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Mini-review

Regulators of carcinogenesis: Emerging roles beyond their primary functions

Lin-Tao Jia [a,*,1], Rui Zhang [a,1], Lan Shen [a], An-Gang Yang [b,*]

[a] State Key Laboratory of Cancer Biology, Department of Biochemistry and Molecular Biology, Fourth Military Medical University, Xi'an, Shaanxi 710032, China
[b] Department of Immunology, Fourth Military Medical University, Xi'an, Shaanxi 710032, China

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ABSTRACT

Cancers are characterized by aberrant cell signaling that results in accelerated proliferation, suppressed cell death, and reprogrammed metabolism to provide sufficient energy and intermediate metabolites for macromolecular biosynthesis. Here, we summarize the emerging "unconventional" roles of these regulators based on their newly identified interaction partners, different subcellular localizations, and/or structural variants. For example, the epidermal growth factor receptor (EGFR) regulates DNA synthesis, microRNA maturation and drug resistance by interacting with previously undescribed partners; cyclins and cyclin-dependent kinases (CDKs) crosstalk with multiple canonical pathways by phosphorylating novel substrates or by functioning as transcriptional factors; apoptosis executioners play extensive roles in necroptosis, autophagy, and in the self-renewal of stem cells; and various metabolic enzymes and their mutants control carcinogenesis independently of their enzymatic activity. These recent findings will supplement the systemic functional annotation of cancer regulators and provide new rationales for potential molecular targeted cancer treatments.

Introduction

Cancer arises from diverse genetic variations and oncogenic signaling pathways, and many of the key players in carcinogenesis have been characterized [1,2]. Nevertheless, given the extensive crosstalk among cellular signaling pathways and the myriad connections among neoplastic cells with different phenotypes, it is to be expected that these pivotal regulators play multiple roles during carcinogenesis; these roles can be distinct from those initially characterized [2,3]. The "unconventional" roles of cancer regulators are fulfilled via several strategies which may be causally linked. Examples include activities mediated by newly identified interacting partners or substrates; unconventional subcellular location or translocation in response to upstream signaling; and unusual variants due to alternative transcription or translation, or protease processing of these regulators [1,4,5].

"Unexpected" substrates or interaction partners for the regulators

The hallmarks of autonomous neoplastic cell behavior include: 1) uncontrolled proliferation, i.e., cell cycle progression fueled predominantly by growth factor signaling; 2) resistance to physiological cell death, e.g., apoptosis; and 3) reprogramming of metabolism to facilitate rapid energy production and macromolecular biosynthesis. Therefore, the key regulators of malignancy may conceivably include growth factor receptors, cell cycle regulators, mediators of apoptosis, and drivers of metabolic reprogramming [6–9]. Recent studies have identified a large number of novel interaction partners for these well-documented cancer regulators [1,3].

Growth factor receptors

Growth factor receptors are single-transmembrane receptors that may have enzymatic (kinase or phosphatase) activity; alternatively, these proteins may be associated with intracellular enzymes [10]. Of particular importance in the context of oncogenesis are epidermal growth factor (EGF) and its specific receptor, EGFR [11,12]. EGF binding to the extracellular domain of EGFR induces the dimerization, autophosphorylation, and activation of the receptor, which subsequently activates canonical cellular signaling pathways including the Ras/MAPK, PI3K/Akt, phospholipase C (PLC), and

* Corresponding authors. Tel.: +86 29 84774528; fax: +86 29 84773947.
E-mail address: lintaojia73@163.com (L-T. Jia); agyang@fmmu.edu.cn (A-G. Yang).
[1] These authors contributed equally to this work.

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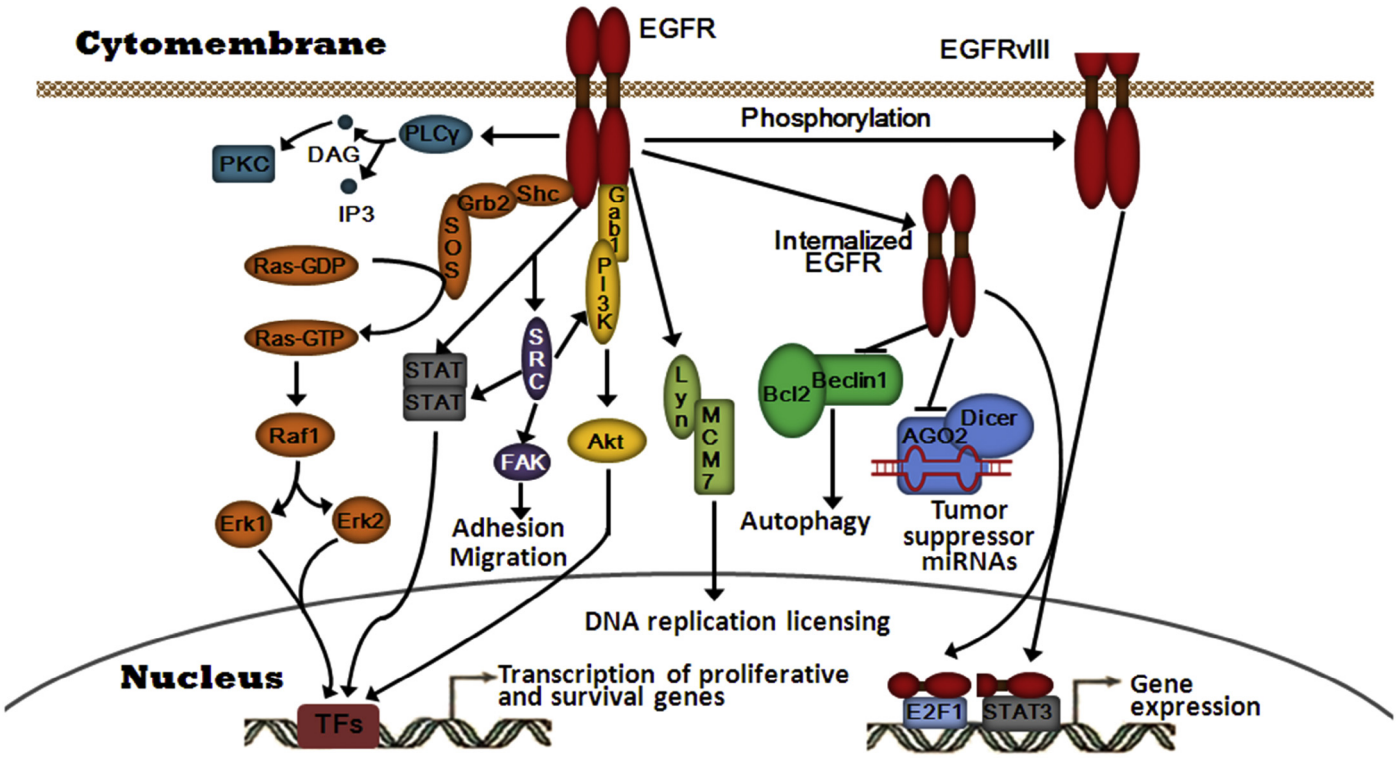

Fig. 1. An updated model of the EGFR signaling pathway. In addition to the classical Ras/MAPK and PI3K/AKT pathways and the activation of Src and PLCγ, EGFR phosphorylates and activates Lyn to license DNA replication in mitosis. Endocytosed EGFR also phosphorylates Beclin 1 to suppress autophagy, and inhibits the maturation of a class of tumor suppressor miRNA by phosphorylating AGO2. EGFRvIII, a ligand-independent variant of EGFR, can be phosphorylated and activated by EGFR; both nuclear EGFR and EGFRvIII can modulate gene expression by directly associating with transcriptional factors on related chromosomal loci.

Src pathways [13]. Aberrant or excessive EGF/EGFR signaling is common in a wide range of cancers [14].

The substantial involvement of the EGF/EGFR pathway in carcinogenesis is far from being fully explained by the interaction partners documented to date [13,15]. For example, until recently it was unclear how EGFR directly regulates DNA synthesis, which is required for cell division [15,16]. Huang et al. established that activated EGFR binds to and phosphorylates the p56 isoform of the tyrosine kinase Lyn, which then phosphorylates MCM7, a licensing factor critical for DNA replication [16]. This phosphorylation increases the association between MCM7 and other minichromosome maintenance complex proteins, thereby promoting assembly of the DNA synthesis complex and cell proliferation [16].

The EGF/EGFR pathway is also crucially involved in other cellular events. First, the pathway plays a role in regulating microRNAs (miRNAs), which are themselves critically involved in regulating carcinogenesis [17,18]. Intriguingly, EGFR binds and phosphorylates the RNA-induced silencing complex (RISC) component, Argonaute 2 (AGO2), in response to hypoxia; this interaction suppresses the association between Dicer and AGO2 and inhibits the generation of mature miRNAs from precursor miRNAs [17,19]. Because Dicer prefers to bind to the long-loop structure of precursor miRNAs, this hypoxia-induced mechanism specifically downregulates long-loop miRNAs, most of which are tumor suppressors, resulting in increased cell survival and invasiveness [19]. Second, EGFR influences autophagy (literally "self-eating"), a catabolic process involved in maintaining the homeostasis of protein aggregates and organelles [20,21]. In lung carcinoma cells, activated EGFR directly binds to and phosphorylates Beclin 1, a crucial mediator of autophagy. Consequently, activity of the Beclin1-associated VPS34 kinase is suppressed, thereby reducing autophagy but increasing tumor growth and resistance to tyrosine kinase inhibitors (TKIs) [22]. Third, in glioblastoma cells, EGFRvIII, a ligand-independent, constitutively-active variant of EGFR, is phosphorylated by wild-type EGFR, resulting in nuclear translocation of EGFRvIII. The resultant nuclear EGFRvIII then binds to and phosphorylates STAT3 in cooperation with EGFR, providing evidence that crosstalk between EGFR and its variants plays a role in carcinogenesis and resistance to TKI treatment [23]. Together, these novel interaction partners of EGFR add weight to the intricate roles played by the EGF/EGFR pathway during carcinogenesis (Fig. 1).

Other growth factor receptors with newly recognized signaling partners include fibroblast growth factor receptor (FGFR), hepatocyte growth factor receptor (HGF/Met), and placental growth factor (PIGF) receptor [24–26]. A fusion between FGFR and transforming acidic coiled-coil (TACC) protein has been detected in a small subset of glioblastomas [25]. The resulting chimeric protein has constitutive kinase activity, but is unable to activate classical FGF pathways; instead, it localizes to mitotic spindle poles, triggering mitotic and chromosomal segregation defects and aneuploidy by interacting with as-yet-unidentified proteins that have not yet been identified [25]. Met binds to the insulin receptor (INSR) and reinforces insulin signaling, through which it promotes hepatic glucose uptake and suppresses hepatic glucose output [24]. PIGF, a member of the vascular endothelial growth factor (VEGF) family, promotes medulloblastoma by engaging a membrane co-receptor, neuropilin 1 (Nrp1), rather than the documented VEGF receptor 1 (VEGFR1); the interaction between the Nrp1 intracellular domain and an unknown downstream partner is required for its role in carcinogenesis [26]. These findings provide novel evidence for the divergent roles of growth factor signaling in the development of cancer.