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Quantified Indices Determine Differential Qualitative Phenomena in Performance Dynamics of the Erbb Receptor Network



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Abstract

Deeply embedded cellular systems that arise as transmembrane receptivity of the ERBB family of receptors operate in terms primarily of quantitative modulation of the intra-cytoplasmic and especially of the intra-nuclear dimensions of cooperative performance attributes. Such attributes implicate important roles for both activating and de-sensitizing events within a milieu that is profoundly operative with respect to juxtacrine and paracrine extracellular domains and that include the transduction and transmodulation in many instances of ERBB receptors in cases of malignant transformation. Summation of quantitative indices is conducive to strictly qualitative differentiation of effector and activator mechanisms as indicated by such systems as the constitutive activities of the mutant EGFR vIII receptor in glioblastoma. Quantitation determines qualitative effects in stimulus response.

Introduction

The HER (ERBB) network of receptors constitutes a transducing and transmodulating series of mechanisms that may at times exert potent intra-nuclear and also intra-cytoplasmic effects. Management of human epidermal growth factor receptor-2-positive (HER2+) breast cancer patients includes combined adjuvant chemotherapy and trastuzumab [1]. It forms heterodimers in a manner that is conducive towards the rendering of quantitative and qualitative modes of activation within a specific or broader context of the intracellular milieu. It appears that extracellular growth factor heregulin expression defines a drug-tolerant cancer cell phenotype that persists in most solid tumors and may contribute to rapid clinical progression [2]. Indeed, a broader range of effects may result due especially to a rich variety of co-activators and co-suppressors in terms of the induction of transcription and secondary post-translational protein modifications in the cell. Using two antibodies to block the HER2 receptor or combinatorial approaches with HER2 antibodies and standard therapies have provided additional therapeutic benefits [3]. The metabolites secreted by probiotic bacteria down regulate the expression of ERBB-2 and ERBB-3 genes in colon cancer cells [4].

Plasma Membrane Receptivity

The ERBB/HER family comprises four distinct tyrosine kinase receptors and trigger essential functions that include differentiation, survival, proliferation and cell migration [5]. There develops a series of pathways that may be based on plasma membrane receptivity or else a series of shuttle mechanistic steps that by-pass canonical intra-cytoplasmic pathways to eventually induce transcriptional modifications within the nucleus. Signaling pathways that underlie activation of receptor tyrosine kinases converge at the nuclear factor-kappaB node, and hypoxic, inflammatory and free radicals exacerbate pathway effects [6]. Within the cytoplasm, altered mitochondrial dynamics may exert effects on the pro- or anti-apoptotic pathways. A significant proportion of patients with breast cancer still experiences progression of the disease after receiving trastuzumab [7].

Heterodimerization is particularly significant as effector pathways of the ERBB receptors since activating and activated dimer members include phosphorylation of the large kinase domains of the intra-cellular portion of the membrane-based phenomena in particular. HER2/hErbB2 is an exceptional case

and occurs in one fixed overall open conformation and thus resembles the ligand-bound form of the other ERBB receptors [8]. Pathologic complete response has been suggested as a surrogate marker for the prediction of long-term clinical benefits, and microRNAs are recognised biomarkers of breast cancer progression [9]. Both immunohistochemistry and fluorescence in situ hybridisation (FISH) should be used for HER2 assessment [10].

Mechanistic Pathways

There develops a dual series of mechanistic pathways with contrasting dynamics that involve plasma membrane receptors on the one hand, and a non-canonical number of pathways that target the nuclear membrane and intra-nuclear micro-environment. The Nuclear Localization motif allows for such targeting to act in concert with co-adaptors and co-effectors in activating transcription of genes. Such a phenomenon obligates both activator and repressor pathways in RNA modulation in terms of gene expression and in the protein secondary modifications that include phosphorylation as well. De-sensitization of ERBB receptors may utilize endocytosis and the intra-vesicular localization of the receptors within early endosomes and late endosomes as the intra-vesicular pH decreases and hydrolytic enzyme complexes become concentrated within the multi-locular vesicles. Prior phosphorylation of the receptors allows for endocytotic machinery to promote degradation. Recycling of the receptors is integral to the proposed construction and recycling of the receptors based on the plasma membrane.

Intra-Nuclear Events

The intra-nuclear localization of the receptor cargo allows for targeting of a whole variety of genes in a manner that is specific and deterministic towards differential responses such as migratory versus proliferative effectors pathways. Serum HER2 when elevated is associated with worse prognosis that is independent of the HER2 status of the tumor; it does not, however, provide additional prognostic information in patients with circulating tumor cell status [11].

The contrasting evolution of receptor pathways allows for induced onset based primarily on the ERBB2 heterodimerization of "half receptors" situated primarily in the plasma membrane. Dynamics of such dimerized receptors are coated by the clathrin-enveloped vesicles arising from caveolae that subsequently pinch off from the membrane micro-domains. The clathrin coat is shed and the receptor is immersed within the intra-cellular milieu. Various stimuli besides ligand binding to the receptor operate within such milieu arising initially from the plasma membrane and may include mechanical, chemical, oxidative stress, nitric oxide and various other stimulants in transmodulation of the receptors.

Transduction arises as inter-type receptivity in terms of a wide variety of membrane receptors that interact with such systems as ERBB2, ERBB3 and ERBB4 that may modulate

such receptivity. The ERBB family of receptor tyrosine kinases mediates activation of a wide network of signaling pathways; ERBB3 has weak kinase activity but contributes significantly to proliferative signaling [12] through its six kinase domains.

Phosphorylation

Phosphorylation of the tyrosine kinase domains found in the large intracellular cytoplasmic tail of the ERBB receptor allows for both activation of the receptors and also for regulation by the endocytotic de-sensitizing mechanism. On the other hand, cleavage of the extra-cellular domain by such effectors as matrix metalloproteases adds layers of regulation of the often potent actions of the ERBB receptors. ERBB receptors are over expressed or mutated in many types of cancer including breast, ovarian and non-small cell lung cancer; over expression and over activation of these receptors are related to poor prognosis, drug resistance, and lower rates of survival [13].

There hence emerges a multi-layered and embedded series of regulating and modulating events in the creation of waves of modulation of the ERBB receptor activation pathways that further contribute to differential intra-cellular response. Fra-1 not only plays an essential role as a transcription factor in breast cancer but also drives expression of a highly prognostic gene set [14]. Particularly significant is ligand binding in increased degree and also amplified gene action to increase receptivity and to increase receptor numbers within the plasma membrane. mTOR is over-active in multiple cancer types including breast cancer and may implicate mTOR mutations or increased activity of ERBB family receptors; PI3K signaling may be mutated or altered [15]. Such phenomena allow for quantitative and qualitative differential effects in a manner that selectively induces intra-cytoplasmic and intra-nuclear events.

Differential Actions

Such a concept of differential actions arises as quantified strata of effects that permit the creation of qualitative differences in receptor-induced phenomena. Such a premise is supported by the multi-layered induction of events that may accentuate and also de-sensitize systems of cooperative response within the cytoplasm and especially within the nucleus of particular significance is the bi-lobed kinase domain of the intra-cellular cytoplasmic tail of heterodimerized ERBB2 receptors that allow switching of the C and N lobes of the kinase domains as activating and activated modulators of the receptor action. HER2 signaling regulates its localization and membrane retention and involves formation and/or maintenance of multi-protein signaling complexes that prolong HER2/EGFR or HER2/HER3 signaling by inhibiting HER2 ubiquitination and internalization [16].

Constitutive Action

Constitutive activation of the receptor is based on the ligand-less activation of the receptors that allows for instability of the kinase domains in response to loss of symmetry and the rotation

of the juxta-membrane portion of the trans-membrane receptors. Such destabilization permits the evolutionary role of mutant EGFR vIII to operate in the absence of ligand binding to the receptor. Mutated EGFR vIII is commonly found in glioblastoma and to a lesser extent in various epithelial cancers that permit constitutional activation to operate in increased quantitative excess in order to secondarily induce differential qualitative actions within the target cells.

Scaffold Proteins

Co-adaptor and co-effector scaffold proteins play an essential role in such quantitative phenomena that propagate effects of the activated receptors as induced for example in non-small-cell lung cancer. Such dimensional expression of quantitative and excessively expressed ERBB receptor activation accounts for the otherwise fine-tuning and fine-grained effects within normal cells, but also allows for highly differential actions within cells that modulate cell cycling, migration, and even receptivity to various phenomena of diverse ligand-binding. It is further to such reconstruction of generic stimuli arising through juxtacrine and paracrine activities in the extra-cellular milieu that ERBB receptors come to play profound inducing and permissive activities.

Conclusion

Dimensions of differential distinction between constitutive and ligand-binding receptivity of the ERBB receptor network operate essentially towards both a sensing and de-sensitizing milieu of receptivity that quantitatively determines effects of distinctive constitutive versus responsive ligand-binding ERBB receptors. Quantitation of the series of ongoing pathway networks involves also de-sensitizing pathways as constituted by ubiquitination and subsequent endocytosis. Performance dimensions include the realization of protein post-translation modifications such as phosphorylation of the kinase domains in a manner that is permissive and modulating in its own right. Highly differential activity results in the acquisition of cellular modes of response in terms of ongoing pathways of network amplification that secondarily translate as suppressor or oncogene patterns of activity.

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