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Review

Regulation of the ErbB network by the MIG6 feedback loop in physiology, tumor suppression and responses to oncogene-targeted therapeutics

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ABSTRACT

The ErbB signaling network instructs the execution of key cellular programs, such as cell survival, proliferation and motility, through the generation of robust signals of defined strength and duration. In contrast, unabated ErbB signaling disrupts tissue homeostasis and leads to cell transformation. Cells oppose the threat inherent in excessive ErbB activity through several mechanisms of negative feedback regulation. Inducible feedback inhibitors (IFIs) are expressed in the context of transcriptional responses triggered by ErbB signaling, thus being uniquely suited to regulate ErbB activity during the execution of complex cellular programs. This review focuses on MIG6, an IFI that restrains ErbB signaling by mediating ErbB kinase suppression and receptor down-regulation. We will review key issues in MIG6 function, regulation and tumor suppressor activity. Subsequently, the role for MIG6 loss in the pathogenesis of tumors driven by ErbB oncogenes as well as in the generation of cellular addiction to ErbB signaling will be discussed. We will conclude by analyzing feedback inhibition by MIG6 in the context of therapies directed against ErbB and non-ErbB oncogenes.

Contents

Abbreviations: RTK, receptor tyrosine kinase; EGF, epidermal growh factor; EGFR, epidermal growth factor receptor; LRIG1, leucin-rich repeats and immunoglobulin-like domains1; MIG, 6mitogen inducible gene 6; RALT, receptor associated late transducer; ERRFI1, ErbB receptor feedback inhibitor 1; SOCS, suppressor of cytokine signaling; EBR, ErbB binding region; TKD, tyrosine kinase domain; ARF, ADP-ribosylation factor; RED, RALT endocytic domain; CBL, casitas B-lineage lymphoma; HGF, hepatocyte growth factor; PDGF, platelet-derived growth factor; FGF, fibroblast growth factor; GPCR, G-protein coupled receptor; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; ERK, extracellular signal-regulated kinase; FOS, FBJ osteosarcoma oncogene; AP-1, activator protein 1; LPA, lysophosphatidic acid; FOXO, forkhead box, subgroup O; EMT, epithelial-mesenchimal transition; UTR, untranslated region; HSP, heat shock protein; TKI, tyrosine kinase inhibitor; NSCLC, non-small cell lung carcinoma; IHC, immuno-hystochemistry; GBM, glioblastoma multiforme; TGFβ, transforming growth factor beta; PTEN, phosphatase and tensin homolog; SMAD, similar to mothers against decapentaplegic; CRC, colorectal cancer; DMBA, dimethylbenzantracene; DNMT, DNA methyl-transferase; PTC, papillary thyroid carcinoma.

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1. Introduction

In mammals, the ErbB family of receptor tyrosine kinases (RTKs) is composed by four members, namely the archetypal epidermal growth factor receptor (EGFR, also known as HER or ERBB1), ERBB2, ERBB3 and ERBB4. The structural organization of ErbB receptors features an extracellular ligand binding domain connected via a single-pass transmembrane segment to the intracellular domain, which consists of a tyrosine kinase domain (TKD) flanked by a juxtamembrane and C-terminal regulatory regions. ErbB RTKs adopt a default inactive conformation, which is relieved by ligand binding and attendant formation/stabilization of receptor dimers. Dimerization initiated in the extracellular space is transmitted across the plasmamembrane and leads sequentially to asymmetric dimerization between juxtaposed TKDs, catalytic activation, phosphorylation of Tyr residues located in the receptor C-terminal tail and downstream signal transduction [1] (Fig. 1B). Exceptions to this general model are ERBB2, unable to bind ligands and yet prone to promiscuous dimerization with any ligand-bound ErbB RTK, and ERBB3, which has impaired kinase activity and can therefore signal only upon hetero-dimerization with and cross-phosphorylation by catalytically competent ErbB RTKs [2]. Eleven ligands can bind to ErbB RTKs with different specificities/affinities, thus driving formation of combinatorial ErbB dimers endowed with partly distinct signaling properties, a functional organization which has been conceptualized as signaling network [2].

Activated ErbB receptors instruct the execution of key cellular programs such as cell survival, proliferation and motility. However, excessive ErbB signaling may disrupt tissue homeostasis and lead to cell transformation [3,4]. Developmental studies in worms [5] and flies [6] were the first to show that normal cells guard themselves against the threat inherent to excessive ErbB activity by elaborating negative signals capable of limiting the strength and duration of receptor activity. These findings motivated follow-up studies aimed at dissecting the molecular bases of negative signaling to ErbB RTKs in mammalian cells, also in view of the ascertained role of ErbB RTKs as oncogenes [4] and the consequent proposition that negative regulators of ErbB RTKs could act as tumor suppressors.

Among negative regulators of ErbB RTKs, an operational distinction can be drawn on the basis of their requirement for novel protein synthesis [7]. Protein synthesis-independent feedback inhibitors pre-exist receptor triggering and readily target activated ErbB RTKs. For instance, upon ligation by EGF, the EGFR is immediately bound by CBL proteins, which drive EGFR ubiquitylation and ensuing down-regulation [8]. A second class of negative feedback regulators becomes expressed in the context of transcriptional programs regulated by ErbB signaling and integrate over time the activity of protein synthesis-independent regulatory loops [9]. Four inducible feedback inhibitors (IFIs), namely LRIG1, MIG6 (also known as RALT or ERRFI1 according to the HUGO gene nomenclature) and SOCS4/5 were identified as ErbB suppressors in mammalian cells [9]. The demonstration that Mig6 [10] and Lrig1 [11–13] play a necessary role in preventing Egfr-driven tissue overgrowth in several mouse tissues provided compelling genetic evidence for the biological relevance of ErbB IFIs in mammalian organisms and raised interest in addressing their role as tumor suppressors.

Cardinal features of ErbB IFIs have been reviewed elsewhere [9]. Here, we focus on MIG6, which has been the most intensively studied among all ErbB IFIs. We will review our current understanding of how MIG6 regulates the signaling activity of ErbB receptors and then elaborate on how loss of MIG6 expression in cancer cells may foster the ability of ErbB RTKs to act as driver oncogenes. Because the plasticity of the ErbB network has emerged as a recurrent cause of clinical resistance to targeted therapeutics directed against ErbB and *non*-ErbB oncogenes [4], we will conclude by elaborating on how loss of MIG6 is expected to foster ErbB-driven resistance to targeted therapies.

2. Molecular mechanisms underpinning the function of MIG6 as suppressor of ErbB receptors

2.1. MIG6 binds to the kinase domain of ErbB RTKs to suppress their catalytic activation

MIG6 interacts directly with ligand-activated ErbB RTKs through an evolutionarily conserved modular domain named EBR (ErbB binding region) (Fig. 1). The EBR interacts with the TKD of catalytically active ErbB receptors, namely EGFR, ERBB2 and ERBB4 [14,15]. ERBB3 does not bind directly to the MIG6 EBR; however ERBB3 could be co-immunoprecipitated with MIG6 in the context of ligand-driven ERBB2:ERBB3 heterodimers, most likely because recruited by the ERBB2 kinase [14].

Results from functional and structural studies indicate that the MIG6 EBR consists of two modules, named segments 1 and 2 [16] (henceforth referred to as S1 and S2). S1 binds to an extended surface, located in the distal portion of the C lobe of the EGFR TKD and largely super-imposable to that responsible for the binding of the donor TKD to its receiver partner [17]. S2, instead, contacts the active site of the EGFR TKD and becomes phosphorylated on Tyr 394 by EGFR itself (see Fig. 1 for details). Tyrosine phosphorylated S2 remains bound to the TKD active site as part of a β-hairpin-like structure, which prevents substrate phosphorylation and stabilizes the EBR:EGFR interaction [18]. In aggregate, recruitment of MIG6 EBR onto the EGFR TKD is envisioned to (a) cause immediate termination of EGFR catalytic activity via peptide-substrate competition enforced by S2 [18]; (b) preclude further allosteric activation of kinase dimers via S1 [16], should asymmetric dimers break apart and reform.

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