells have been proposed as the dominant T-cell type that secretes cytokines and interacts with the local cell population, thereby promoting the formation of a psoriatic plaque.[69,71,92] The cytoplasmic TK JAK3 plays a critical role in T-cell development, activation, and proliferation.[93] Whereas other members of the JAK family are involved in a broad array of cytokine signaling, JAK3 is expressed predominantly by lymphocytes. The JAK1/3-specific TK inhibitor R333 was recently shown to provide therapeutic efficacy in the CD18-deficient PL/J mouse model of psoriasis.[94] CP-690,550, a more specific JAK3 inhibitor,[95] also showed significant benefit in a psoriasis phase I clinical trial.[96] Thus, inhibiting T-cell signaling by targeting JAK3 may have potential as an alternative treatment strategy for psoriasis.

Case reports have documented both beneficial and detrimental effects of currently available oral small-molecule TK inhibitors in human psoriasis. Psoriasis improved in a 64-year-old man receiving sunitinib for the treatment of metastatic renal cell carcinoma.[97] Sunitinib inhibits several TKs including VEGFR, PDGFR, c-Kit, c-Fms, FLT3, and RET; this broad inhibitory spectrum makes it difficult to determine whether or not angiogenesis was the primary process targeted by sunitinib. Case reports on the use of imatinib for the treatment of psoriasis are conflicting. An early case report detailed the prompt disappearance of long-standing psoriasis in

a 64-year-old man whose metastatic gastrointestinal stromal tumor was treated with imatinib[98]; the psoriasis partially reappeared when the dose of imatinib was lowered.[98] In contrast, more recent cases have been described in which treatment of chronic myelogenous leukemia or gastrointestinal stromal tumor with imatinib exacerbated underlying psoriasis.[99-101]

EGFR inhibitors have proven to be an effective therapy for several types of cancers. The majority of patients with cancer treated with EGFR inhibitors exhibit skin toxicities as a result of the effects of EGFR blockade in normal keratinocytes.[102] However, in the correct clinical setting, EGFR inhibition could potentially provide benefit against skin pathology. A recent report described the effects of lapatinib, an EGFR/ErbB2 TK inhibitor, used to treat a 53-year-old man with renal cell carcinoma who simultaneously had long-standing severe psoriasis.[103] Although 1 month of lapatinib treatment completely resolved his psoriasis, the patient developed skin toxicities—including acneiform rash and facial seborrheic dermatitis—that typically occur secondary to EGFR inhibitor treatment.[103] Cetuximab, a monoclonal antibody against EGFR, reduced psoriasis in a patient treated for metastatic colorectal cancer.[104] In sharp contrast, 1 month of treatment with gefitinib, an EGFR inhibitor that exhibits minimal activity against ErbB2,[105] exacerbated psoriasis in a 69-year-old man with non-small cell lung cancer.[106] Clearly, further clinical data are needed to determine whether inhibition EGFR family members may provide benefit in patients with psoriasis.

Pemphigus vulgaris

Pemphigus vulgaris (PV) is a potentially fatal autoimmune blistering disease caused by antibodies against desmoglein (Dsg) 1 and Dsg 3—transmembrane adhesion proteins located on the cell surface of keratinocytes[107]—and non-Dsg antigenic targets.[108] More than 25 years have elapsed since the landmark study by Anhalt et al[109] demonstrating that passive transfer of the IgG fraction of PV sera (PV-IgG) induces pemphigus in mice. Although the molecular mechanisms by which PV-IgG leads to loss of adhesion between adjacent endothelial cells (acantholysis) and to skin blistering remain uncertain, recent studies indicate that keratinocyte TK signaling pathways are critical in the pathogenesis of PV-IgG-mediated acantholysis.

In a study on the role of EGFR in PV-IgG-mediated acantholysis, PV-IgG was shown to induce EGFR phosphorylation in cultured keratinocytes and the consequent activation of downstream signaling molecules including the MAPK extracellular signal-regulated kinase.[110] Moreover, AG1478, a specific EGFR inhibitor, reversed PV-IgG-mediated apoptosis in cultured keratinocytes.[110] The mechanisms by which PV-IgG induced EGFR activation were not elucidated. In a separate study, injection of human PV-IgG was shown to induce the phosphorylation of EGFR, ErbB2, and ErbB3 in mice.[111] Clinical and molecular findings could be reversed with erlotinib, which inhibits EGFR, ErbB2, and ErbB3. Furthermore, TGF-α, EGF, and betacellulin were up-regulated in PV epidermal lesions after injection of human PV-IgG compared with injection of normal human IgG.[111] Whether the up-regulation of EGFR family ligands is a direct effect of PV-IgG binding to keratinocytes, or an indirect effect resulting from the induction of acantholysis, remains unclear. However, PV-IgG may activate keratinocytes to produce these EGFR family ligands, which in turn drive the EGFR/ErbB2/ErbB3 signaling cascade.

Activation of Src has been observed in the epidermis after injection of PV-IgG in mice, and in vivo administration of the Src inhibitor PP1 successfully prevented acantholysis.[111] Recent analyses suggest that PV-IgG induction of Src signaling occurs upstream of EGFR activation. PV-IgG stimulation of keratinocytes elicited peak phosphorylation activities of Src, EGFR, and p38 MAPK at 30, 60, and 240 minutes, respectively.[112] Thus, Src signaling preceded EGFR activation. However, Src inhibition with PP2 after PV-IgG stimulation only partially abrogated EGFR and p38 MAPK phosphorylation.[112] Together, these studies suggest that either: (1) the concentration of PP2 did not completely inhibit Src activation; or (2) PP1 may inhibit kinases other than Src (as has been previously suggested[113]) and that non-Src pathways also trigger EGFR activation.

Whether or not it is regulated primarily by Src, EGFR appears to play a critical role in acantholysis, making it an attractive therapeutic target in PV. Genistein, a pan-TK inhibitor,[114] has been shown to block PV-IgG-induced acantholysis in vivo.[115,116] TK inhibition with genistein has also been shown to block Dsg 3 internalization in PV-IgG-stimulated keratinocytes.[117] Further insight into the functional significance of Dsg 3 internalization will be important in attempts to identify therapeutic targets in keratinocyte signaling pathways. In addition, blocking p38, which is activated downstream of EGFR, with specific inhibitors prevented acantholysis in the IgG passive-transfer model of PV.[118] Despite the availability of Food and Drug Administration (FDA)-approved inhibitors—such as gefitinib, erlotinib, cetuximab, lapatinib, and panitumumab—that target members of the EGFR family, there have been no case reports describing the use of EGFR inhibitors in human PV.

Therapies that target key signaling molecules in PV acantholysis, such as EGFR, may represent a novel strategy to treat this life-threatening autoimmune disease. On the basis of the availability and increasingly extensive use of EGFR inhibitors, we expect that there will soon be case reports that document the use of EGFR inhibitors in patients with a primary oncologic disease who concomitantly have PV.

Bullous pemphigoid

Bullous pemphigoid, a common autoimmune blistering disease,[119] exhibits increased VEGFR1 and VEGFR2 expression in affected and surrounding skin lesions compared with normal-appearing skin, and increased VEGF levels in serum and in blister fluid.[120,121] Further evidence implicating TKs in the pathogenesis of bullous pemphigoid stems from a case report that describes a patient with severe hypereosinophilic syndrome and bullous pemphigoid whose skin lesions and eosinophilia both dramatically regressed when treated with imatinib at 400 to 600 mg per day.[122] Additional research is necessary to define the role of TK inhibitors in the treatment of bullous pemphigoid.

Dermatomyositis and systemic lupus erythematosus

Dermatomyositis (DM) is a chronic inflammatory disorder that exhibits progressive proximal symmetric muscle weakness and cutaneous disease. It is an autoimmune disorder involving deposition of autoantibodies in the microvasculature, which leads to complement activation and subsequently to capillary necrosis and a mixed leukocytic infiltration.[123] Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by autoantibody formation, chronic inflammation, and immune complex deposition leading to irreversible end-organ failure. Cutaneous manifestations of SLE occur in the majority of patients and the 3 forms are acute cutaneous lupus, subacute cutaneous lupus, and chronic cutaneous (discoid) lupus.[124] Recent studies have implicated the type I interferons (IFN-α and IFN-β) in the pathogeneses of DM and SLE. Tyrosine kinase 2 (Tyk2), a nonreceptor TK, is essential for type I IFN signaling and may represent a novel target for DM and SLE therapy. Large-scale analysis of transcriptional profiles in muscle biopsy specimens from patients with DM, other myopathies, or neuromuscular disorders identified a gene-expression profile characteristic of DM, in which 12 of the 14 most highly up-regulated genes were type I IFN-inducible genes.[125] Myovirus resistance A (MxA), a type I IFN-inducible protein that is not induced by other cytokines including IFN-γ,[126] was highly expressed in DM muscle fibers and

capillaries.[125] Type I IFN-inducible genes were also found to be the most highly up-regulated genes in peripheral blood mononuclear cells from patients with DM, in which the level of type I IFN-inducible transcripts correlated with DM disease activity.[127] Levels of MxA protein are also significantly increased in DM skin lesions compared with healthy skin[128] and our data based on transcriptional profiling demonstrate a clear IFN signature in the skin. Plasmacytoid dendritic cells, whose numbers were shown to be increased in DM skin lesions compared with normal-appearing skin, are proposed to be the primary source of type I IFN in DM skin lesions[128]; however, keratinocytes and other cell types are also known to produce type I IFNs. Expression of type I IFNs and type I IFN-inducible genes is also increased in patients with SLE, and has been shown to correlate with disease activity.[129] In SLE, immune complexes containing nucleic acids are thought to be endocytosed by plasmacytoid dendritic cells, resulting in activation of Toll-like receptor (TLR)-7 and TLR-9, and the consequent up-regulation of type I IFN gene expression.[129]

Tyk2, a member of the JAK family, is a crucial TK in signal transduction through type I IFN receptors.[130] Splenocytes isolated from Tyk2-deficient mice were unable to respond to a low concentration of IFN-α.[131] dendritic cells from a separate mouse strain that also exhibit defective Tyk2 signaling were significantly less responsive to stimulation through TLR-9 or TLR-4, and mice were protected against collagen-induced arthritis.[132] These mice were also resistant to experimental allergic encephalomyelitis.[133] In addition, polymorphisms in the Tyk2 gene are associated with certain subtypes of SLE.[134,135] These studies suggest that Tyk2 signaling may contribute to the etiology and pathogenesis of certain autoimmune diseases; given the role of type I IFN in DM and SLE, we speculate that targeting Tyk2 may provide therapeutic benefit in these diseases. Although Tyk2 inhibitors are being developed, there are currently no Tyk2 inhibitors in clinical trials. We await the availability of Tyk2 inhibitors and suggest that there is rationale to targeting Tyk2 in DM and SLE.

Other TKs have also been implicated in SLE and DM. The nonreceptor TK spleen TK, which is critical for T-cell receptor, B-cell receptor, and activating Fc (fragment, crystallizable) receptor signaling, is up-regulated in lymphocytes from patients with SLE, and spleen TK inhibition ameliorated disease in an animal model of SLE.[136,137] Imatinib has also been found to treat systemic manifestations of SLE and enhance survival in mice, possibly through interruption of the PDGFR pathway.[138,139] A recent case report found that sorafenib, which inhibits PDGFR
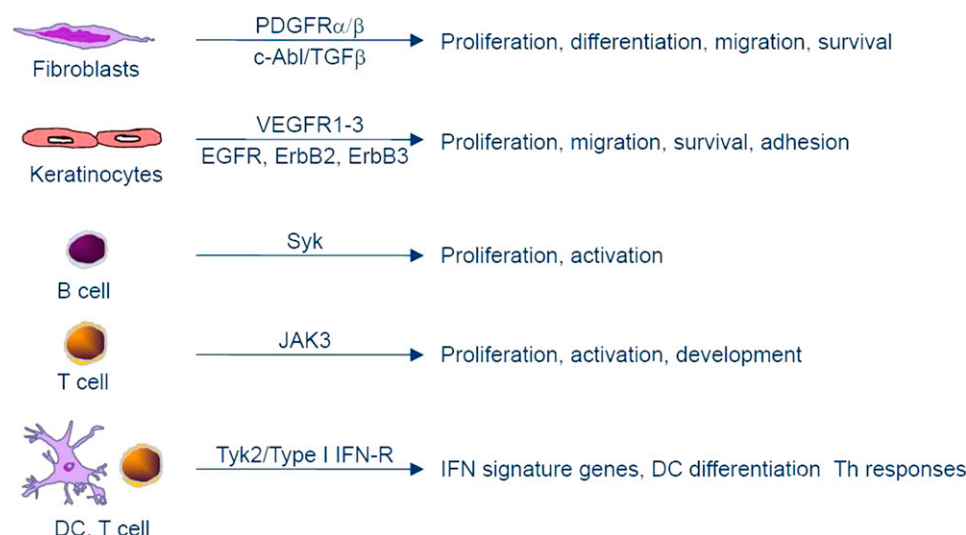
Fig 3. Cell types and responses mediated by exemplary kinases that may contribute to pathogenesis of inflammatory dermatologic disorders. Fibroblast proliferation, differentiation, migration, and survival are promoted by signaling through platelet-derived growth factor receptors (*PDGFR*), and through transforming growth factor (*TGF*)-*β* receptors via c-Abelson (*Abl*). Signaling through vascular endothelial cell growth factor receptor (*VEGFR*) or epidermal growth factor receptor (*EGFR*) induces proliferation, migration, survival, and adhesion of keratinocytes and endothelial cells. Spleen tyrosine kinase (*Syk*) contributes to B-cell receptor signaling, inducing B-cell proliferation and activation. Janus kinase (*JAK*) 3 propagates T-cell signals through type I cytokine receptors that contain common gamma chain, thereby promoting T-cell proliferation, activation, and development. Tyrosine kinase 2 (Tyk2) is important in type I interferon (*IFN*) signaling, which leads to cellular responses including IFN signature gene up-regulation, dendritic cell (*DC*) differentiation, and T-helper cell (Th) responses. *IFN-R*, IFN receptor.

and VEGFR in addition to the serine-threonine kinases Raf-1 and B-Raf, administered to a patient with DM and hepatocellular carcinoma led to improvement of DM severity, although therapy was discontinued after only 6 weeks.[140] These studies suggest the potential usefulness of TK inhibitors in the treatment of DM and SLE.

Concluding remarks

TKs play pivotal roles in cellular responses that may contribute to the pathogenesis of several autoimmune and inflammatory dermatologic diseases (Fig 3). Targeting implicated TKs with small-molecule inhibitors may provide a powerful therapeutic approach for these difficult-to-treat disorders. It will be important to continue to define the relative contributions of specific TKs to the disease processes to determine which inhibitors have potential as therapeutic agents.

Findings from oncology studies have taught us that the presence of a target, for example an up-regulated TK, does not guarantee clinical response to targeted therapy, for example with a TK inhibitor.[141] Nor do animal models always mirror human disease to a degree that would allow for confident translation

of therapies from mouse to human. Nevertheless, the studies described herein suggest that TKs have central roles in the pathogenesis of several important dermatologic diseases. Effective targeting of the appropriate molecules with specific TK inhibitors may provide significant benefit in these diseases (Tables I and II).

Taking another lesson from oncology research, we may find that specific inhibition of a single TK is not sufficient to provide substantial benefit in certain inflammatory dermatologic diseases. A landmark study demonstrated that, in cells from patients with glioblastoma multiforme, multiple receptor TKs are activated simultaneously and cooperate in the maintenance of pathogenic signaling.[142] Inhibition of multiple receptor TKs, rather than inhibition of a single receptor TK, was required to disrupt pathogenic signaling.[142] PDGFR and fibroblast growth factor receptor signaling pathways have been shown to synergize in the neovascularization of tumors. Likewise, our group has shown that PDGF and TGF-*β*, by activating c-Abl, synergize in the induction of SSc fibroblast proliferation, suggesting that inhibiting multiple TKs may be more efficacious than inhibiting a single TK in autoimmune diseases as well.[143] Thus, treatment with TK

Table I. Tyrosine kinases implicated in pathogenesis of select dermatologic diseases and tyrosine kinase inhibitors with at least one case report describing potential therapeutic benefit

Disease	Implicated TKs	TK inhibitors reported to provide potential benefit
Systemic sclerosis	PDGFR,[20-27,39] c-Abl,[32,34-39] EGFR[144]	Imatinib,[34,35,39-42,44-46,49] nilotinib,[43] dasatinib[43]
GVHD	PDGFR[56]	Imatinib[57]
NSF	c-Abl[64]	Imatinib[65-67]
Psoriasis	VEGFR,[73,74,77-80] JAK1/3,[94] EGFR,[83-89,145-147] Src[148,149]	NVP-BAW2881,[72] R333,[94] PD169540,[91] sunitinib,[97] imatinib,[98] lapatinib,[103] cetuximab[104]
Pemphigus vulgaris	EGFR,[110-112] Src[112]	AG1478[110]
Bullous pemphigoid	VEGFR[120,121]	Imatinib[122]
Dermatomyositis	Tyk2[125,127,128,130]	Sorafenib[140]
SLE	Tyk2,[129,134,135,150,151] Syk[136,137]	Imatinib[138,139]

Abl, Abelson; *EGFR*, epidermal growth factor receptor; *GVHD*, graft-versus-host disease; *JAK*, janus kinase; *NSF*, nephrogenic systemic fibrosis; *PDGFR*, platelet-derived growth factor receptor; *SLE*, systemic lupus erythematosus; *Src*, sarcoma; *Syk*, spleen tyrosine kinase; *TK*, tyrosine kinase; *Tyk2*, tyrosine kinase 2; *VEGFR*, vascular endothelial growth factor receptor.
Note that TK inhibitors are not necessarily directly linked to TKs in middle column.

Table II. Small-molecule tyrosine kinase inhibitors described in this article

Generic name	Kinase targets	Stage of development
Imatinib (Novartis, Cambridge, MA)[7,34,42,152]	PDGFRα, PDGFRβ, c-Fms, c-Kit, c-Abl, Lck	Approved
Nilotinib (Novartis, Cambridge, MA)[43,152]	PDGFRα, PDGFRβ, c-Kit, c-Abl, Lck	Approved
Dasatinib (Bristol-Myers Squibb, New York, NY)[43,153,154]	PDGFRα, PDGFRβ, c-Kit, c-Abl, Src, Lck, Fyn, Yes, Btk, Tec	Approved
Sunitinib (Pfizer Inc, New York, NY)[97,155]	VEGFR1, VEGFR2, VEGFR3, PDGFRα, PDGFRβ, c-Fms, c-Kit, FLT3, RET	Approved
Lapatinib (GlaxoSmithKline, London, England)[103,156]	EGFR, ErbB2	Approved
Gefitinib (AstraZeneca, London, England)[105]	EGFR	Approved
Erlotinib (Genentech, South San Francisco, CA)[105]	EGFR	Approved
Sorafenib (Bayer, Leverkusen, Germany)[140,157]	VEGFR1, VEGFR2, VEGFR3, PDGFRβ, c-Kit, FLT3, RET, Raf	Approved
CP-690,550 (Pfizer Inc, New York, NY)[95,96]	JAK3	Phase III
NVP-BAW2881 (Novartis, Cambridge, MA)[72]	VEGFR1, VEGFR2, VEGFR3, PDGFRβ, c-Kit, RET	Preclinical
PD169540 (Pfizer Inc, New York, NY)[91]	EGFR, ErbB2	Preclinical
R333 (Rigel Pharmaceuticals Inc, San Francisco, CA)[94]	JAK1, JAK3	Preclinical

Btk, Bruton agammaglobulinemia tyrosine kinase; *c-Abl*, Abelson; *c-Fms*, colony-stimulating factor-1 receptor; *EGFR*, epidermal growth factor receptor; *FLT3*, Fms-like tyrosine kinase 3; *JAK*, janus kinase; *Lck*, lymphocyte-specific protein tyrosine kinase; *PDGFR*, platelet-derived growth factor receptor; *RET*, rearranged during transfection; *Src*, sarcoma; *VEGFR*, vascular endothelial growth factor receptor; *Yes*, Yamaguchi sarcoma oncogene.

inhibitors that target multiple pathways should not be neglected as an approach to the treatment of complex inflammatory dermatologic diseases. However, inhibition of more TKs increases the likelihood of detrimental side effects, such that the optimal TK inhibitor will represent a trade-off between efficacy and toxicity.

Cancer is frequently driven by mutations in kinases, and thus successful treatment of cancer requires high doses of TK inhibitors. In contrast, autoimmune diseases are mediated by aberrant activation of wild-type kinases, against which low doses of inhibitor may be effective. The use of low doses of TK inhibitors in autoimmune disease would result in enhanced tolerability and safety.

We expect that the next generation of TK inhibitors will include topical formulations, which may specifically treat the cutaneous manifestations of inflammatory dermatologic diseases. Topical TK inhibitors should theoretically provide local benefit while avoiding the systemic toxicity observed with orally administered TK inhibitors.

Inhibition of TKs by molecules that are already FDA approved or in earlier stages of clinical development represents a promising treatment strategy for inflammatory dermatologic diseases. Significant

rationale exists for prospective clinical trials to determine whether TK inhibitors may provide therapeutic efficacy, and it is essential that data from rigorous clinical trials be used to guide treatment decisions in this important clinical area.

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