REVIEW

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 10.1016/j.jaad.2010.04.026.)

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

In 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.

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

TYROSINE KINASES

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

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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.

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.

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

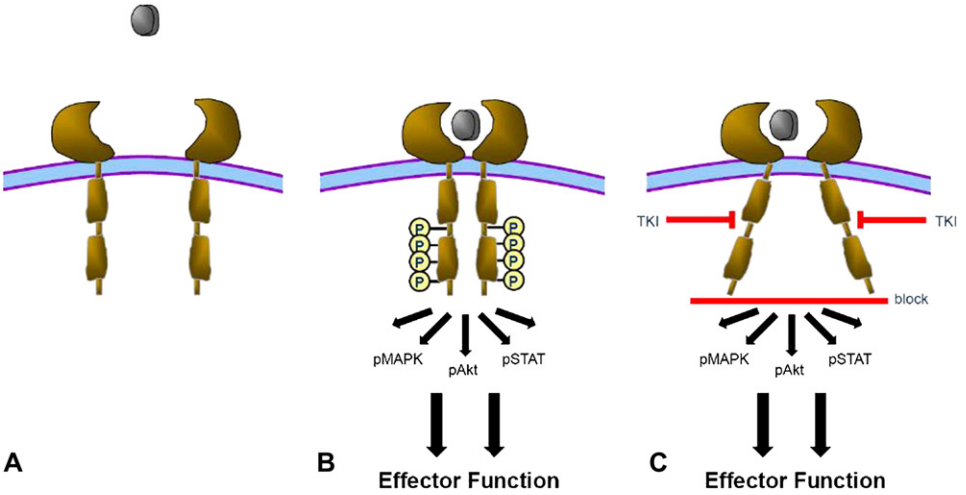

Fig 1. Receptor tyrosine kinase (TK) activation. **A**, In absence of ligand binding, receptor TKs usually exist in cell membrane in monomeric and nonphosphorylated form. **B**, Ligand binding to extracellular domain causes conformational changes that induce and stabilize oligomerization of receptor 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.

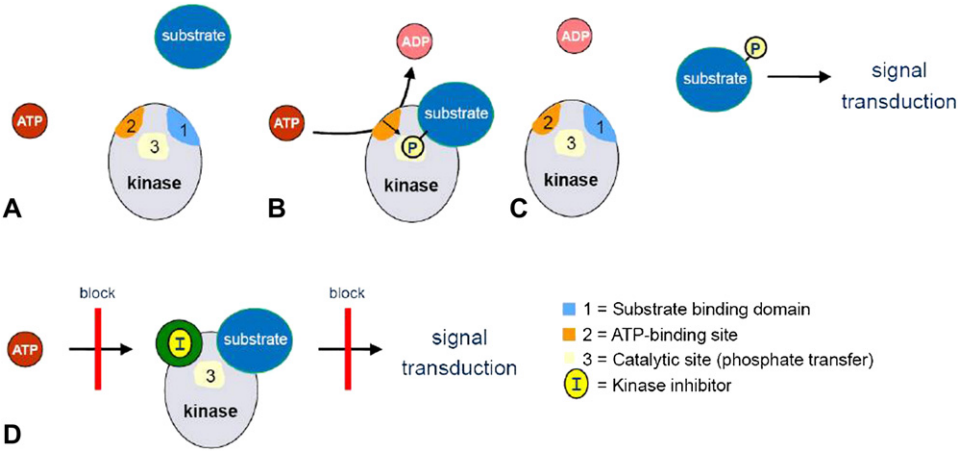

Fig 2. Activation of tyrosine kinases (TKs). **A**, TKs contain substrate-binding domain, adenosine triphosphate (*ATP*)-binding site, and catalytic site where phosphate group (*P*) will be transferred. Substrate is molecule to which phosphate will be transferred. Under basal conditions, TKs exist in 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

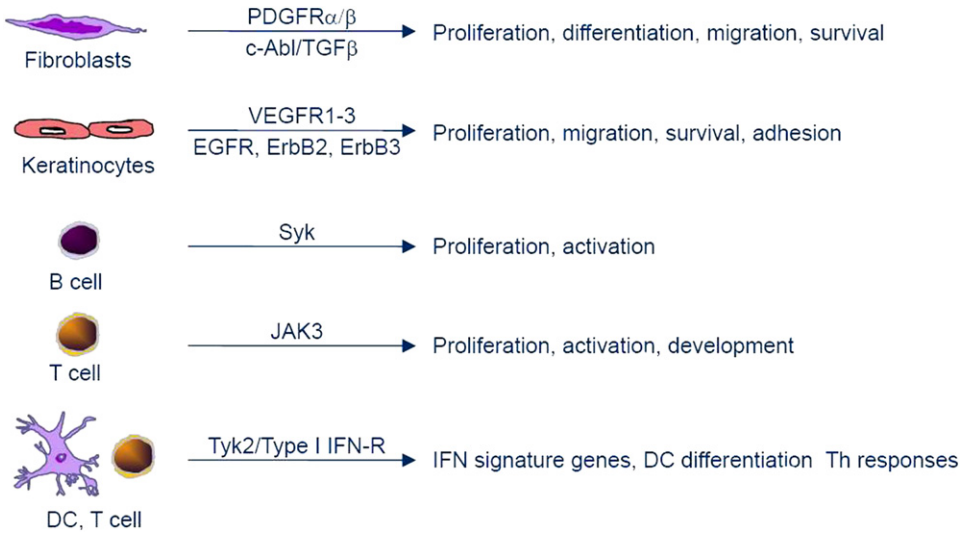

Fig 3. Cell types and responses mediated by exemplary kinases that may contribute to pathogenesis of inflammatory dermatologic disorders. Fibroblast proliferation, differentiation, migration, and survival are promoted by signaling through platelet-derived growth factor receptors (*PDGFR*), and through 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,

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.

treatment with TK 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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REFERENCES

1. Schermuly RT, Dony E, Ghofrani HA, Pullamsetti S, Savai R, Roth M, et al. Reversal of experimental pulmonary hypertension by PDGF inhibition. J Clin Invest 2005;115:2811-21.
2. Ghofrani HA, Seeger W, Grimminger F. Imatinib for the treatment of pulmonary arterial hypertension. N Engl J Med 2005;353:1412-3.
3. Wong BR, Grossbard EB, Payan DG, Masuda ES. Targeting Syk as a treatment for allergic and autoimmune disorders. Expert Opin Investig Drugs 2004;13:743-62.
4. Louvet C, Szot GL, Lang J, Lee MR, Martinier N, Bollag G, et al. Tyrosine kinase inhibitors reverse type 1 diabetes in nonobese diabetic mice. Proc Natl Acad Sci U S A 2008;105: 18895-900.
5. D'Aura Swanson C, Paniagua RT, Lindstrom TM, Robinson WH. Tyrosine kinases as targets for the treatment of rheumatoid arthritis. Nat Rev Rheumatol 2009;5:317-24.
6. Eklund KK, Lindstedt K, Sandler C, Kovanen PT, Laasonen L, Juurikivi A, et al. Maintained efficacy of the tyrosine kinase inhibitor imatinib mesylate in a patient with rheumatoid arthritis. J Clin Rheumatol 2008;14:294-6.
7. Paniagua RT, Sharpe O, Ho PP, Chan SM, Chang A, Higgins JP, et al. Selective tyrosine kinase inhibition by imatinib mesylate for the treatment of autoimmune arthritis. J Clin Invest 2006; 116:2633-42.
8. Manning G, Whyte DB, Martinez R, Hunter T, Sudarsanam S. The protein kinase complement of the human genome. Science 2002;298:1912-34.
9. Robinson DR, Wu YM, Lin SF. The protein tyrosine kinase family of the human genome. Oncogene 2000;19:5548-57.
10. Schlessinger J. Cell signaling by receptor tyrosine kinases. Cell 2000;103:211-25.
11. Hubbard SR, Till JH. Protein tyrosine kinase structure and function. Annu Rev Biochem 2000;69:373-98.
12. Krause DS, Van Etten RA. Tyrosine kinases as targets for cancer therapy. N Engl J Med 2005;353:172-87.
13. Ghoreschi K, Laurence A, O'Shea JJ. Selectivity and therapeutic inhibition of kinases: to be or not to be? Nat Immunol 2009;10:356-60.
14. Johnson LN. Protein kinase inhibitors: contributions from structure to clinical compounds. Q Rev Biophys 2009;42: 1-40.
15. Schindler T, Bornmann W, Pellicena P, Miller WT, Clarkson B, Kuriyan J. Structural mechanism for STI-571 inhibition of Abelson tyrosine kinase. Science 2000;289:1938-42.
16. Gabrielli A, Avvedimento EV, Krieg T. Scleroderma. N Engl J Med 2009;360:1989-2003.
17. Mayes MD, Lacey JV Jr, Beebe-Dimmer J, Gillespie BW, Cooper B, Laing TJ, et al. Prevalence, incidence, survival, and disease characteristics of systemic sclerosis in a large US population. Arthritis Rheum 2003;48:2246-55.
18. Dibb NJ, Dilworth SM, Mol CD. Switching on kinases: oncogenic activation of BRAF and the PDGFR family. Nat Rev Cancer 2004;4:718-27.
19. Andrae J, Gallini R, Betsholtz C. Role of platelet-derived growth factors in physiology and medicine. Genes Dev 2008; 22:1276-312.
20. Gay S, Jones RE Jr, Huang GQ, Gay RE. Immunohistologic demonstration of platelet-derived growth factor (PDGF) and sis-oncogene expression in scleroderma. J Invest Dermatol 1989;92:301-3.
21. Ludwicka A, Ohba T, Trojanowska M, Yamakage A, Strange C, Smith EA, et al. Elevated levels of platelet derived growth factor and transforming growth factor-beta 1 in bronchoalveolar lavage fluid from patients with scleroderma. J Rheumatol 1995;22:1876-83.
22. Pandolfi A, Florita M, Altomare G, Pigatto P, Donati MB, Poggi A. Increased plasma levels of platelet-derived growth factor activity in patients with progressive systemic sclerosis. Proc Soc Exp Biol Med 1989;191:1-4.
23. Klareskog L, Gustafsson R, Scheynius A, Hallgren R. Increased expression of platelet-derived growth factor type B receptors in the skin of patients with systemic sclerosis. Arthritis Rheum 1990;33:1534-41.
24. Zheng XY, Zhang JZ, Tu P, Ma SQ. Expression of platelet-derived growth factor B-chain and platelet-derived growth factor beta-receptor in fibroblasts of scleroderma. J Dermatol Sci 1998;18:90-7.
25. Yamakage A, Kikuchi K, Smith EA, LeRoy EC, Trojanowska M. Selective upregulation of platelet-derived growth factor alpha receptors by transforming growth factor beta in scleroderma fibroblasts. J Exp Med 1992;175:1227-34.
26. Soria A, Cario-Andre M, Lepreux S, Rezvani HR, Pasquet JM, Pain C, et al. The effect of imatinib (Glivec) on scleroderma and normal dermal fibroblasts: a preclinical study. Dermatology 2008;216:109-17.
27. Baroni SS, Santillo M, Bevilacqua F, Luchetti M, Spadoni T, Mancini M, et al. Stimulatory autoantibodies to the PDGF receptor in systemic sclerosis. N Engl J Med 2006;354: 2667-76.
28. Loizos N, Lariccia L, Weiner J, Griffith H, Boin F, Hummers L, et al. Lack of detection of agonist activity by antibodies to platelet-derived growth factor receptor alpha in a subset of normal and systemic sclerosis patient sera. Arthritis Rheum 2009;60:1145-51.
29. Balada E, Simeon-Aznar CP, Ordi-Ros J, Rosa-Leyva M, Selva-O'Callaghan A, Pardos-Gea J, et al. Anti-PDGFR-alpha antibodies measured by non-bioactivity assays are not specific for systemic sclerosis. Ann Rheum Dis 2008;67:1027-9.
30. Classen JF, Henrohn D, Rorsman F, Lennartsson J, Lauwerys BR, Wikstrom G, et al. Lack of evidence of stimulatory autoantibodies to platelet-derived growth factor receptor in patients with systemic sclerosis. Arthritis Rheum 2009;60: 1137-44.
31. Varga J, Pasche B. Transforming growth factor beta as a therapeutic target in systemic sclerosis. Nat Rev Rheumatol 2009;5:200-6.
32. Sonnylal S, Denton CP, Zheng B, Keene DR, He R, Adams HP, et al. Postnatal induction of transforming growth factor beta signaling in fibroblasts of mice recapitulates clinical, histologic, and biochemical features of scleroderma. Arthritis Rheum 2007;56:334-44.
33. Derynck R, Zhang YE. Smad-dependent and Smad-independent pathways in TGF-beta family signaling. Nature 2003;425:577-84.
34. Daniels CE, Wilkes MC, Edens M, Kottom TJ, Murphy SJ, Limper AH, et al. Imatinib mesylate inhibits the profibrogenic activity of TGF-beta and prevents bleomycin-mediated lung fibrosis. J Clin Invest 2004;114:1308-16.

35. Wang S, Wilkes MC, Leof EB, Hirschberg R. Imatinib mesylate blocks a non-Smad TGF-beta pathway and reduces renal fibrogenesis in vivo. FASEB J 2005;19:1-11.
36. Boureux A, Furstoss O, Simon V, Roche S. Abl tyrosine kinase regulates a Rac/JNK and a Rac/Nox pathway for DNA synthesis and Myc expression induced by growth factors. J Cell Sci 2005;118:3717-26.
37. Plattner R, Koleske AJ, Kazlauskas A, Pendergast AM. Bidirectional signaling links the Abelson kinases to the platelet-derived growth factor receptor. Mol Cell Biol 2004;24: 2573-83.
38. Sini P, Cannas A, Koleske AJ, Di Fiore PP, Scita G. Abl-dependent tyrosine phosphorylation of Sos-1 mediates growth-factor-induced Rac activation. Nat Cell Biol 2004;6: 268-74.
39. Chung L, Fiorentino DF, Benbarak MJ, Adler AS, Mariano MM, Paniagua RT, et al. Molecular framework for response to imatinib mesylate in systemic sclerosis. Arthritis Rheum 2009; 60:584-91.
40. Yoshiji H, Noguchi R, Kuriyama S, Ikenaka Y, Yoshii J, Yanase K, et al. Imatinib mesylate (STI-571) attenuates liver fibrosis development in rats. Am J Physiol Gastrointest Liver Physiol 2005;288:G907-13.
41. Akhmetshina A, Venalis P, Dees C, Busch N, Zwerina J, Schett G, et al. Treatment with imatinib prevents fibrosis in different preclinical models of systemic sclerosis and induces regression of established fibrosis. Arthritis Rheum 2009;60:219-24.
42. Distler JH, Jungel A, Huber LC, Schulze-Horsel U, Zwerina J, Gay RE, et al. Imatinib mesylate reduces production of extracellular matrix and prevents development of experimental dermal fibrosis. Arthritis Rheum 2007;56:311-22.
43. Akhmetshina A, Dees C, Pileckyte M, Maurer B, Axmann R, Jungel A, et al. Dual inhibition of c-abl and PDGF receptor signaling by dasatinib and nilotinib for the treatment of dermal fibrosis. FASEB J 2008;22:2214-22.
44. van Daele PL, Dik WA, Thio HB, van Hal PT, van Laar JA, Hooijkaas H, et al. Is imatinib mesylate a promising drug in systemic sclerosis? Arthritis Rheum 2008;58:2549-52.
45. Sfikakis PP, Gorgoulis VG, Katsiari CG, Evangelou K, Kostopoulos C, Black CM. Imatinib for the treatment of refractory, diffuse systemic sclerosis. Rheumatology (Oxford) 2008;47: 735-7.
46. ten Freyhaus H, Dumitrescu D, Bovenschulte H, Erdmann E, Rosenkranz S. Significant improvement of right ventricular function by imatinib mesylate in scleroderma-associated pulmonary arterial hypertension. Clin Res Cardiol 2009;98: 265-7.
47. Sabnani I, Zucker MJ, Rosenstein ED, Baran DA, Arroyo LH, Tsang P, et al. A novel therapeutic approach to the treatment of scleroderma-associated pulmonary complications: safety and efficacy of combination therapy with imatinib and cyclophosphamide. Rheumatology (Oxford) 2009;48:49-52.
48. Pope J, McBain DL, Petrlich L, Watson S, Bender L, Deleon F, et al. A proof of concept trial of Gleevec (imatinib) in active diffuse scleroderma (DSSc) [abstract]. American College of Rheumatology (ACR)/Association of Rheumatology Health Professionals (ARHP) Scientific Meeting 2009 [database online]. Philadelphia, PA; Accessed October 22, 2009.
49. Gordon J, Mersten J, Lyman S, Kloiber SA, Wildman HF, Crow MK, et al. Imatinib mesylate (Gleevec) in the treatment of systemic sclerosis: interim results of a phase IIa, one year, open label clinical trial [abstract]. American College of Rheumatology (ACR)/Association of Rheumatology Health Professionals (ARHP) Scientific Meeting 2009 [database online]. Philadelphia, PA; Accessed October 22, 2009.
50. Welniak LA, Blazar BR, Murphy WJ. Immunobiology of allogeneic hematopoietic stem cell transplantation. Annu Rev Immunol 2007;25:139-70.
51. Copelan EA. Hematopoietic stem-cell transplantation. N Engl J Med 2006;354:1813-26.
52. Ferrara JL, Levine JE, Reddy P, Holler E. Graft-versus-host disease. Lancet 2009;373:1550-61.
53. Small TN, Robinson WH, Miklos DB. B cells and transplantation: an educational resource. Biol Blood Marrow Transplant 2008;15:104-13.
54. Schaffer JV, McNiff JM, Seropian S, Cooper DL, Bolognia JL. Lichen sclerosus and eosinophilic fasciitis as manifestations of chronic graft-versus-host disease: expanding the sclerodermoid spectrum. J Am Acad Dermatol 2005;53: 591-601.
55. Creamer D, Martyn-Simmons CL, Osborne G, Kenyon M, Salisbury JR, Devereux S, et al. Eczematoid graft-vs-host disease: a novel form of chronic cutaneous graft-vs-host disease and its response to psoralen UV-A therapy. Arch Dermatol 2007;143:1157-62.
56. Svegliati S, Olivieri A, Campelli N, Luchetti M, Poloni A, Trappolini S, et al. Stimulatory autoantibodies to PDGF receptor in patients with extensive chronic graft-versus-host disease. Blood 2007;110:237-41.
57. Olivieri O, Locatelli F, Zecca M, Cimminiello M, Raimondi R, Gini G, et al. Imatinib for refractory chronic graft-versus-host disease with fibrotic features. Blood 2009;119:709-18.
58. Cowper SE, Robin HS, Steinberg SM, Su LD, Gupta S, LeBoit PE. Scleromyxoedema-like cutaneous diseases in renal-dialysis patients. Lancet 2000;356:1000-1.
59. Kribben A, Witzke O, Hillen U, Barkhausen J, Daul AE, Erbel R. Nephrogenic systemic fibrosis: pathogenesis, diagnosis, and therapy. J Am Coll Cardiol 2009;53:1621-8.
60. Bangsgaard N, Marckmann P, Rossen K, Skov L. Nephrogenic systemic fibrosis: late skin manifestations. Arch Dermatol 2009;145:183-7.
61. Daram SR, Cortese CM, Bastani B. Nephrogenic fibrosing dermopathy/nephrogenic systemic fibrosis: report of a new case with literature review. Am J Kidney Dis 2005;46:754-9.
62. Galan A, Cowper SE, Bucala R. Nephrogenic systemic fibrosis (nephrogenic fibrosing dermopathy). Curr Opin Rheumatol 2006;18:614-7.
63. Quan TE, Cowper S, Wu SP, Bockenstedt LK, Bucala R. Circulating fibrocytes: collagen-secreting cells of the peripheral blood. Int J Biochem Cell Biol 2004;36:598-606.
64. Jimenez SA, Artlett CM, Sandorfi N, Derk C, Latinis K, Sawaya H, et al. Dialysis-associated systemic fibrosis (nephrogenic fibrosing dermopathy): study of inflammatory cells and transforming growth factor beta1 expression in affected skin. Arthritis Rheum 2004;50:2660-6.
65. Kay J, High WA. Imatinib mesylate treatment of nephrogenic systemic fibrosis. Arthritis Rheum 2008;58:2543-8.
66. Chandran S, Petersen J, Jacobs C, Fiorentino D, Doeden K, Lafayette RA. Imatinib in the treatment of nephrogenic systemic fibrosis. Am J Kidney Dis 2009;53:129-32.
67. Kay J, Sullivan ME, Patel TV. Efficacy and safety of oral imatinib mesylate in patients with nephrogenic systemic fibrosis [abstract]. American College of Rheumatology (ACR)/Association of Rheumatology Health Professionals (ARHP) Scientific Meeting 2009 [database online]. Philadelphia, PA; Accessed October 22, 2009.
68. Schon MP, Boehncke WH. Psoriasis. N Engl J Med 2005;352: 1899-912.
69. Bowcock AM, Krueger JG. Getting under the skin: the immunogenetics of psoriasis. Nat Rev Immunol 2005;5:699-711.

70. Zenz R, Eferl R, Kenner L, Florin L, Hummerich L, Mehic D, et al. Psoriasis-like skin disease and arthritis caused by inducible epidermal deletion of Jun proteins. Nature 2005;437:369-75.
71. Boniface K, Diveu C, Morel F, Pedretti N, Froger J, Ravon E, et al. Oncostatin M secreted by skin infiltrating T lymphocytes is a potent keratinocyte activator involved in skin inflammation. J Immunol 2007;178:4615-22.
72. Halin C, Fahrngruber H, Meingassner JG, Bold G, Littlewood-Evans A, Stuetz A, et al. Inhibition of chronic and acute skin inflammation by treatment with a vascular endothelial growth factor receptor tyrosine kinase inhibitor. Am J Pathol 2008;173:265-77.
73. Kunstfeld R, Hirakawa S, Hong YK, Schacht V, Lange-Asschenfeldt B, Velasco P, et al. Induction of cutaneous delayed-type hypersensitivity reactions in VEGF-A transgenic mice results in chronic skin inflammation associated with persistent lymphatic hyperplasia. Blood 2004;104:1048-57.
74. Xia YP, Li B, Hylton D, Detmar M, Yancopoulos GD, Rudge JS. Transgenic delivery of VEGF to mouse skin leads to an inflammatory condition resembling human psoriasis. Blood 2003;102:161-8.
75. Roy H, Bhardwaj S, Yla-Herttuala S. Biology of vascular endothelial growth factors. FEBS Lett 2006;580:2879-87.
76. Wilgus TA, Matthies AM, Radek KA, Dovi JV, Burns AL, Shankar R, et al. Novel function for vascular endothelial growth factor receptor-1 on epidermal keratinocytes. Am J Pathol 2005;167:1257-66.
77. Detmar M, Brown LF, Claffey KP, Yeo KT, Kocher O, Jackman RW, et al. Overexpression of vascular permeability factor/vascular endothelial growth factor and its receptors in psoriasis. J Exp Med 1994;180:1141-6.
78. Man XY, Yang XH, Cai SQ, Bu ZY, Zheng M. Overexpression of vascular endothelial growth factor (VEGF) receptors on keratinocytes in psoriasis: regulated by calcium independent of VEGF. J Cell Mol Med 2008;12:649-60.
79. Zhang Y, Matsuo H, Morita E. Vascular endothelial growth factor 121 is the predominant isoform in psoriatic scales. Exp Dermatol 2005;14:758-64.
80. Bhushan M, McLaughlin B, Weiss JB, Griffiths CE. Levels of endothelial cell stimulating angiogenesis factor and vascular endothelial growth factor are elevated in psoriasis. Br J Dermatol 1999;141:1054-60.
81. Pastore S, Mascia F, Mariani V, Girolomoni G. The epidermal growth factor receptor system in skin repair and inflammation. J Invest Dermatol 2008;128:1365-74.
82. Schneider MR, Antsiferova M, Feldmeyer L, Dahlhoff M, Bugnon P, Hasse S, et al. Betacellulin regulates hair follicle development and hair cycle induction and enhances angiogenesis in wounded skin. J Invest Dermatol 2008;128:1256-65.
83. Gottlieb AB, Chang CK, Posnett DN, Fanelli B, Tam JP. Detection of transforming growth factor alpha in normal, malignant, and hyperproliferative human keratinocytes. J Exp Med 1988;167:670-5.
84. Elder JT, Fisher GJ, Lindquist PB, Bennett GL, Pittelkow MR, Coffey RJ Jr, et al. Overexpression of transforming growth factor alpha in psoriatic epidermis. Science 1989;243:811-4.
85. Cook PW, Pittelkow MR, Keeble WW, Graves-Deal R, Coffey RJ Jr, Shipley GD. Amphiregulin messenger RNA is elevated in psoriatic epidermis and gastrointestinal carcinomas. Cancer Res 1992;52:3224-7.
86. Piepkorn M. Overexpression of amphiregulin, a major autocrine growth factor for cultured human keratinocytes, in hyperproliferative skin diseases. Am J Dermatopathol 1996;18:165-71.
87. Zheng Y, Peng Z, Wang Y, Tan S, Xi Y, Wang G. Alteration and significance of heparin-binding epidermal-growth-factor-like growth factor in psoriatic epidermis. Dermatology 2003;207:22-7.
88. Shirakata Y, Kishimoto J, Tokumaru S, Yamasaki K, Hanakawa Y, Tohyama M, et al. Epiregulin, a member of the EGF family, is over-expressed in psoriatic epidermis. J Dermatol Sci 2007;45:69-72.
89. Cook PW, Piepkorn M, Clegg CH, Plowman GD, DeMay JM, Brown JR, et al. Transgenic expression of the human amphiregulin gene induces a psoriasis-like phenotype. J Clin Invest 1997;100:2286-94.
90. Varani J, Kang S, Stoll S, Elder JT. Human psoriatic skin in organ culture: comparison with normal skin exposed to exogenous growth factors and effects of an antibody to the EGF receptor. Pathobiology 1998;66:253-9.
91. Varani J, Lateef H, Fay K, Elder JT. Antagonism of epidermal growth factor receptor tyrosine kinase ameliorates the psoriatic phenotype in organ-cultured skin. Skin Pharmacol Physiol 2005;18:123-31.
92. Di Cesare A, Di Meglio P, Nestle FO. The IL-23/Th17 axis in the immunopathogenesis of psoriasis. J Invest Dermatol 2009;129:1339-50.
93. Pesu M, Laurence A, Kishore N, Zwillich S, Chan G, O'Shea JJ. Therapeutic targeting of janus kinases. Immunol Rev 2008;223:132-42.
94. Chang BY, Zhao F, He X, Ren H, Braselmann S, Taylor V, et al. JAK3 inhibition significantly attenuates psoriasiform skin inflammation in CD18 mutant PL/J mice. J Immunol 2009;183:2183-92.
95. Changelian PS, Flanagan ME, Ball DJ, Kent CR, Magnuson KS, Martin WH, et al. Prevention of organ allograft rejection by a specific Janus kinase 3 inhibitor. Science 2003;302:875-8.
96. Boy MG, Wang C, Wilkinson BE, Chow VF, Clucas AT, Krueger JG, et al. Double-blind, placebo-controlled, dose-escalation study to evaluate the pharmacologic effect of CP-690,550 in patients with psoriasis. J Invest Dermatol 2009;129:2299-302.
97. Keshtgarpour M, Dudek AZ. SU-011248, a vascular endothelial growth factor receptor-tyrosine kinase inhibitor, controls chronic psoriasis. Transl Res 2007;149:103-6.
98. Miyagawa S, Fujimoto H, Ko S, Hirota S, Kitamura Y. Improvement of psoriasis during imatinib therapy in a patient with a metastatic gastrointestinal stromal tumor. Br J Dermatol 2002;147:406-7.
99. Woo SM, Huh CH, Park KC, Youn SW. Exacerbation of psoriasis in a chronic myelogenous leukemia patient treated with imatinib. J Dermatol 2007;34:724-6.
100. Cheng H, Geist DE, Piperdi M, Virk R, Piperdi B. Management of imatinib-related exacerbation of psoriasis in a patient with a gastrointestinal stromal tumor. Australas J Dermatol 2009;50:41-3.
101. Dickens E, Lewis F, Bienz N. Imatinib: a designer drug, another cutaneous complication. Clin Exp Dermatol 2009;34:603-4.
102. Lacouture ME. Mechanisms of cutaneous toxicities to EGFR inhibitors. Nat Rev Cancer 2006;6:803-12.
103. Wierzbicka E, Tourani JM, Guillet G. Improvement of psoriasis and cutaneous side-effects during tyrosine kinase inhibitor therapy for renal metastatic adenocarcinoma: a role for epidermal growth factor receptor (EGFR) inhibitors in psoriasis? Br J Dermatol 2006;155:213-4.
104. Neyns B, Meert V, Vandenbroucke F. Cetuximab treatment in a patient with metastatic colorectal cancer and psoriasis. Curr Oncol 2008;15:196-7.
105. Herbst RS, Fukuoka M, Baselga J. Gefitinib—a novel targeted approach to treating cancer. Nat Rev Cancer 2004;4:956-65.

106. Zorzou MP, Stratigos A, Efstathiou E, Bamias A. Exacerbation of psoriasis after treatment with an EGFR tyrosine kinase inhibitor. Acta Derm Venereol 2004;84:308-9.
107. Stanley JR, Amagai M. Pemphigus, bullous impetigo, and the staphylococcal scalded-skin syndrome. N Engl J Med 2006; 355:1800-10.
108. Nguyen VT, Ndoye A, Shultz LD, Pittelkow MR, Grando SA. Antibodies against keratinocyte antigens other than desmogleins 1 and 3 can induce pemphigus vulgaris-like lesions. J Clin Invest 2000;106:1467-79.
109. Anhalt GJ, Labib RS, Voorhees JJ, Beals TF, Diaz LA. Induction of pemphigus in neonatal mice by passive transfer of IgG from patients with the disease. N Engl J Med 1982;306:1189-96.
110. Frusic-Zlotkin M, Raichenberg D, Wang X, David M, Michel B, Milner Y. Apoptotic mechanism in pemphigus autoimmunoglobulins-induced acantholysis—possible involvement of the EGF receptor. Autoimmunity 2006;39:563-75.
111. Pretel M, Espana A, Marquina M, Pelacho B, Lopez-Picazo JM, Lopez-Zabalza MJ. An imbalance in Akt/mTOR is involved in the apoptotic and acantholytic processes in a mouse model of pemphigus vulgaris. Exp Dermatol 2009;18:771-80.
112. Chernyavsky AI, Arredondo J, Kitajima Y, Sato-Nagai M, Grando SA. Desmoglein versus non-desmoglein signaling in pemphigus acantholysis: characterization of novel signaling pathways downstream of pemphigus vulgaris antigens. J Biol Chem 2007;282:13804-12.
113. Tatton L, Morley GM, Chopra R, Khwaja A. The Src-selective kinase inhibitor PP1 also inhibits Kit and Bcr-Abl tyrosine kinases. J Biol Chem 2003;278:4847-53.
114. Akiyama T, Ishida J, Nakagawa S, Ogawara H, Watanabe S, Itoh N, et al. Genistein, a specific inhibitor of tyrosine-specific protein kinases. J Biol Chem 1987;262:5592-5.
115. Sanchez-Carpintero I, Espana A, Pelacho B, Lopez Moratalla N, Rubenstein DS, Diaz LA, et al. In vivo blockade of pemphigus vulgaris acantholysis by inhibition of intracellular signal transduction cascades. Br J Dermatol 2004;151:565-70.
116. Marquina M, Espana A, Fernandez-Galar M, Lopez-Zabalza MJ. The role of nitric oxide synthases in pemphigus vulgaris in a mouse model. Br J Dermatol 2008;159:68-76.
117. Delva E, Jennings JM, Calkins CC, Kottke MD, Faundez V, Kowalczyk AP. Pemphigus vulgaris IgG-induced desmoglein-3 endocytosis and desmosomal disassembly are mediated by a clathrin- and dynamin-independent mechanism. J Biol Chem 2008;283:18303-13.
118. Berkowitz P, Hu P, Warren S, Liu Z, Diaz LA, Rubenstein DS. p38MAPK inhibition prevents disease in pemphigus vulgaris mice. Proc Natl Acad Sci U S A 2006;103:12855-60.
119. Joly P, Roujeau JC, Benichou J, Picard C, Dreno B, Delaporte E, et al. A comparison of oral and topical corticosteroids in patients with bullous pemphigoid. N Engl J Med 2002;346:321-7.
120. Ameglio F, D'Auria L, Cordiali-Fei P, Mussi A, Valenzano L, D'Agosto G, et al. Bullous pemphigoid and pemphigus vulgaris: correlated behavior of serum VEGF, sE-selectin and TNF-alpha levels. J Biol Regul Homeost Agents 1997;11:148-53.
121. Brown LF, Harrist TJ, Yeo KT, Stahle-Backdahl M, Jackman RW, Berse B, et al. Increased expression of vascular permeability factor (vascular endothelial growth factor) in bullous pemphigoid, dermatitis herpetiformis, and erythema multiforme. J Invest Dermatol 1995;104:744-9.
122. Hofmann SC, Technau K, Muller AM, Lubbert M, Bruckner-Tuderman L. Bullous pemphigoid associated with hypereosinophilic syndrome: simultaneous response to imatinib. J Am Acad Dermatol 2007;56(Suppl):S68-72.
123. Krathen MS, Fiorentino D, Werth VP. Dermatomyositis. Curr Dir Autoimmun 2008;10:313-32.
124. Rothfield N, Sontheimer RD, Bernstein M. Lupus erythematosus: systemic and cutaneous manifestations. Clin Dermatol 2006;24:348-62.
125. Greenberg SA, Pinkus JL, Pinkus GS, Burleson T, Sanoudou D, Tawil R, et al. Interferon-alpha/beta-mediated innate immune mechanisms in dermatomyositis. Ann Neurol 2005;57:664-78.
126. Wenzel J, Worenkamper E, Freutel S, Henze S, Haller O, Bieber T, et al. Enhanced type I interferon signaling promotes Th1-biased inflammation in cutaneous lupus erythematosus. J Pathol 2005;205:435-42.
127. Walsh RJ, Kong SW, Yao Y, Jallal B, Kiener PA, Pinkus JL, et al. Type I interferon-inducible gene expression in blood is present and reflects disease activity in dermatomyositis and polymyositis. Arthritis Rheum 2007;56:3784-92.
128. Wenzel J, Schmidt R, Proelss J, Zahn S, Bieber T, Tuting T. Type I interferon-associated skin recruitment of $CXCR3^+$ lymphocytes in dermatomyositis. Clin Exp Dermatol 2006; 31:576-82.
129. Ronnblom L, Alm GV, Eloranta ML. Type I interferon and lupus. Curr Opin Rheumatol 2009;21:471-7.
130. Ghoreschi K, Laurence A, O'Shea JJ. Janus kinases in immune cell signaling. Immunol Rev 2009;228:273-87.
131. Shimoda K, Kato K, Aoki K, Matsuda T, Miyamoto A, Shibamori M, et al. Tyk2 plays a restricted role in IFN alpha signaling, although it is required for IL-12-mediated T cell function. Immunity 2000;13:561-71.
132. Ortmann R, Smeltz R, Yap G, Sher A, Shevach EM. A heritable defect in IL-12 signaling in B10.Q/J mice. I: in vitro analysis. J Immunol 2001;166:5712-9.
133. Spach KM, Noubade R, McElvany B, Hickey WF, Blankenhorn EP, Teuscher C. A single nucleotide polymorphism in Tyk2 controls susceptibility to experimental allergic encephalomyelitis. J Immunol 2009;182:7776-83.
134. Hellquist A, Jarvinen TM, Koskenmies S, Zucchelli M, Orsmark-Pietras C, Berglind L, et al. Evidence for genetic association and interaction between the TYK2 and IRF5 genes in systemic lupus erythematosus. J Rheumatol 2009;36:1631-8.
135. Jarvinen TM, Hellquist A, Koskenmies S, Einarsdottir E, Koskinen LL, Jeskanen L, et al. Tyrosine kinase 2 and interferon regulatory factor 5 polymorphisms are associated with discoid and subacute cutaneous lupus erythematosus. Exp Dermatol 2010;19:123-31.
136. Krishnan S, Juang YT, Chowdhury B, Magilavy A, Fisher CU, Nguyen H, et al. Differential expression and molecular associations of Syk in systemic lupus erythematosus T cells. J Immunol 2008;181:8145-52.
137. Bahjat FR, Pine PR, Reitsma A, Cassafer G, Baluom M, Grillo S, et al. An orally bioavailable spleen tyrosine kinase inhibitor delays disease progression and prolongs survival in murine lupus. Arthritis Rheum 2008;58:1433-44.
138. Zoja C, Corna D, Rottoli D, Zanchi C, Abbate M, Remuzzi G. Imatinib ameliorates renal disease and survival in murine lupus autoimmune disease. Kidney Int 2006;70:97-103.
139. Sadanaga A, Nakashima H, Masutani K, Miyake K, Shimizu S, Igawa T, et al. Amelioration of autoimmune nephritis by imatinib in MRL/lpr mice. Arthritis Rheum 2005;52: 3987-96.
140. Apostolidis L, Kahlert C, Siegmund A, Thom R, Horstmann S, Jager D, et al. Remission of paraneoplastic dermatomyositis associated with hepatocellular carcinoma under prednisolone and azathiopin, and concomitant sorafenib. Onkologie 2009;32:50-3.
141. Bergsland EK. When does the presence of the target predict response to the targeted agent? J Clin Oncol 2006; 24:213-6.

142. Stommel JM, Kimmelman AC, Ying H, Nabioullin R, Ponugoti AH, Wiedemeyer R, et al. Coactivation of receptor tyrosine kinases affects the response of tumor cells to targeted therapies. Science 2007;318:287-90.
143. Nissen LJ, Cao R, Hedlund EM, Wang Z, Zhao X, Wetterskog D, et al. Angiogenic factors FGF2 and PDGF-BB synergistically promote murine tumor neovascularization and metastasis. J Clin Invest 2007;117:2766-77.
144. Planque S, Zhou YX, Nishiyama Y, Sinha M, O'Connor-Mccourt M, Arnett FC, et al. Autoantibodies to the epidermal growth factor receptor in systemic sclerosis, lupus, and autoimmune mice. FASEB J 2003;17:136-43.
145. Amagai M, Ozawa S, Ueda M, Nishikawa T, Abe O, Shimizu N. Distribution of EGF receptor expressing and DNA replicating epidermal cells in psoriasis vulgaris and Bowen's disease. Br J Dermatol 1988;119:661-8.
146. Nanney LB, Stoscheck CM, Magid M, King LE Jr. Altered [125I]epidermal growth factor binding and receptor distribution in psoriasis. J Invest Dermatol 1986;86:260-5.
147. Higashiyama M, Hashimoto K, Matsumoto K, Yoshikawa K. Differential expression of transforming growth factor-alpha (TGF-alpha) and EGF receptor in transitional area of psoriatic epidermis. J Dermatol Sci 1994;7:45-53.
148. Ayli EE, Li W, Brown TT, Witkiewicz A, Elenitsas R, Seykora JT. Activation of Src-family tyrosine kinases in hyperproliferative epidermal disorders. J Cutan Pathol 2008;35:273-7.
149. Pulitzer M, Li W, Hanson M, Singh F, Elenitsas R, Gelfand JM, et al. Srcasm overexpression in psoriasis-insights into pathogenesis. J Cutan Pathol 2007;34:160-5.
150. Cunninghame Graham DS, Akil M, Vyse TJ. Association of polymorphisms across the tyrosine kinase gene, TYK2 in UK SLE families. Rheumatology (Oxford) 2007;46:927-30.
151. Sigurdsson S, Nordmark G, Goring HH, Lindroos K, Wiman AC, Sturfelt G, et al. Polymorphisms in the tyrosine kinase 2 and interferon regulatory factor 5 genes are associated with systemic lupus erythematosus. Am J Hum Genet 2005;76:528-37.
152. Blake S, Lyons A, Hughes T. Nilotinib inhibits the Src-family kinase Lck and T-cell function in vivo. J Cell Mol Med 2008;13:599-601.
153. Hantschel O, Rix U, Schmidt U, Burckstummer T, Kneidinger M, Schutze G, et al. The Btk tyrosine kinase is a major target of the Bcr-Abl inhibitor dasatinib. Proc Natl Acad Sci U S A 2007;104:13283-8.
154. Blake S, Hughes T, Mayrhofer G, Lyons A. The Src/Abl inhibitor dasatinib (BMS-354825) inhibits function of normal human T-lymphocytes in vitro. Clin Immunol 2008;127:330-9.
155. Faivre S, Demetri G, Sargent W, Raymond E. Molecular basis for sunitinib efficacy and future clinical development. Nat Rev Drug Discov 2007;6:734-45.
156. Cameron D, Stein S. Drug insight: intracellular inhibitors of HER2—clinical development of lapatinib in breast cancer. Nat Clin Pract Oncol 2008;5:512-20.
157. Wilhelm S, Adnane L, Newell P, Villanueva A, Llovet J, Lynch M. Preclinical overview of sorafenib, a multikinase inhibitor that targets both Raf and VEGF and PDGF receptor tyrosine kinase signaling. Mol Cancer Ther 2008;7:3129-40.