

# The Role of Tyrosine Kinases in the Pathogenesis and Treatment of Lung Disease

Jonathan Lam and Stewart J. Levine  
*Laboratory of Asthma and Lung Inflammation,  
Cardiovascular and Pulmonary Branch,  
National Heart, Lung, and Blood Institute,  
National Institutes of Health, Bethesda,  
USA*

## 1. Introduction

Tyrosine kinases (TKs) are key regulators of signal transduction pathways that modulate essential biological processes, such as cellular differentiation, metabolism and proliferation, as well as, protein synthesis, cell cycle progression and apoptosis (Schlessinger, 2000). These enzymes modify protein function by transferring phosphate groups from adenosine triphosphate (ATP) or guanosine triphosphate (GTP) to free hydroxyl groups on tyrosine residues. Under physiological conditions, kinase activity is regulated by protein phosphatases that dephosphorylate and inactivate signaling pathways. However, these signaling pathways can become dysregulated in lung diseases, such as non-small cell lung cancer (NSCLC), asthma, chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF). This chapter will provide an overview of the pathways mediated by receptor and non-receptor tyrosine kinases, as well as their role in the pathogenesis of lung disease. Furthermore, the emerging role of TK inhibitors (TKIs) for the treatment of NSCLC, asthma, COPD and IPF will be discussed.

### 1.1 Receptor tyrosine kinases and non-receptor tyrosine kinases

Receptor tyrosine kinases (RTKs) play essential roles in growth factor and cytokine receptor signaling. Over 58 RTKs have been identified, which include epidermal growth factor receptors (EGFR), ephrin receptors, fibroblast growth factor receptors (FGFR), platelet derived growth factor receptors (PDGFR), RAR-related orphan receptors (ROR), vascular endothelial growth factor receptors (VEGFR), the hepatocyte growth factor receptor (MET) and the insulin receptor (Hubbard & Miller, 2007; Robinson, Wu, & Lin, 2000). RTKs are comprised of an extracellular ligand-binding domain, a transmembrane domain and an intracellular kinase domain (Robinson et al., 2000). Upon ligand binding, RTKs undergo conformational changes that induce homo- or hetero- dimerization and autophosphorylation of intracellular kinase domains at specific tyrosine residues. This activates downstream signaling pathways that recruit non-receptor tyrosine kinases (non-RTKs) and activate serine/threonine kinase signaling pathways.

The EGFR belongs to a family of RTKs that includes EGFR, ERBB2 (HER2), ERBB3 (HER3) and ERBB4 (HER4), which play key roles in cellular growth, proliferation and differentiation. All EGFR family members have intrinsic TK activity, except ERBB3 (Sibilia, Kroismayr, Lichtenberger, Natarajan, Hecking, & Holcman, 2007). EGF receptors exist as inactive monomers that undergo conformational changes upon binding of EGF or transforming growth factor- $\alpha$  (TGF- $\alpha$ ), which facilitates receptor homodimerization or heterodimerization (Fig. 1) (Garrett et al., 2002; Odaka, Kohda, Lax, Schlessinger, & Inagaki, 1997; Ogiso et al., 2002). This is followed by intermolecular autophosphorylation of key tyrosine residues in the activation loop of catalytic TK domains (Grandal & Madhus, 2008). The carboxy-terminal phosphotyrosine residues then recruit signaling molecules with Src homology 2 (SH2) and protein tyrosine-binding domains to activate downstream signaling pathways. Downstream EGF receptor signaling pathways include the mitogen-activated protein kinase (MAPK) pathway, phosphoinositol 3'-kinase (PI3K), phospholipase C (PLC) and Janus tyrosine kinases (JAK) and signal transducers and activators of transcription (STAT)

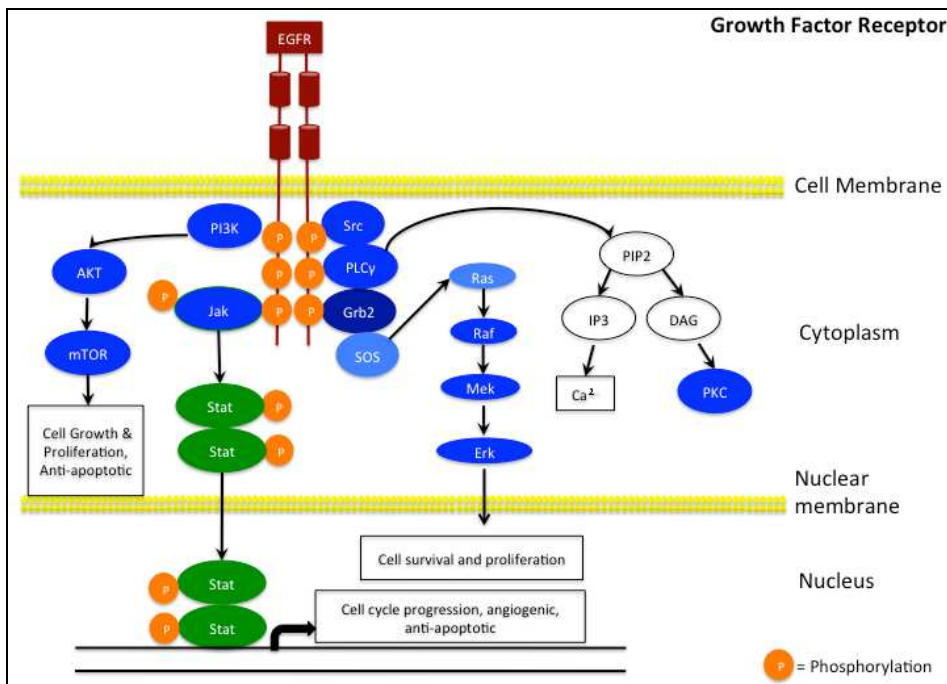


Fig. 1. Growth Factor Receptor Signaling Pathways. Upon ligand binding, tyrosine residues on the EGFR intracellular domain become autophosphorylated. This allows the receptor to interact with SH2 or PTB adaptor proteins (e.g., Grb2), which activates downstream signaling pathways, such as PLC- $\gamma$ , PI3K-Akt, Ras-Raf-Mek-Eer and JAK-STATs, to modulate cell proliferation, migration, differentiation, and apoptosis. mTOR, mammalian target of rapamycin; Sos, son of sevenless; Grb2, growth factor receptor-bound protein 2; Mek, MAPK kinase; Erk, extracellular signal-regulated kinase. Adapted from reference (Ratushny, Astsaturov, Burtness, Golemis, & Silverman, 2009).

(Ciardiello & Tortora, 2008; Laskin & Sandler, 2004). Activation of the MAPK signaling pathway occurs via the small GTPase, Ras, which exchanges GDP for GTP and stimulates the Raf-Mek-Erk cascade, to modulate key cellular processes, including gene transcription, G1/S cell-cycle progression and cell proliferation (Ho & Laskin, 2009). The PLC pathway is activated via cleavage of phosphatidylinositol (4,5)-bisphosphate (PIP<sub>2</sub>) on the cell membrane to form second messenger molecules, inositol triphosphate (IP<sub>3</sub>) and diacylglycerol (DAG). IP<sub>3</sub> triggers the release of intracellular calcium stores, while DAG activates protein kinase C (PKC) (Milano, De Rosa, Iaffaioli, & Caponigro, 2007). The PI3K pathway activates Akt and mammalian target of rapamycin (mTOR), which regulates gene transcription, cell proliferation and migration (Herbst, Heymach, & Lippman, 2008). The JAK-STAT pathway (JAK2, STAT1, STAT3 and STAT5) stimulates transcription of nuclear factors that promote inflammation, cell survival and oncogenesis (Quesnelle, Boehm, & Grandis, 2007; Silva, 2004).

In contrast, non-RTKs cannot bind ligands and do not possess a transmembrane domain, but are activated by cytoplasmic tyrosine kinases. There are 32 cytoplasmic non-RTKs that can be divided into nine sub-families, which include Src, Csk (cytoplasmic tyrosine kinase), Ack (activated p21CDC42 kinase, tyrosine kinase, non-receptor 2 (Trk2)), Fak (focal adhesion kinase), Tec, Fes/Fer, Syk (spleen tyrosine kinase), Abl (Abelson murine leukemia viral oncogene homolog), and JAKs (Manning, Whyte, Martinez, Hunter, & Sudarsanam, 2002; Parsons & Parsons, 2004). These non-RTKs activate downstream signaling cascades and transcription factors to initiate gene transcription and thereby modify important cellular functions. As discussed below, cytokine receptors and immune receptors are examples of receptors that signal via non-RTKs.

## 1.2 Cytokine receptors

Cytokines are small signaling proteins that regulate key physiological cellular functions, such as inflammation, and innate and adaptive immune responses. Receptors for cytokines belonging to the Type I and Type II cytokine families, as well as members of the interleukin (IL)-6 and IL-11 families, signal via JAK non-RTKs. For example, Type I cytokine receptors, such as IL-4 and IL-13 receptors, are multimeric receptors that share the common cytokine receptor  $\gamma$ -subunit ( $\gamma_c$ ), whereas the IL-3, IL-5 and granulocyte-macrophage colony stimulating factor (GM-CSF) receptors share the common cytokine receptor  $\beta$ -chain ( $\beta_c$ ), (Pesu, Laurence, Kishore, Zwillich, Chan, & O'Shea, 2008). Upon ligand binding, receptor oligomerization and signal transduction occur via the interaction of specific JAK isoforms (JAK1, JAK2, JAK3 and TYK2) with the intracytoplasmic domains of cytokine receptors (Fig. 2) (Ghoreschi, Laurence, & O'Shea, 2009).

The Type I cytokines, prolactin, erythropoietin, thrombopoietin, GM-CSF, IL-3 and IL-5, signal through JAK2, while IL-6 family members (IL-6, IL-11), IL-10 family members (IL-10, IL-19, IL-20, IL-22) and the Type II cytokine, interferon (IFN)- $\gamma$ , signal through JAK1 and JAK2 (Ghoreschi et al., 2009). In contrast, JAK3 only associates with receptors that share the common  $\gamma$ -chain ( $\gamma_c$ ), such as receptors for IL-2, IL-4, IL-7, IL-9, IL-15 and IL-21 (Argetsinger et al., 1993; Bacon, McVicar, Ortaldo, Rees, O'Shea, & Johnston, 1995; Johnston et al., 1994; Muller et al., 1993; Parganas et al., 1998; Parham et al., 2002). The biological importance of JAK signaling pathways is illustrated by the congenital absence of JAK3, which causes a

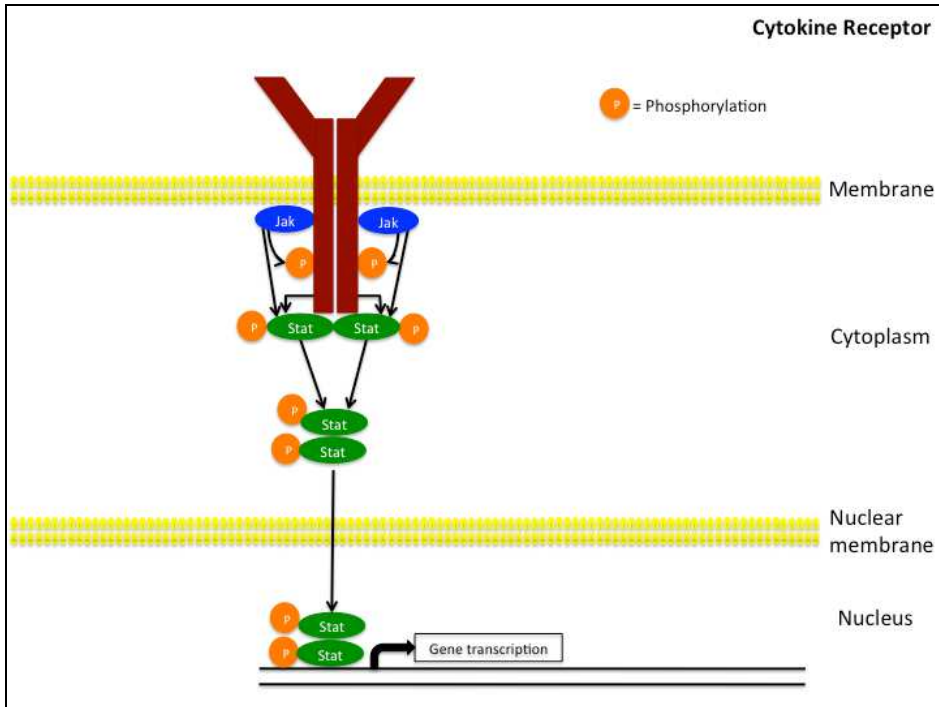


Fig. 2. Cytokine Receptor Signaling Pathways. Following ligand binding to cytokine receptors, receptor-associated JAKs become activated and phosphorylate specific receptor tyrosine residues on the receptor intracytoplasmic domain. This leads to the recruitment of STATs, which are then tyrosine-phosphorylated. Activated STATs dimerize, translocate to the nucleus, and bind to STAT binding sites in the promoter regions of target genes to induce gene transcription. Adapted from reference (Malaviya & Laskin, 2010).

primary immunodeficiency disorder termed T-B+NK- severe combined immunodeficiency disease. This demonstrates the key role for JAK3 in the development of T cells and natural killer cells (Macchi et al., 1995; Russell et al., 1995). JAK activation leads to tyrosine phosphorylation and the recruitment and activation of STAT transcription factors. There are seven STAT family members (STAT1-6 with two STAT5 proteins) that form homo- or hetero-dimers and translocate to the nucleus after being phosphorylated in the cytoplasm to regulate gene transcription (Darnell, 1997). For example, activation of the IL-4 receptor stimulates JAK1 to associate with the IL-4R $\alpha$  chain and JAK3 to associate with the  $\gamma$ c chain, which results in the activation of STAT6 (Takeda et al., 1996). In contrast, IL-13 can interact with both the IL-4R $\alpha$  chain and the IL-13R $\alpha$ 1 chain to activate JAK1, JAK2, Tyk2, and STAT6 (Pernis & Rothman, 2002; Schindler, 2002; Wills-Karp et al., 1998).

### 1.3 Immune receptors

The high affinity IgE receptor (Fc $\epsilon$ RI), the T cell receptor (TCR) and the B cell receptor (BCR) are immune receptors expressed by mast cells, T cells and B cells, respectively. These

receptors are composed of antigen-binding subunits and signal transducing subunits that consist of one or more immunoreceptor tyrosine-based activation motifs (ITAMs), [Y(2X)I/L(6-8X)Y(2X)I/L] (Pitcher & van Oers, 2003). Fc $\epsilon$ RI, is a tetrameric protein ( $\alpha\beta\gamma_2$  chains) consisting of the IgE binding  $\alpha$  chain, a signal-amplifying  $\beta$  chain and two disulfide-linked  $\gamma$  chains, which contain ITAMs for signal transduction (Fig. 3) (Novak, Kraft, & Bieber, 2001). The TCR consists of either  $\alpha\beta$  or  $\gamma\delta$  heterodimer subunits that recognize antigen presented within the context of Major Histocompatibility Complex (MHC) molecules (Fig. 4). The BCR consists of a membrane immunoglobulin isotype molecule (IgD, IgM, IgE or IgG) that binds antigen and Ig $\alpha\beta$  heterodimers, which contain ITAM sequences (Fig. 5) (Schamel & Reth, 2000). Upon tyrosine phosphorylation, ITAMs act as docking sites for non-RTKs and SH2 containing adaptor proteins or as phosphotyrosine-binding domains to activate signal transduction cascades.

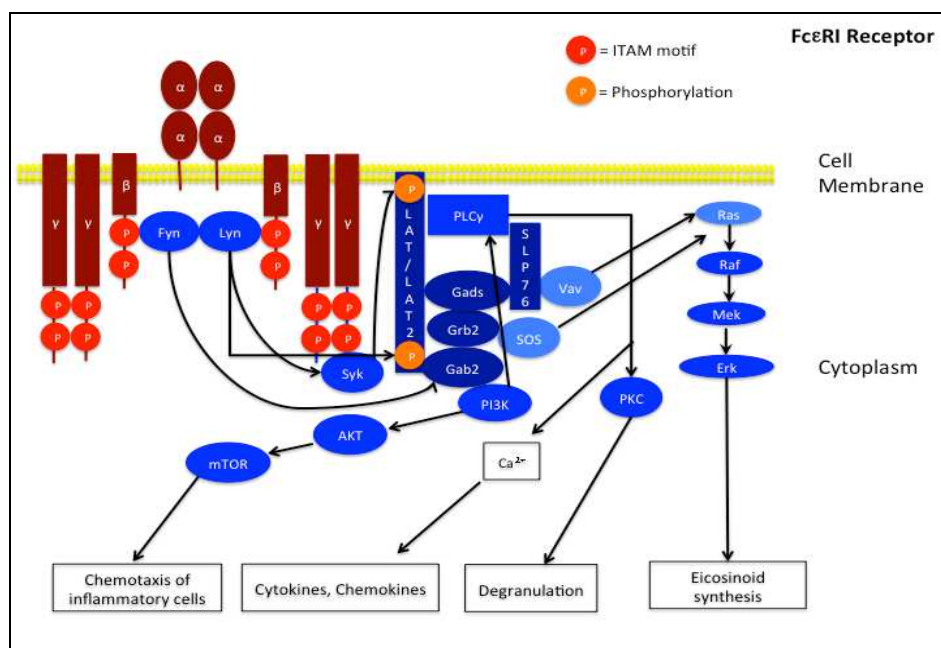


Fig. 3. Fc $\epsilon$ RI Receptor Signaling Pathways. Engagement of the high affinity Fc $\epsilon$ RI on mast cells and basophils by the Fc region of IgE results in phosphorylation of receptor ITAMs by Lyn and Fyn, thereby generating docking sites for these proteins, as well as for Syk. Binding to ITAMs up-regulates Fyn, Lyn and Syk kinase activity that phosphorylate downstream signaling molecules. Multi-protein complexes are then formed, which activate MAPK pathways and generate second messenger molecules, leading to cellular activation. Adapted from reference (Colgan & Hankel, 2010).

Signaling via immune receptors is initiated by Src-family kinases (SFKs) that phosphorylate ITAMs (Lowell, 2011). This recruits Syk to the SH2 domain of phosphorylated ITAM motifs and activates downstream signaling pathways. SFKs consist of nine members; Src, Fyn, Lck, Hck, Lyn, Fgr, Blk, Yes, and Yrk. Src is widely expressed, whereas the expression of

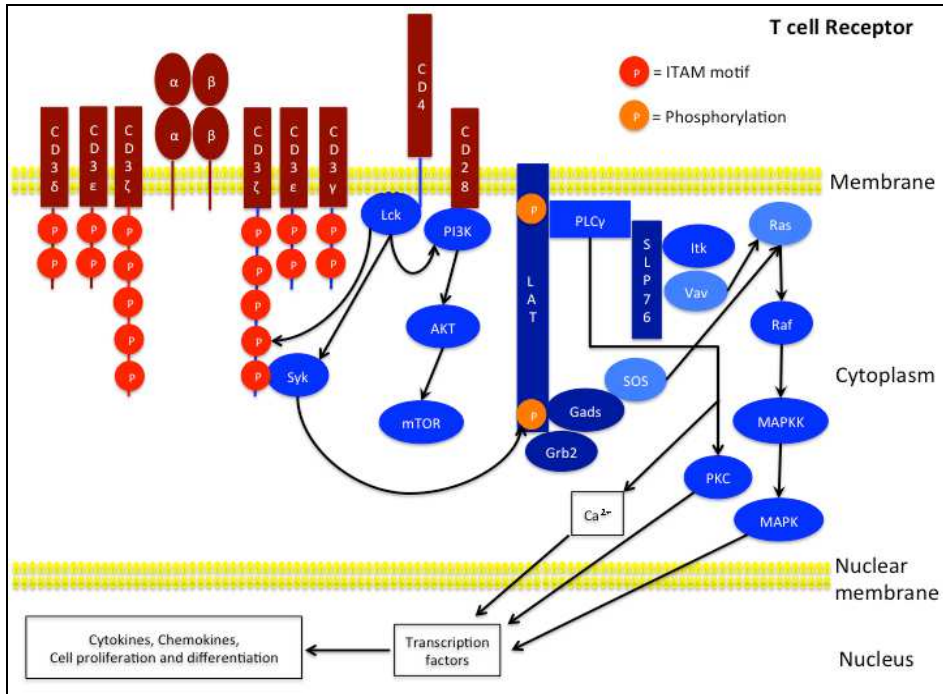


Fig. 4. T Cell Receptor (TCR) Signaling Pathways. TCR engagement by antigen bound to major histocompatibility complex proteins activates Lck, which phosphorylates ITAMs in the CD3 zeta chains to recruit and activate Syk. This leads to phosphorylation of downstream signaling molecules and formation of multi-protein complexes nucleated by the LAT adapter protein. Components of these complexes activate MAPK pathways, generate second messenger molecules and activate transcription factors that induce T cell proliferation and differentiation. Adapted from reference (Colgan & Hankel, 2010).

hematopoietic cell kinase (Hck) and lymphoid cell kinase (Lck) are more restricted (Thomas & Brugge, 1997). Src normally adopts an inactive conformation, such that Y416 in the activation loop is buried between the N-lobe and C-lobe of the kinase domain. This conformation is maintained by interactions between the SH3 domain and the linker region connecting the SH2 domain with the catalytic domain, as well as by binding of the SH2 domain to the C-terminal tail in response to phosphorylation of Y527. Activation occurs when the high affinity ligand binding disrupts the interactions between the SH2 and SH3 domains, thereby allowing unfolding and exposure of Y416 for autophosphorylation (Benati & Baldari, 2008). This recruits the SH2-containing Syk to phosphorylate the adaptor proteins, LAT and LAB (linker for activation of T and B cells, respectively), Grb2, Gab2, Gads, SLP-76 and SLP-65 (SH2 domain-containing leukocyte protein of 76kDa/65kDa), as well as the GTP exchange factors, Sos and Vav, which activate MAPK signaling (Colgan & Hankel, 2010). This activates the Tec family non-RTKs, Itk (inducible T cell kinase) and Btk (Bruton's tyrosine kinase), as well as PLC $\gamma$  and PI3K. The Tec family can also activate PLC $\gamma$  to hydrolyse PIP<sub>2</sub> into IP<sub>3</sub> and DAG, which in turn mobilizes intracellular calcium and

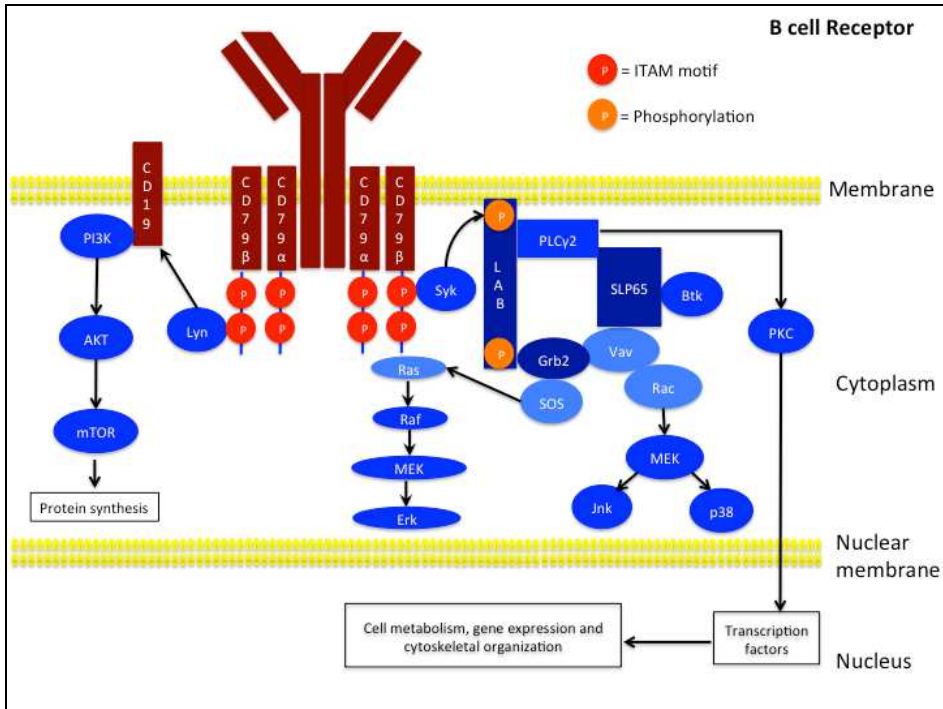


Fig. 5. B Cell Receptor Signaling Pathways. Aggregation of the B-cell antigen receptor (BCR) by antigen leads to rapid activation of the Src family kinases, Lyn, Blk, and Fyn, as well as the Syk and Btk. This initiates the formation of a ‘signalosome’ composed of the BCR, Src family kinases, adaptor proteins such as CD19, and signaling enzymes, such as PLC $\gamma$ 2, PI3K, and Vav. Signals emanating from the signalosome activate multiple signaling cascades that involve kinases, GTPases, and transcription factors, which modulate cell proliferation and differentiation, as well as antibody generation. Adapted from reference (Wong, 2005).

activates PKC isoforms  $\beta$ ,  $\zeta$  and  $\theta$  (Miller & Berg, 2002). This is essential for activation of the transcription factor nuclear factor- $\kappa$ B (NF- $\kappa$ B), which mediates immune receptor signaling via CARMA1/BCL10/MALT1 and I $\kappa$ B kinases (Li, Rickert, & Karin, 2004).

Cross-linking of IgE bound to Fc $\epsilon$ RI by multivalent antigen activates Lyn, followed by activation of Syk, which phosphorylates LAT and SLP-76 (Kawakami & Galli, 2002). This activates Btk and induces mast cell degranulation and activation. The TCR heterodimer associates with CD3 molecules that contain ITAM sequences (Colgan & Hankel, 2010). During TCR activation, Lck and Fyn phosphorylate ITAMs on CD3, which recruits Syk to phosphorylate LAT and SLP-76. This activates Itk causing T cell activation (Nel, 2002; Samelson, 2002). Upon BCR activation, phosphorylation of ITAMs by Lyn, Fyn or Blk recruits Syk, which phosphorylates LAB and SLP-65 to activate Btk (Dal Porto, Gauld, Merrell, Mills, Pugh-Bernard, & Cambier, 2004). This leads to cellular proliferation and differentiation, which generates a population of antibody-secreting plasma and memory B cells.

## 2. The role of tyrosine kinases in non small cell lung cancer

Lung cancer is the leading cause of cancer-related death worldwide and accounted for an estimated 157,300 deaths in the US in 2010 (Jemal, Siegel, Xu, & Ward, 2010). Approximately 85% to 90% of all lung cancer cases are NSCLCs, such as adenocarcinoma, squamous cell carcinoma and large-cell carcinoma. Advanced-stage NSCLC is currently an incurable disease and less than 30% of patients with metastatic NSCLC respond to platinum-based chemotherapy. The EGFR is activated in more than half of the patients with NSCLC as a result of either protein over-expression, gene mutations or an increase in gene copy number (Balak et al., 2006; Chitale et al., 2009; Ding et al., 2008; Soh et al., 2009; Weir et al., 2007). EGFR mutations are usually heterozygous, with the mutant alleles showing gene amplification involving exons 18 to 21 that encode the kinase domain. Therefore, inhibitors of EGFR signaling have been developed as a novel approach for the treatment of NSCLC.

### 2.1 Use of EGFR inhibitors for the treatment of NSCLC

The EGFR inhibitors, erlotinib and gefitinib, were developed to attenuate excessive EGFR signaling as a novel approach for the treatment of NSCLC (Cataldo, Gibbons, Perez-Soler, & Quintas-Cardama, 2011). Erlotinib (Tarceva®) is currently approved by the U.S. Food and Drug Administration as a second line therapy for patients with locally advanced or metastatic NSCLC after failure of at least one prior chemotherapy regimen or as maintenance therapy for patients with NSCLC whose disease has not progressed after four cycles of platinum-based first-line chemotherapy (Genentech, 2011). In contrast, continued treatment with gefitinib (Iressa®) as monotherapy is limited to patients who are responding or have previously responded to gefitinib treatment for NSCLC after failure of both platinum-based and docetaxel chemotherapies (AstraZeneca, 2005). This restriction is based upon a large, placebo-controlled, randomized trial in patients with advanced NSCLC, which did not show an improvement in survival with gefitinib as second- or third-line treatment for NSCLC (Thatcher et al., 2005). Gefitinib may continue to be used in clinical trials under a new drug application.

These tyrosine kinase inhibitors (TKIs) are small molecules that bind orthosteric and/or allosteric sites to competitively inhibit ATP phosphorylation or irreversibly inhibit its activity (Noble, Endicott, & Johnson, 2004). Erlotinib and gefitinib are most effective in patients with EGFR mutations, such as L858R and G719S, which result in increased EGFR activation (Carey et al., 2006; Yun et al., 2007; Yun et al., 2008). Inhibition of EGFR mutants leads to increased cell death mediated by an apoptotic pathway that is dependent upon Bim, a Bcl-2 family member that is pro-apoptotic and regulated by Erk signaling (Costa et al., 2008; Cragg, Kuroda, Puthalakath, Huang, & Strasser, 2007; Deng et al., 2007; Gong et al., 2007). Although most patients tolerate erlotinib and gefitinib, some patients experience serious side effects such as diarrhea, rash, nausea and interstitial lung disease (Makris et al., 2007; Shah et al., 2005; Shepherd et al., 2005). Patients may have primary resistance due to EGFR drug-resistant mutations, such as EGFRvIII, which is a constitutively active form of EGFR caused by the deletion of exons 2 - 7 (Greulich et al., 2005; Inukai et al., 2006; Maheswaran et al., 2008; Prudkin, Tang, & Wistuba, 2009; Wu et al., 2008), mutations in downstream signaling pathways that co-occur with EGFR mutations, such as the PI3K catalytic subunit, PIK3CA (Kawano et al., 2006), or mutations that occur in other downstream genes, such as k-Ras and b-Raf (Brose et al., 2002; Davies et al., 2002; Linardou



et al., 2008; Mok et al., 2009; Pao et al., 2005b; Wheeler, Dunn, & Harari, 2010; Zhang & Chang, 2008). Furthermore, despite an initial positive response to treatment, acquired resistance can develop following 6 to 12 months of therapy with erlotinib or gefitinib. Acquired resistance to erlotinib or gefitinib can occur via several mechanisms, such as second-site mutations and amplification of the *MET* oncogene, which encodes a RTK for hepatocyte growth factor that activates a ERBB3 (HER3)-dependent PI3K/Akt pathway (Bean et al., 2007; Engelman et al., 2007; Wheeler et al., 2010; Zhang & Chang, 2008). For example, the T790M mutation occurs in 50% of EGFR-mutant tumors that develop acquired resistance to erlotinib or gefitinib via a mechanism that involves increased affinity for ATP binding (Fig. 6) (Kobayashi et al., 2005; Pao et al., 2005a; Wheeler et al., 2010; Yun et al., 2008).

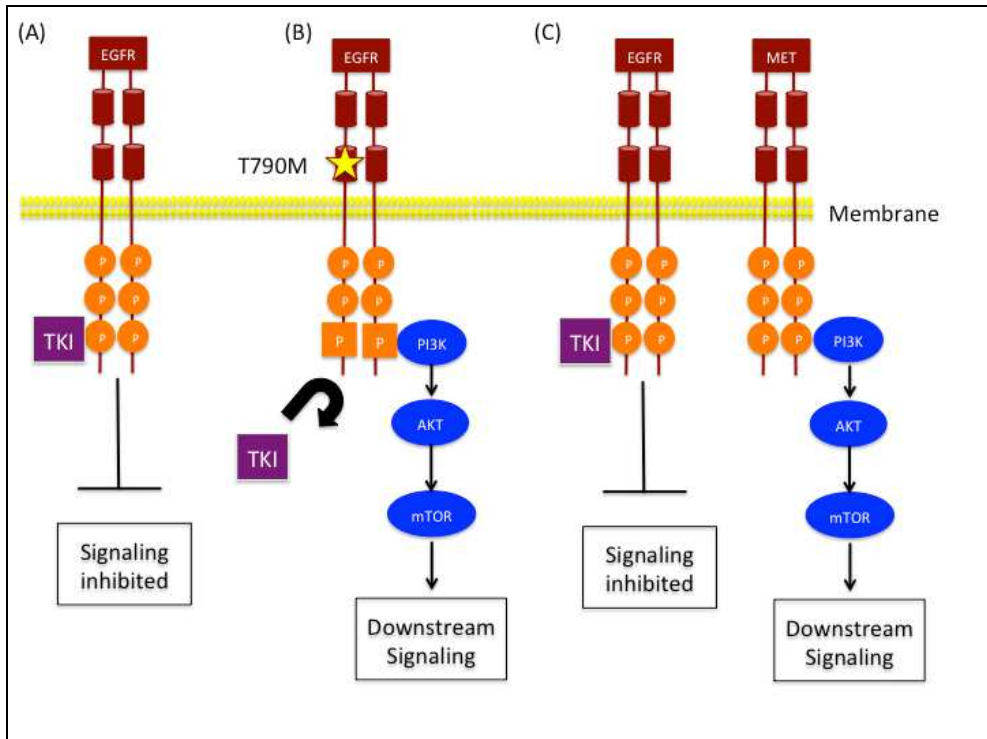


Fig. 6. Inhibition of EGFR Signaling by Tyrosine Kinase Inhibitors and Mechanisms of Resistance in Non-small Cell Lung Cancers. **Panel A.** Intracellular binding of TKIs, erlotinib or gefitinib, to the ATP-binding site of the tyrosine kinase domain of EGFR blocks kinase activity and inhibits downstream signaling pathways responsible for cellular proliferation. **Panel B.** The T790M mutation, detected in approximately 50% of patients who relapse while receiving an EGFR TKI, causes steric hindrance that prevents TKI binding and promotes constitutive activation of the mutated EGFR kinase. **Panel C.** Amplification of the *MET* oncogene activates downstream signaling through the PI3K–Akt pathway in an EGFR-independent fashion despite effective EGFR tyrosine kinase inhibition by TKI. Adapted from reference (Cataldo et al., 2011).

## 2.2 Strategies to overcome EGFR resistance

Various strategies have been developed to address TKI resistance, such as the development of second and third generation TKIs. The irreversible inhibitor, BIBW2992 (Afatinib; Boehringer Ingelheim), has been shown to have potent activity against EGFR and ERBB2 that overcomes resistance secondary to T790M EGFR mutations. BIBW2992 has been shown to reduce the survival of cancer cell lines and induce tumor regression in xenograft and transgenic lung cancer models (Li et al., 2008). Phase I clinical trials have demonstrated that daily oral BIBW2992 has durable anti-tumor activity and is safely tolerated (Yap et al., 2010). Combination therapy with BIBW2992 and an EGFR-specific antibody, cetuximab, further overcame T790M EGFR resistance in a murine model (Regales et al., 2009), which suggests that this approach may represent an alternative treatment option. Although combined inhibition of VEGFR and EGFR has been reported to reduce tumor growth in xenograft models of EGFR inhibitor resistance (Naumov et al., 2009), this approach did not improve survival in a phase III clinical trial of NSCLC when erlotinib was combined with bevacizumab, an antibody against VEGF (Herbst et al., 2011). Combination of erlotinib with sorafenib, a multi-TKI of VEGFR, c-Kit, PDGFR, b-Raf and c-Raf, had some therapeutic benefit in EGFR resistant patients with NSCLC as the median overall survival was prolonged to 8 months in the erlotinib/sorafenib group as compared to 4.5 months in the placebo/erlotinib group ( $P = 0.019$ ) (Spigel et al., 2011). The same strategy might also be used to overcome mutations in pathways downstream of EGFR (Sos et al., 2010). For example, simultaneous targeting of EGFR and its downstream target, Akt, using BIBW2992 and rapamycin, reduced tumor size and protein phosphorylation in murine NSCLC models (Perera et al., 2009). Similar findings have been shown using erlotinib combined with rapamycin to treat NSCLC cell lines (A549, H1299, H1650 and H1975) *in vitro* (Nakachi et al., 2010). Furthermore, alternative TKIs, such as sorafenib and crizotinib, an inhibitor of anaplastic lymphoma kinase (Alk) and Met, might be used to overcome mutations in other EGFR-related genes, such as b-Raf (Brose et al., 2002; Davies et al., 2002), k-Ras (Pao et al., 2005b) and Alk (Soda et al., 2007) (Comoglio, Giordano, & Trusolino, 2008; Ou et al., 2011; Takezawa et al., 2009).

## 3. Therapeutic use of TKIs in inflammatory airway diseases

New treatments are needed for patients with severe asthma or COPD. While the majority of asthmatics can be adequately controlled with low-to-moderate doses of inhaled corticosteroids, approximately 5% to 10% of patients have severe disease that is refractory to standard treatments (Program, 2007; Wenzel & Busse, 2007). These individuals have persistent symptoms and recurrent disease exacerbations despite high-doses of inhaled corticosteroids plus long-acting  $\beta_2$ -agonists or oral corticosteroids. New treatment options are needed as oral corticosteroids are associated with serious and potentially debilitating side effects, such as diabetes, hypertension, weight gain, impaired host defense, reduced bone density, cataracts, skin atrophy, and myopathy. Limited treatment options also exist for patients with COPD, which include inhaled and oral corticosteroids, inhaled  $\beta_2$ -agonists, inhaled anti-cholinergics and phosphodiesterase inhibitors.

Signaling via RTKs and non-RTKs has been implicated in the pathogenesis of asthma and COPD, especially in patients with severe disease who are resistant to corticosteroid therapy (Adcock, Chung, Caramori, & Ito, 2006). Therefore, TKIs have been proposed as an

alternative approach for the treatment of asthma and COPD. In addition, although TKIs are designed to target specific protein kinases, they frequently have activity towards additional targets, which may be valuable in treating diseases other than those for which the TKI was originally developed. For example, imatinib (Gleevec™) was originally designed as a Bcr-Abl inhibitor for the treatment of chronic myelogenous leukemia (CML), but was also found to inhibit c-Kit, PDGFR $\alpha/\beta$ , and CSF1R (Buchdunger et al., 2000; Druker et al., 1996; Heinrich, Griffith, Druker, Wait, Ott, & Zigler, 2000). Although these off-target effects may lead to unanticipated toxicities, it may also represent an opportunity to extend the utility of TKIs for the treatment of lung disease.

### 3.1 Asthma

Asthma is a common respiratory illness that afflicts roughly 300 million people worldwide (Braman, 2006). Asthma prevalence is highest in developed countries, including the UK (>15%), USA (~11%) and Australia (~15%), where it accounts for approximately 1% to 2% of the healthcare annual budget (Masoli, Fabian, Holt, & Beasley, 2004). There is a positive correlation between healthcare costs and asthma severity, as individuals with severe disease and frequent exacerbations represent approximately 5% to 10% of patients, but account for up to 50% of the costs (Godard, Chanez, Siraudin, Nicoloyannis, & Duru, 2002). Asthma is characterized by airway inflammation, airway remodeling, mucus hypersecretion and enhanced smooth muscle contractility (i.e., airway hyperreactivity) (Anderson, 2008; Barnes, 2008; Fanta, 2009; Holgate & Polosa, 2006; Rogers, 2004). Allergic airway inflammation is mediated by the recruitment of eosinophils, neutrophils, basophils, activated mast cells, and Th2-type CD4+ T cells that produce a characteristic set of cytokines, typified by IL-4, IL-5, IL-9, and IL-13 (Barnes, 2008). Structural changes that lead to airway wall remodeling include mucous cell metaplasia, airway smooth muscle cell hypertrophy and hyperplasia, epithelial cell proliferation, subepithelial fibrosis, basement membrane thickening, and vascular hyperplasia (Anderson, 2008; Barnes, 2008; Cohen et al., 2007; Fanta, 2009; Holgate & Polosa, 2006). Airway hyperreactivity (AHR) is an additional cardinal feature of asthma that results in increased airflow resistance and airflow obstruction (Fanta, 2009). Mucus hypersecretion also contributes to airway obstruction via mucus plugging in the airway (Del Donno, Bittesnich, Chetta, Olivieri, & Lopez-Vidriero, 2000; Rogers, 2007).

#### 3.1.1 The potential role of RTK inhibitors for the treatment of asthma

Multiple lines of evidence support a role for RTKs in the pathogenesis of asthma. For example, increased tyrosine phosphorylation has been observed in the airway epithelium of patients with severe asthma who are resistant to corticosteroids (Hamilton et al., 2005). Similarly, PDGFR- $\beta$  expression is increased in patients with severe asthma and may contribute to fibrotic airway remodeling responses (Lewis et al., 2005). Furthermore, a WNT/tenascin/PDGFR pathway has been implicated in the pathogenesis of airway smooth muscle hyperplasia and hypertrophy in a murine model of allergen-induced asthma (Cohen, Ihida-Stansbury, Lu, Panettieri, Jones, & Morrisey, 2009). Expression of c-Kit and its ligand stem cell factor (SCF) are also increased in the airways of asthmatic patients as compared to non-asthmatic control subjects (Al-Muhsen, Shablovsky, Olivenstein, Mazer, & Hamid, 2004; Bradding, Walls, & Holgate, 2006). Enhanced c-Kit signaling plays an important role in the activation of mast cells and dendritic cells, AHR, mucus hyperproduction, collagen

deposition, and airway inflammation in asthma (Krishnamoorthy et al., 2008; Paniagua et al., 2006; Yu, Tsai, Tam, Jones, Zehnder, & Galli, 2006). In experimental models of asthma, SCF has been shown to mediate AHR, airway remodeling, and the production of pro-inflammatory cytokines (TNF, IL-5) and chemokines (CCL2, CCL5, CCL6, CCL17), and mucous cell metaplasia (Berlin, Hogaboam, & Lukacs, 2006; Berlin, Lincoln, Tomkinson, & Lukacs, 2004; Campbell, Hogaboam, Lincoln, & Lukacs, 1999; Dolgachev, Thomas, Berlin, & Lukacs, 2007). Lastly, VEGF signaling has been shown to induce an asthmatic phenotype in murine models (Lee et al., 2004).

These data support the concept of investigating the role of TKIs for the treatment of asthma. For example, imatinib has been shown to attenuate airway inflammation, AHR and fibrosis in murine models of allergic disease (Berlin & Lukacs, 2005). This was also demonstrated with sunitinib, a RTK inhibitor of VEGFR, PDGFR, c-Kit and fetal liver tyrosine kinase receptor 3 (FLT-3), which is used as an alternative treatment for imatinib-resistant CML (Huang, Liu, Du, Yao, & Yin, 2009). Furthermore, masitinib, a multi-target RTK inhibitor of c-Kit and PDGFR, has recently been shown to improve disease control in a clinical trial of severe, corticosteroid-resistant asthma (Humbert et al., 2009). Finally, EGFR activation plays a central role in the induction of mucin synthesis and mucous cell hyperplasia (Burgel & Nadel, 2004; Tamaoka et al., 2008). Gefinitib treatment inhibits EGFR and PI3K/Akt activation in ovalbumin (OVA) sensitized mice, which suggests that this approach might be beneficial for the treatment of asthma (Hur et al., 2007). House dust mite (HDM), a common aeroallergen that causes atopic asthma, has been shown to enhance EGFR signaling and epithelial-to-mesenchymal transition (EMT) in airway epithelial cells and thereby promote airway remodeling in asthma (Heijink, Postma, Noordhoek, Broekema, & Kapus, 2010). Furthermore, inhibition of EGFR signaling prevents TGF- $\beta$ /HDM-induced EMT, which suggests that this approach might be utilized to attenuate airway remodeling in asthma.

### **3.1.2 Treatment of asthma with non-RTK inhibitors**

#### **3.1.2.1 Src kinase inhibitors**

In human eosinophils, binding of eotaxin (CCL11) to CCR3 activates SFKs, such as Hck, Fgr and Lyn, as well as Syk, to enhance tyrosine phosphorylation, chemotaxis and respiratory burst. Cross-linking of Fc $\epsilon$ RI with multivalent antigen in mast cells and basophils activates Lyn with resultant calcium mobilization, actin polymerization, shape change, and secretion of pro-inflammatory cytokines, such as IL-6, IL-13 and TNF- $\alpha$  (Amoui, Draberova, Tolar, & Draber, 1997; Furumoto, Nunomura, Terada, Rivera, & Ra, 2004; Kepley, Wilson, & Oliver, 1998; Vonakis et al., 2005). Lyn deficient mice develop severe persistent asthma, which demonstrates that Lyn is a critical negative regulator of Th2 immunity (Beavitt et al., 2005). Furthermore, a Lyn blocking peptide and the Src-selective inhibitor, PP1, can attenuate eosinophil activation, differentiation and survival (Adachi, Stafford, Sur, & Alam, 1999; Lynch, Giembycz, Daniels, Barnes, & Lindsay, 2000). Lck is expressed primarily by T lymphocytes and plays an essential role in immune responses (Faith, Akdis, Akdis, Simon, & Blaser, 1997; Molina et al., 1992). Lck deficient mice have impaired thymocyte development, lack Th2 cells and are unable to mount antigen-dependent immune responses (Karnitz et al., 1992). Thus, Lck plays a crucial role in T-cell maturation and antigen-induced T-cell activation, which suggests that a Lck inhibitor could be utilized for the treatment of autoimmune and inflammatory diseases (Burchat et al., 2002). SFKs have also been reported

to mediate angiotensin II-induced hyperresponsiveness of rat bronchial smooth muscle (Sakai et al., 2010).

### 3.1.2.2 Syk inhibitors

Syk, which is activated by integrins and oxidative stress, has an important role in signal transduction (Au-Yeung et al., 2009). Syk is expressed by all hematopoietic cells, as well as by fibroblasts, endothelial cells, hepatocytes and epithelium (Ulanova et al., 2005). Its role in modulating the function of non-hematopoietic cells, however, is uncertain. Mice with a spontaneous point mutation in Syk have altered TCR signaling that leads to the positive selection of autoimmune T cells and autoimmune arthritis (Sakaguchi et al., 2003). Interestingly, this was not observed in a patient with a Syk variant (Picard et al., 2009). Syk induces mast cell degranulation via FcεRI signaling, T and B lymphocyte development and activation, as well as IL-5- and GM-CSF-mediated eosinophil survival (Yanagi, Inatome, Takano, & Yamamura, 2001). The inhibition of Syk by antisense nucleotides blocks eosinophil survival and its deletion in mast cells prevents IgE-induced mast cell activation and AHR (Matsubara et al., 2006; Stenton et al., 2002). Thus, Syk inhibition has the potential to suppress mast cell-driven airway bronchoconstriction, hyperreactivity and inflammation. Consistent with this, mice with an inducible deletion of Syk or those treated with a pharmacological Syk inhibitor (BAY61-3606) displayed reduced OVA-induced eosinophilia (Wex et al., 2011). BAY61-3606 has also been reported to attenuate OVA-induced airway inflammation, lipid mediator release, cytokine synthesis and mast cell degranulation in rats (Yamamoto et al., 2003). Similarly, another Syk inhibitor, R406, inhibited airway hyperreactivity, pulmonary eosinophilia and goblet cell metaplasia in a murine model of OVA-induced asthma (Matsubara et al., 2006). The Syk-selective inhibitor, piceatannol, has also been shown to attenuate antigen-mediated bronchial contraction of guinea pig airways *in vitro* (Seow, Chue, & Wong, 2002). Anti-sense approaches to knockdown Syk expression have also suppressed airway inflammation in rat asthma models, as well as antigen-induced contraction of isolated tracheas (Stenton et al., 2002). Finally, the Syk inhibitor, R-112, has also been shown to improve symptoms of seasonal allergic rhinitis (Meltzer, Berkowitz, & Grossbard, 2005). An alternative compound, R-343, has completed phase I clinical trials for asthma and phase II trials are being planned (Norman, 2009).

### 3.1.2.3 Tec inhibitors

Inducible T cell kinase (Itk) plays an important role in T cell activation and differentiation, as well as in the differentiation and function of Th2-type cells, which modulate the pathogenesis of asthma. Consistent with this, Itk deficient mice have reduced antigen-specific T cell recruitment to the lung, decreased IL-5 and IL-13 production, reduced antigen-mediated T cell proliferative responses, as well as attenuated eosinophil infiltration and mucus production (Mueller & August, 2003). Reduced airway inflammation in Itk knockout mice is caused by an increase in  $\gamma\delta$  T cells that attenuate mast cell responses (Felices, Yin, Kosaka, Kang, & Berg, 2009; Qi et al., 2009). Itk deficient mice also have reduced AHR (Ferrara, Mueller, Sahu, Ben-Jebria, & August, 2006). Itk deficiency is also associated with a decrease in IL-17A expression by Th17 cells that is mediated via the transcription factor, NFATc1 (nuclear factor of activated T cells) (Gomez-Rodriguez et al., 2009). Lastly, double Itk and Btk knockout mice have severely impaired FcεRI-dependent

mast cell responses (Iyer et al., 2011). Pharmacological Itk inhibitors have been developed as potential new treatments for inflammatory diseases (Das et al., 2006). BMS-488516 and BMS-509744 inhibit Itk kinase activity by reducing TCR-induced functions, including PLC $\gamma$ 1 tyrosine phosphorylation, calcium mobilization, IL-2 secretion, and T-cell proliferation *in vitro*, as well as suppress IL-2 production in mice (Lin et al., 2004). BMS-509744 also significantly diminished lung inflammation in a mouse model of OVA-induced allergic asthma (Lin et al., 2004). Additional Itk inhibitors have been synthesized based upon the (4 or 5-aryl)pyrazolyl-indole scaffold that is selective for Itk (Velankar et al., 2010). Furthermore, irreversible inhibition of Btk with the highly selective inhibitor, PCI-32765, has been shown to block IgE-mediated activation of human basophils (MacGlashan, Honigberg, Smith, Buggy, & Schroeder, 2011).

### 3.1.2.4 JAK inhibitors

JAK inhibition represents another potential therapeutic approach for the treatment of asthma. JAK3 is expressed by many cells involved in the pathogenesis of asthma, such as mast cells, T cells, macrophages and dendritic cells. For example, RANTES induces rapid tyrosine phosphorylation of CCR5, activation of JAK2 and JAK3, and formation of STAT1 and STAT3 dimers in human T cells (Bacon, Szabo, Yssel, Bolen, & Schall, 1996; Wong & Fish, 1998; Wong et al., 2001). Stromal cell-derived factor-1a (SDF-1a) triggers CXCR4 receptor dimerization and activates JAK2, JAK3, and Syk, causing transendothelial migration of human T cell lines (Ticchioni et al., 2002; Vila-Coro, Rodriguez-Frade, Martin De Ana, Moreno-Ortiz, Martinez, & Mellado, 1999). Although JAK3 is primarily responsible for cytokine signaling, it also has other functional roles. For example, JAK3 plays a pivotal role in Fc $\epsilon$ RI-mediated mast cell responses. Consistent with this, the JAK3 inhibitor, CP-690550 attenuated pulmonary eosinophilia, as well as IL-13 and eotaxin production in an OVA-model of allergic airway disease, while targeting JAK3 with WHI-P97 attenuated both pulmonary eosinophilia and AHR (Kudlacz, Conklyn, Andresen, Whitney-Pickett, & Changelian, 2008; Malaviya et al., 2000; Malaviya, Zhu, Dibirdik, & Uckun, 1999). Similarly, the JAK3 inhibitor, WHI-P131 has been shown to inhibit IgE-mediated mast cell degranulation (Kudlacz et al., 2008; Malaviya et al., 2000; Malaviya et al., 1999). Furthermore, a pan-JAK inhibitor, pyridone 6 encapsulated in polyactic-coglycolic acid nanoparticles, has been shown to suppress Th2 inflammation and pulmonary eosinophilia, but not airway hyperreactivity in a murine OVA-challenge model (Matsunaga et al., 2011).

## 3.2 Chronic Obstructive Pulmonary Disease

COPD is a common lung disease, with an estimated prevalence of 210 million individuals in 2007. Furthermore, COPD is the fifth most common cause of mortality worldwide and accounted for approximately 3 million deaths in 2005 (Marwick & Chung, 2010). COPD-related deaths are predicted to rise by 30% in the next 10 years and will become the third leading cause of death worldwide by 2030. COPD is typically caused by the exposure of noxious particles or gases, such as those contained in cigarette smoke or fossil fuels found in environmental air pollution (Buist et al., 2007; Chung & Adcock, 2008; Mannino & Buist, 2007). COPD is manifested by the destruction of the lung parenchyma with resultant emphysema and inflammation. Patients with COPD have an increase in lung macrophages, neutrophils and CD8+ T cells (Hogg et al., 2004; Saetta, Turato, Maestrelli, Mapp, & Fabbri, 2001). This inflammatory process is

orchestrated by chemokines, such as CCL2, CXCL1, CXCL8, and cytokines, such as TNF, IL-1 $\beta$ , IL-6, and IFN- $\gamma$  (Barnes, 2008).

Mucous cell metaplasia is another important manifestation of COPD that results in mucus overproduction and airway obstruction in patients with chronic bronchitis. Consistent with this, expression of EGFRs and airway mucins are increased in airway epithelial cells of smokers, as compared with non-smokers (de Boer, Hau, van Schadewijk, Stolk, van Krieken, & Hiemstra, 2006; Takeyama et al., 2001). Signaling through EGFR involves dual oxidase 1 and the production of reactive oxygen species to activate TNF-alpha converting enzyme (TACE, ADAM17), which induces mucin production via a pathway involving increased TGF- $\alpha$  shedding and EGFR phosphorylation (Shao & Nadel, 2005). Binding of CCL20 to CCR6 has been shown to exaggerate EGFR-dependent MUC5AC production by human airway epithelial cells (Kim, Lewis, & Nadel, 2011). EGFR activation also participates in CXCL8 (IL-8) production by bronchial epithelial cells (Richter et al., 2002). Furthermore, EGFR signaling via STAT and Erk1/2 reduces expression of IL-8 and ICAM-1 by bronchial epithelial cells following rhinovirus infection, which is a common trigger of COPD exacerbations (Liu, Gualano, Hibbs, Anderson, & Bozinovski, 2008). The role of EGFR activation in airway mucin production and IL-8 expression suggests that EGFR blockade might be considered as a treatment approach for COPD. However, a clinical trial of an inhaled EGFR inhibitor (BIBW2948 BS) in 48 patients with COPD did not significantly decrease airway epithelial cell mucin stores and was also poorly tolerated (Woodruff et al., 2010). Thus, additional studies will be required to establish whether there is a role for EGFR inhibition in the treatment of COPD. Lastly, COPD patients may develop NSCLC due to altered EGFR signaling and aberrant methylation, which may have a unique genetic profile compared to NSCLC patients without COPD (Suzuki et al., 2010).

### 3.3 Idiopathic Pulmonary Fibrosis

Idiopathic pulmonary fibrosis (IPF) is a progressive lung disorder that is associated with a relentless deterioration in lung function and a median survival of only 2.5 to 3.5 years after diagnosis (King, Pardo, & Selman, 2011; Ley, Collard, & King, 2011). IPF has an estimated prevalence of 13 to 20 cases per 100,000 and has a higher predominance in men than women. In addition, the frequency of IPF increases with age, with disease typically occurring in patients greater than 50 years of age. The etiology of IPF may reflect a dysregulated airway epithelial cell repair response to repetitive injury, which causes apoptosis of epithelial and endothelial cells. This results in the release of pro-fibrotic mediators that mediate the migration and proliferation of mesenchymal cells, the formation of fibroblast/myofibroblast foci, alveolar destruction and excessive collagen deposition despite minimal inflammation. Various stimuli such as cigarette smoke, wood or metal dust, viral infection and gastro-esophageal reflux/aspiration can contribute to the development of IPF (Iwai, Mori, Yamada, Yamaguchi, & Hosoda, 1994; Raghu, Yang, Spada, Hayes, & Pellegrini, 2006; Steele et al., 2005; Tobin, Pope, Pellegrini, Emond, Sillery, & Raghu, 1998; Ueda et al., 1992). Genes that have been associated with the pathogenesis of IPF include surfactant protein C (Thomas et al., 2002), surfactant protein A2 (Nogee, Dunbar, Wert, Askin, Hamvas, & Whitsett, 2002; Wang et al., 2009), mucin 5B (*MUC5B*) (Seibold et al., 2011) and human telomerase reverse transcriptase (*TERT*) and telomerase RNA component (*TERC*) (Alder et al., 2008; Armanios et al., 2007; Cronkhite et al., 2008; Tsakiri et al., 2007).

At present, there is no effective treatment for IPF. Only lung transplantation has reported to prolong survival (King et al., 2011). The finding that fibrogenic growth factors, such as TGF- $\beta$ , PDGF, FGF and VEGF signal via RTKs has led to the concept that TKIs might be utilized as a novel treatment approach for IPF (Downey, 2011). Consistent with this, inhibition of pro-fibrotic signaling pathways mediated by TGF- $\alpha$ , PDGF, FGF, IGF and VEGF can prevent matrix deposition and fibroblast proliferation (Abdollahi et al., 2005; Chaudhary et al., 2007; Choi et al., 2009). Furthermore, the EGFR inhibitor, gefitinib has been reported to prevent bleomycin-induced IPF in murine models (Ishii, Fujimoto, & Fukuda, 2006; Wang et al., 2010), while gefitinib and erlotinib have been shown to reduce TGF- $\alpha$ -induced IPF in a murine model (Hardie et al., 2008). The role of TKIs for the treatment of IPF has been investigated in clinical trials. A recent multicenter, double-blind trial of imatinib in 119 patients with mild-to-moderate IPF did not improve survival or lung function (Daniels, Lasky, Limper, Mieras, Gabor, & Schroeder, 2010). In contrast, more promising results were reported by a recent 12-month, phase 2 clinical trial of 432 patients that investigated the efficacy of the TKI, BIBF 1120 (Indedanib), as compared to placebo (Richeldi et al., 2011). BIBF 1120 is a multi-receptor tyrosine kinase inhibitor that targets PDGFR, VEGFRs 1, 2 and 3 and FGFRs 1, 2 and 3. This study found a trend towards a reduction in decline of lung function, with fewer acute exacerbations and preserved quality of life. This result suggests that TKIs that target multiple fibrogenic pathways might represent an efficacious treatment approach for IPF (Downey, 2011). This could represent a major advance for the treatment of IPF patients.

#### 4. Conclusion

Activation of RTKs and non-RTKs play key roles in the pathogenesis of NSCLC and lung diseases, such as asthma, COPD and IPF. Although the TKI, erlotinib, has advanced to clinical practice as a second-line treatment for NSCLC, TKIs have not yet been shown to be effective for the treatment of severe asthma or COPD. Recent results, however, have suggested that use of a TKI that inhibits multiple tyrosine kinase targets, might slow disease progression in IPF. If confirmed to be efficacious, TKI treatment could represent a major advance for the treatment of this progressive and fatal lung disease. Thus, the future is bright as continued advances in the development of TKIs may lead to novel treatment approaches for patients with severe lung diseases with high associated mortalities, such as IPF and NSCLC. Furthermore, personalizing TKI therapy to target specific RTKs and non-RTKs that mediate disease pathogenesis may allow for more accurate treatment and reduce unwanted off-target effects.

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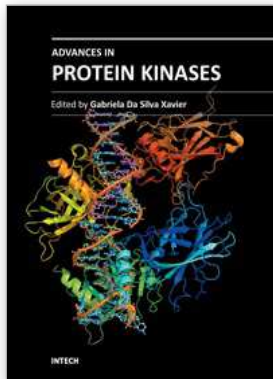
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Proteins are the work horses of the cell. As regulators of protein function, protein kinases are involved in the control of cellular functions via intricate signalling pathways, allowing for fine tuning of physiological functions. This book is a collaborative effort, with contribution from experts in their respective fields, reflecting the spirit of collaboration - across disciplines and borders - that exists in modern science. Here, we review the existing literature and, on occasions, provide novel data on the function of protein kinases in various systems. We also discuss the implications of these findings in the context of disease, treatment, and drug development.

### **How to reference**

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### **InTech Europe**

University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
[www.intechopen.com](http://www.intechopen.com)

### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

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