Inflammation, Epithelial to Mesenchymal Transition, and Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitor Resistance

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Inflammation is an important contributor to lung tumor development and progression. In addition, inflammatory signaling may promote epithelial to mesenchymal transition, development of aggressive metastatic tumor phenotypes, and play a role in resistance to targeted therapies. New insights in inflammatory signaling have led to the evaluation of combination therapies that target these specific pathways. In addition to developing the optimal combination of targeted agents, biomarker-based selection of patients who will likely benefit will be critical to the success of this strategy. Here we focus on the potential contribution of inflammatory mediator-induced resistance to epidermal growth factor receptor tyrosine kinase inhibitors.

Key Words: EGFR TK inhibitor, G-protein coupled receptors, Inflammation, Cyclooxygenase-2, PGE2, Epithelial to mesenchymal transition, Drug resistance, NSCLC.

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Targeted therapies for non–small-cell lung cancer (NSCLC), such as epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI), have become important therapeutic options; however, the overall initial response rate is low and development of resistance is common.[1,2] It has recently been suggested that resistance to targeted therapies may be overcome by identifying optimal combinations of drugs that target specific molecules.[3–5]

Although underlying molecular mechanisms are not fully understood, substantial experimental data suggest a contributing role for inflammation in lung carcinogenesis.[6] Certain inflammatory mediators also pave the way for epithelial to mesenchymal transition (EMT), the developmental shift from a polarized epithelial phenotype to a highly motile mesenchymal phenotype essential in embryogenesis, organ development, and cancer progression.[7] Recent work indicates that the progression of EMT, including loss of E-cadherin, may also promote resistance to EGFR TKI in NSCLC. In contrast, restoration of gene expression associated with the epithelial phenotype can sensitize NSCLC cells to targeted therapies.[8–10] Thus, identifying the specific inflammatory signals governing EMT and EGFR TKI resistance maybe an important step toward expanding response to these agents.

The inflammatory enzyme cyclooxygenase-2 (COX-2) is frequently over-expressed in a variety of malignancies[11] and plays a multifaceted role in conferring malignant and metastatic phenotypes.[12] For example, COX-2 expression in NSCLC is associated with apoptosis resistance,[13] angiogenesis,[14,15] and metastasis.[16,17] These tumorigenic effects are, in part, mediated by the COX-2 metabolite, prostaglandin E2 (PGE2), which is abundant in the lung tumor microenvironment. Inflammatory and tumorigenic signaling often converges on the mitogen-activated protein kinase/extracellular signal-regulated kinase (MAPK/Erk) cascade.[18] EGFR transmits mitogenic signals from the cell surface to the nucleus by activating MAPK/Erk (Figure 1), and PGE2 induces rapid Erk phosphorylation in lung cancer cells.[19] Recent studies have shown that PGE2 and other inflammatory mediators derived from neoplastic as well as stromal and immune cells reduce tumor E-cadherin levels via MAPK/Erk-dependent upregulation of the transcriptional repressors zinc-finger E-box binding homeobox 1 (ZEB-1) and zinc-finger factor Snail homologue 1 (Snail) in NSCLC, whereas COX-2 inhibitors reverse this effect.[20,21] Loss of E-cadherin is a hallmark of EMT and is also associated with tumor progression and metastasis.[7,22] High E-cadherin expression or a gene signature associated with a mesenchymal rather than epithelial phenotype is associated with sensitivity to EGFR TKI in NSCLC.[8–10] Therefore, PGE2 or other inflammatory cytokines in the tumor microenvironment may contribute to EGFR TKI resistance in NSCLC by suppressing E-cadherin expression.

PGE2 exerts its effects through four G-protein coupled receptors (GPCRs) designated E-prostanoid receptors (EP) 1

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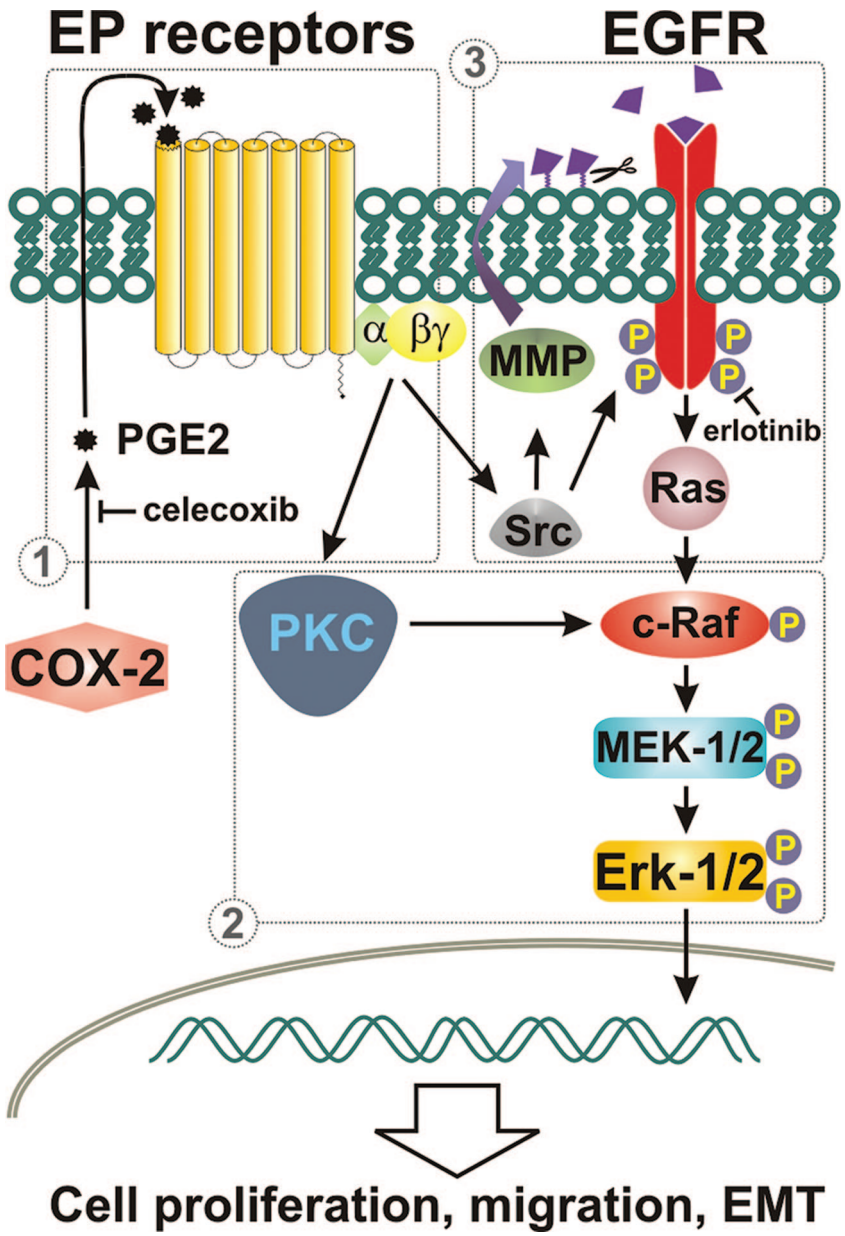

FIGURE 1. Mechanisms of EGFR-dependent and independent MAPK/Erk pathway activation by PGE2. Epidermal growth factor receptor (EGFR) belongs to the tyrosine kinase receptors family and is a major regulator of epithelial cell growth and proliferation. It also plays an important role in tumorigenesis by promoting cancer cell proliferation, invasion, and metastasis. The MAPK/Erk signaling module is located downstream of EGFR and is a critical effector of mitogenic signaling. PGE2 is a major COX-2 metabolite abundantly present in the cancer microenvironment that exerts its effects through four G-protein coupled receptors designated as EP1, EP2, EP3, and EP4 (area 1). PGE2 signaling can promote cell proliferation, migration, and EMT by directly activating intracellular mitogenic pathways or by stimulating proteolytic release of extracellular growth factor receptor ligands that activate the mitogenic cell-surface receptors. In NSCLC, PGE2-induced MAPK/Erk activation occurs by the intracellular pathway and is therefore EGFR-independent, encouraging resistance to EGFR TKI (area 2). In contrast, in colon cancer, PGE2 can induce EGFR ligand release, activating the receptor to increase MAPK/Erk signaling through a mechanism that is sensitive to EGFR inhibition (area 3). Here the scissors indicate MMP-induced release of cell membrane-bound EGFR ligands that can occur in colon cancer. Inhibition of COX-2 abrogates both EGFR-dependent and independent PGE2-induced MAPK/Erk activation in NSCLC (area 1). COX-2: cyclooxygenase-2 (selectively inhibited by COX-2 inhibitors such as celecoxib); PGE2: prostaglandin E2; EP: E-prostanoid receptors; α, β, and γ, G-proteins: components of the G-protein coupled receptors; EGFR, epidermal growth factor receptor (P indicates tyrosines phosphorylated upon receptor activation; this process is blocked by tyrosine kinase inhibitors such as erlotinib); Ras: Ras small guanosine triphosphatase; Raf: Raf serine/threonine kinase; MEK: MAPK/Erk kinase; Erk: extracellular signal-regulated kinase; PKC: protein kinase C; MMP: matrix metalloproteinase; EMT: epithelial to mesenchymal transition.