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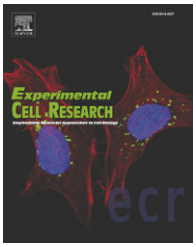

Review

Trafficking of receptor tyrosine kinases to the nucleus

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ABSTRACT

It has been known for at least 20 years that growth factors induce the internalization of cognate receptor tyrosine kinases (RTKs). The internalized receptors are then sorted to lysosomes or recycled to the cell surface. More recently, data have been published to indicate other intracellular destinations for the internalized RTKs. These include the nucleus, mitochondria, and cytoplasm. Also, it is recognized that trafficking to these novel destinations involves new biochemical mechanisms, such as proteolytic processing or interaction with translocons, and that these trafficking events have a function in signal transduction, implicating the receptor itself as a signaling element between the cell surface and the nucleus.

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Introduction

Growth factor binding to a cognate receptor tyrosine kinase (RTK) initiates receptor activation of several well-described signal transduction pathways that relay biochemical signals to points of signal reception, such as promoter elements in the nucleus, to effect cellular responses [1]. While receptor activation of these pathways occurs predominantly at the cell surface, there are data indicating that signal transduction also occurs from intracellular RTKs [2,3]. Coincident with the initiation of cell surface signaling, growth factor:receptor complexes translocate to clathrin-coated pits and are rapidly internalized as endosomal complexes. Subsequently, the intracellular receptors, which remain active for several minutes, are trafficked to the lysosome where both ligand and receptor are degraded. While the lysosome is the predominant destination and the trafficking pathway to it is reasonably well understood, it is also clear, depending on cell content, that internalized receptors can be recycled to the cell surface [3].

More recently, evidence has accumulated to support the trafficking of the RTKs from the cell surface to other intracellular destinations: cytoplasm, nucleus, and mitochondria. There is, in some instances, mechanistic information regarding the trafficking route, as well as data pertaining to biologic significance. It is the focus of this review to summarize these results. Mechanisms that involve secretase-mediated RTK cleavage are addressed first followed other less extensively understood mechanisms. As ErbB-1 and ErbB-4 are the best understood examples, they will be described in more detail.

γ-Secretase-dependent trafficking

The role of secretase-dependent processing of cell surface molecules is most clear in the case of Notch [4]. In this case, ligand-binding initiates sequential proteolytic processing by α-secretase, which removes the ectodomain, and by γ-secretase, which cleaves within the transmembrane domain of the cell-associated receptor fragment to release an intracellular domain (ICD) fragment into the cytosol. The ICD subsequently escorts a transcription activation factor into the nucleus to initiate a cellular response to the ligand.

The Notch scenario is recapitulated to different extents by several RTKs, as indicated in Table 1. In the case of ErbB-4, all essential steps are repeated and the ErbB-4 data are reviewed below and illustrated in Fig. 1. Secretase processing is reported for several other RTKs (ephrin, CSF-1R, VEGFR1, Tie1, plus preliminarily for the insulin and IGF-1 receptors) and these data are also discussed. It should be mentioned that the list can be expected to lengthen as additional RTKs are known to be subject to ectodomain cleavage and this is a necessary precursor step for intramembranous cleavage by γ-secretase. Since biochemical detection of ICD fragments is known to be problematic, as these fragments are produced in substoichiometric amounts and are metabolically labile, more effective antibodies or protocols may be required.

In addressing these examples of RTK intramembranous cleavage two points are emphasized. First, is the cleavage process stimulatable by a ligand? Second, what is the evidence that the released ICD fragment produces a relevant biologic activity? These issues are important as it has been hypothesized that secretase processing of transmembrane proteins may be a cellular housekeeping mechanism to degrade these molecules, as the presence of a transmembrane domain(s) would seem to present a barrier to other proteolytic systems [5,6]. These are not, however, necessary mutually exclusive interpretations. For example, α- or β-secretase release of an ectodomain fragment may be biologically important, while the γ-secretase degradation of the remaining cell-associated fragment may proceed as a housekeeping function. However, when the cleavage is stimulated by a ligand, especially the cognate ligand, and there is a biologic function to the ICD fragment, then it seems very likely that these trafficking events also represent a signal transduction mechanism.

Also, it is instructive to note that an increasing number of non-RTK cell surface molecules are subject to secretase cleavage and these are tabulated in Table 2. Within the RTK field of research, the processing of receptor phosphotyrosine phosphatases and growth factor precursors are especially relevant. Also, within the RTK and ligand categories are two ligand:receptor pairs: nueregulin1 Type III and ErbB-4 plus ephrin and the ephrin receptor. Available evidence indicates that these are similar to the Notch system in that formation of the ligand:receptor complex in a juxtacrine manner initiates forward and backward signaling between two adjacent cells in a secretase-dependent manner.

Table 1 – Receptor tyrosine kinases subject to intramembrane proteolys[a]

Receptor tyrosine kinase	Stimulating ligand	ICD	
		Location	Functional evidence
ErbB-4	Neuregulin, TPA	Cytoplasm, nucleus, mitochondria	Yes
Ephrin	Ephrin, ionomycin	Cytoplasm, nucleus	No
CSF-1R	CSF-1, LPS, TPA	Cytoplasm, nucleus	No
Tie 1	VEGF, TPA	Cytoplasm	Yes
VEGFR1	PEDGF	Cytoplasm	Yes
Insulin, IGF-1	TPA	Cytoplasm	No

[a] References are in the text.

ErbB-4

Ectodomain proteolytic processing of ErbB-4 includes a basal level, which can be increased by TPA in all cells or by the addition of neuregulin (heregulin) to certain cells [7,8]. As depicted in Fig. 1, this cleavage results in the formation of two receptor fragments: a 120 kDa ectodomain fragment that is released into the media and an 80 kDa membrane-bound fragment, termed m80. Cleavage requires ADAM 17 (TACE) and it is likely this is the enzyme that executes cleavage of ErbB-4 between His651 and Ser652 within the extracellular stalk or ecto-juxtamembrane region [9,10]. Hence, the m80 fragment includes eight ectodomain residues, the transmembrane domain and entire ICD.

Sensitivity to ectodomain shedding is likely determined, at least in part, by the length of the stalk region in various transmembrane proteins, as demonstrated for the selectins [11]. There are two ErbB-4 isoforms termed Jm-a, in which the ectodomain is sensitive to cleavage, and Jm-b, which is not cleavable [12]. Since ADAM-