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Review

Interplay between receptor tyrosine kinases and hypoxia signaling in cancer

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ABSTRACT

Deregulated signaling *via* receptor tyrosine kinase (RTK) pathways is prevalent in numerous types of human cancers and is commonly correlated with worst prognosis, resistance to various treatment modalities and increased mortality. Likewise, hypoxic tumors are often manifested by aggressive mode of growth and progression following an adaptive genetic reprogramming with consequent transcriptional activation of genes encoding proteins, which support tumor survival under low oxygen-related conditions. Consequently, both the hypoxia-inducible factor (HIF) system, which is the major mediator of hypoxia-related signaling, and numerous RTK systems are considered critical molecular targets in current cancer therapy. It is now evident that there is an intricate molecular crosstalk between RTKs and hypoxia-related signaling in the sense that hypoxia can activate expression of particular RTKs and/or their corresponding ligands, while some RTK systems have been shown to trigger activation of the HIF machinery. Moreover, signaling regulation of some RTK systems under hypoxic conditions has also been documented to take place in a HIF-independent manner. With this review we aim at overviewing the most current observations on that topic and highlight the importance of the potential co-drugging the HIF system along with particular relevant RTKs for better tumor growth control.

Contents

Abbreviations: ARNT, aryl hydrocarbon nuclear translocator; BCRP, breast cancer resistant protein; CAD, C-terminal activation domain; CAIX, carbonic anhydrase IX; CAV1, caveolin-1; ccRCC, clear cell renal cell carcinoma; CSC, cancer stem cells; DAG, diacylglycerol; DUSP2, dual specificity phosphatase 2; EGF(R), epidermal growth factor (receptor); EMT, epithelial–mesenchymal transition; FGF(R), fibroblast growth factor (receptor); GAS6, growth arrest-specific 6; GDNF, glial-derived neurotrophic factor; GTP, guanosine triphosphate; GTPases, guanosine triphosphatases; HCC, hepatocellular carcinoma; HGF, hepatocyte growth factor; HIF, hypoxia-inducible factor; HNSCC, head and neck squamous cell carcinoma; HRE, HIF-responsive element; HUVECs, human umbilical vein endothelial cells; IGF(R), insulin-like growth factor (receptor); IR, insulin receptor; IRES, ribosome entry sites; IRS, insulin receptor substrates; MAPK, mitogen-activated protein kinase; miRNA, microRNA; MSP, macrophage stimulating protein; mTOR, mammalian target of rapamycin; Necl-2, nectin-like molecule-2; NF-kB, nuclear factor-kB; NRG-1, neuregulin-1; NSCLC, non-small cell lung cancer; PDGF(R), platelet-derived growth factor (receptor); PHD, prolyl hydroxylase; PI3K, phosphatidylinositol 3-kinase; PKA, protein kinase A; PKC, protein kinase C; PLCγ, phospholipase Cγ; PP2A, protein phosphatase-2A; RACK1, receptor for activated protein kinase C; RCC, renal cell carcinoma; RON, recepteur d'origine nantais; ROS, reactive oxygen species; RTK, receptor tyrosine kinase; TGFα, transforming growth factor α; Top, topoisomerase; uPA, urokinase-type plasminogen activator; UTR, untranslated region; VEGF(R), vascular endothelial growth factor (receptor); VHL, Von Hippel-Lindau; VSMS, vascular smooth muscle cells.

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1. Introduction

Receptor tyrosine kinases (RTKs) are cell surface proteins responsible for a tight regulation of a broad spectrum of downstream intra-cellular processes (Pierce and Keating, 2014). All RTKs are similarly structured, with a ligand binding region in the extracellular domain, a single transmembrane helix and a cytoplasmic region that comprises the protein tyrosine kinase domain as well as additional carboxy-terminal and juxtamembrane regulatory regions (Lemmon and Schlessinger, 2010). Following growth factor binding, the extracellular region undergoes self-association, guiding the intracellular domains into a dimeric conformation, which activates their tyrosine kinase enzymatic activity. One or more tyrosines in one receptor within the dimer are trans-phosphorylated by an adjacent RTK. The phosphorylated receptor subsequently recruits intracellular adaptor and transducing effectors, leading to cascades of signaling events that control growth, proliferation, differentiation and migration (Pierce and Keating, 2014; Lemmon and Schlessinger, 2010; Ullrich and Schlessinger, 1990).

Aberrant activity of RTKs is a hallmark of a wide range of human cancers and frequently correlates with poor prognosis (Choura and Rebai, 2011; Casaletto and McClatchey, 2012). In normal cells, activation of RTKs and downstream signaling pathways is reversible and tightly regulated, whereas in cancer cells, RTKs acquire transforming functions due to activating mutations, gene amplification-dependent or -independent overexpression and aberrant autocrine/paracrine loops (Paul and Mukhopadhyay, 2004). Many cancers of different histotypes often harbor genetic alterations in either RTKs themselves or in transducing elements of their downstream pathways, resulting in deregulated signaling output (Niederst and Engelman, 2013; Hanahan and Weinberg, 2011). Consequently, numerous RTK systems represent attractive therapeutic targets (Takeuchi and Ito, 2011) with two leading approaches that have been translated into clinically-relevant modes to inhibit their corresponding signaling: monoclonal antibodies against the receptor itself or against the putative ligand and small-molecule inhibitors that block the receptor catalytic activity (Gherardi et al., 2012). Although the proof of principle of RTK-targeted therapy has been well documented, acquired resistance to anti-RTKs agents ultimately develops (Rosenzweig, 2012). Drug resistance usually arises through point mutations within the kinase domain, gene amplification or overexpression, or through activation of downstream bypass signaling pathways (Yi-fan and Li-wu, 2011).

Another fundamental biologic feature, which is largely involved in aggressive manifestations of tumor growth and progression, is hypoxia. Solid tumors often become hypoxic when new blood vessels associated with tumor growth develop irregularly, resulting in poor blood flow and subsequent inefficient delivery of oxygen (Harris, 2002). Poor oxygenation induces a series of cellular physiologic adaptations that are largely mediated *via* the hypoxia-inducible factors α (HIF-α's) transcription system that sustains and fosters tumor survival (Multhoff et al., 2014; Michieli, 2009). Mammalian HIF-α subunits are encoded by three distinct genes: *HIF-1α*, *HIF-2α*, and *HIF-3α*. HIF-1α is the most ubiquitously expressed, whereas HIF-2α and HIF-3α exhibit a more restricted tissue distribution (Ruan et al., 2009). Under normoxic conditions, oxygen-dependent prolyl-hydroxylases (PHDs) covalently modify the hypoxic response subunit HIF-1α, converting it to a hydroxylated form, which subsequently undergoes ubiquitination by the von Hippel-Lindau (VHL) E3 ubiquitin ligase and eventual proteasome-dependent degradation (Harris, 2002). In the presence of low oxygen concentrations, PHDs are inhibited, preventing HIF-1α from being degraded. Hence, HIF-1α accumulates in the nucleus, where it associates to the constitutively expressed HIF-1β subunit (also known as the aryl hydrocarbon nuclear translocator (ARNT)). This complex activates gene transcription by binding to specific HIF-responsive elements (HREs) of target genes, which are activated under hypoxic conditions (Boccaccio and Comoglio, 2006).

Under normal physiologic conditions, as during embryogenesis, hypoxia favors the generation of niches that preserve optimal conditions for the maintenance of pluripotent cells (Boccaccio and Comoglio, 2006). Low oxygen tension contributes to both physiologic stemness and invasive growth, traits, which when aberrantly develop in tumor cells, lead to an aggressive malignant phenotype (Boccaccio and Comoglio, 2006).

As to signaling interplays between hypoxia and RTKs pathways, the activation of vascular endothelial growth factor receptor (VEGFR) *via* HIF-mediated VEGF transcriptional activation and consequent accelerated tumor angiogenesis and systemic dissemination, represents one of the first described examples in that respect (Forsythe et al., 1996). In this review, we aim at discussing the far broader emerging molecular crosstalk between RTKs activity and tumor hypoxia, which are important to understand the complex mechanisms that confer aggressive manifestation of hypoxic tumors.

2. Hypoxia-induced regulation of RTK signaling

Numerous genes, including those encoding for RTKs and their ligands and whose expression is regulated under hypoxic conditions, either directly by HIF-1α and HIF-2α transcriptional activation or by distinct hypoxia-driven mechanisms, have been identified and described using expression profiling studies (Denko et al., 2000; Koong et al., 2000; Wykoff et al., 2000a; Lal et al., 2001). In this chapter, we will focus on RTK systems that are transcriptionally activated by HIF-1α and HIF-2α and we will also describe HIF-1α- and HIF-2α-independent mechanisms that were shown to stimulate RTKs signaling under hypoxic conditions (Fig. 1).

2.1. Induction of RTK ligands

Low oxygen tension has been associated with elevated production of several RTK ligands. In that respect, expression of vascular endothelial growth factor-A (VEGF-A) was shown to be induced by hypoxia in most cell types (Harris, 2002; Simiantonaki et al.,