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Graphical Review

# Redox-dependent regulation of epidermal growth factor receptor signaling

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ABSTRACT

Tyrosine phosphorylation-dependent cell signaling represents a unique feature of multicellular organisms, and is important in regulation of cell differentiation and specialized cell functions. Multicellular organisms also contain a diverse family of NADPH oxidases (NOXs) that have been closely linked with tyrosine kinase-based cell signaling and regulate tyrosine phosphorylation via reversible oxidation of cysteine residues that are highly conserved within many proteins involved in this signaling pathway. An example of redox-regulated tyrosine kinase signaling involves the epidermal growth factor receptor (EGFR), a widely studied receptor system with diverse functions in normal cell biology as well as pathologies associated with oxidative stress such as cancer. The purpose of this Graphical Redox Review is to highlight recently emerged concepts with respect to NOX-dependent regulation of this important signaling pathway.

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**Contents**



## 1. Introduction

The epidermal growth factor receptor (EGFR) is a member of the extensively studied ErbB receptor tyrosine kinase family that plays important roles in cell growth, development, differentiation, cytoskeletal organization, and cell migration. The EGFR and other ErbB members are activated by a family of ligands which promote receptor homo- or heterodimerization resulting in autophosphorylation of intracellular tyrosine residues, thereby recruiting various adapter molecules and activating an array of downstream signaling cascades [1]. In addition to this canonical activation mechanism, EGFR is also frequently activated in a cross-talk mechanism by initial stimulation of G-protein coupled receptors (GPCRs), a large receptor family for diverse stimuli including proteins, peptides, lipids, amino acids, biogenic amines, and ions. Such EGFR *transactivation* occurs by two interrelated mechanisms, the first involving a “triple-membrane-passing-signal” in which GPCR activation leads to activation of membrane-bound matrix metalloproteases (MMPs) such as the ADAM (a disintegrin and metalloprotease) family, which subsequently promotes shedding of membrane-anchored EGFR ligands, allowing them to bind to ErbB receptors [2]. In addition, GPCR-dependent EGFR activation also involves ligand-independent mechanisms that result in direct EGFR phosphorylation and activation, which is mediated by intermediate activation of protein kinases that include the non-receptor Src family kinases (SFK) or protein tyrosine kinase 2 (Pyk2) (Fig. 1).

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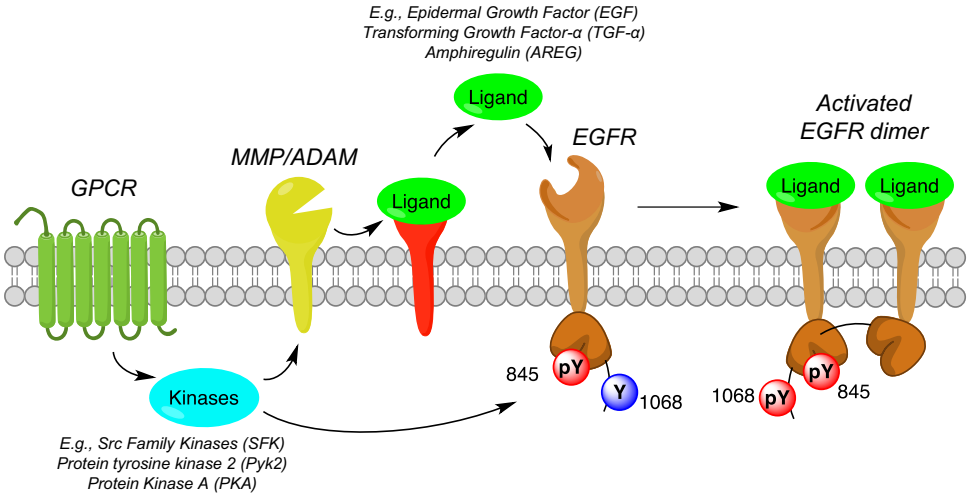


**Fig. 1.** Direct and indirect mechanisms of EGFR activation. Activation of EGFR by cognate ligands results in homo- or heterodimerization and autophosphorylation of intracellular tyrosine residues (e.g., Y1068) to initiate cellular signaling. EGFR is commonly activated indirectly by activation of GPCR (*transactivation*), which involves intermediate activation of protein kinases such as SFK, resulting in MMP/ADAM-dependent EGFR ligand shedding as well as direct phosphorylation of EGFR (Y845) to promote EGFR kinase activation.

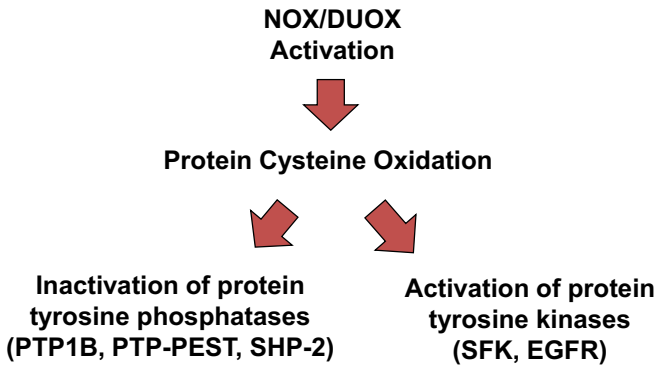


**Fig. 2.** Interrelationships between NOX/DUOX enzymes and protein tyrosine phosphorylation. Regulated activation of NOX/DUOX controls tyrosine phosphorylation by reversible oxidative modification of conserved cysteine residues with protein tyrosine phosphatases (resulting in inactivation) or in protein tyrosine kinases such as Src family kinases (SFK) or EGFR (which often enhances kinase activity).

## 2. Redox control of tyrosine kinase signaling

Tyrosine kinase-based signaling, including EGFR, is well-known to be subject to regulation by redox-dependent mechanisms at various levels [3] (Fig. 2). The coincidence of tyrosine phosphorylation as an important signaling mechanism in multicellular organisms with increased diversity in NADPH oxidase (NOX) isoforms, the major source of regulated ROS production, in these more complex organisms suggests an intricate relationship in the evolution of these systems [4,5]. Pioneering studies by Rhee and co-workers illustrated that activation of EGFR is associated with ROS production, which transiently inactivates protein tyrosine phosphatases (PTPs) to enhance or prolong EGFR activation [6]. Such redox-mediated PTP inactivation is due to oxidation of a susceptible conserved catalytic cysteine residue that is essential for phosphotyrosine hydrolysis [7]. More recent studies highlighted the importance of regulated ROS production by NOX family NADPH oxidases in site-specific PTP inactivation in spatially confined areas, e.g. by NOX4 in the ER [8] or NOX2 at sites of focal adhesion [9]. Indeed, such NOX-dependent PTP inactivation is now well appreciated in promoting EGFR-dependent signaling (Fig. 3A).

In addition to the well-documented negative regulation of PTPs by oxidative mechanisms, evidence is emerging that protein tyrosine kinases are also subject to more direct redox regulation [10]. This is best studied in the SFK family, which contain a number of conserved cysteines, whose oxidation either promotes or restricts kinase activity. The EGFR, like several other protein kinases, contains a non-catalytic nucleophilic cysteine (Cys797 within EGFR), localized in the hinge region of its catalytic domain, which is

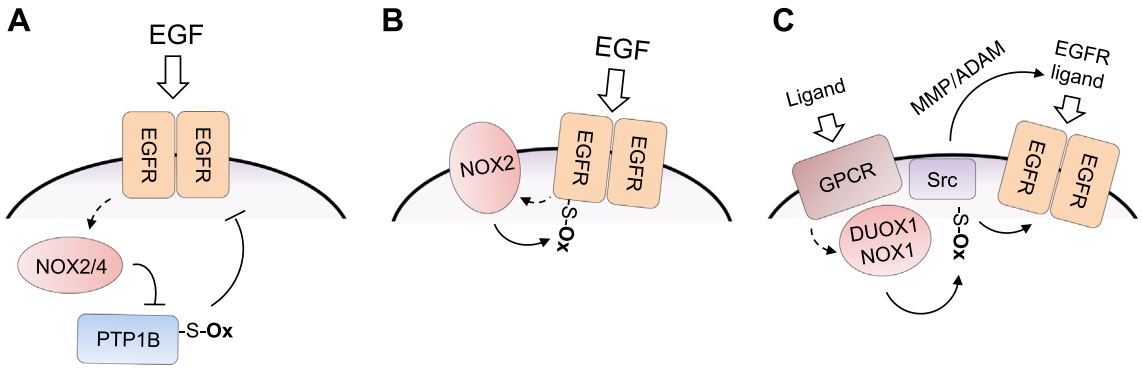


**Fig. 3.** Diverse modes of NOX dependent regulation of EGFR activation. (A) Ligand-induced EGFR activation is associated with transient cysteine oxidation (-S-Ox) within PTP1B through intermediate NOX activation (eg. NOX2 or NOX4), resulting in its inactivation and relieving its inhibitory action of EGFR tyrosine phosphorylation and activation. (B) Ligand-induced EGFR activation results in NOX2-dependent oxidation of a conserved cysteine within the EGFR kinase domain (Cys797), which is associated with enhanced kinase activity. (C) EGFR transactivation by GPCR stimulation (e.g., $P2Y_2R$) involves NOX activation (DUOX1 or NOX1) and cysteine oxidation within Src, which promotes Src activation and subsequent MMP/ADAM-dependent EGFR ligand shedding and as well as direct EGFR phosphorylation.

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