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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.

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 I. In the case of ErbB-4, all essential steps are repeated and the ErbB-4 data are reviewed below and illustrated in Figure 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 stimutable 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.

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 Figure 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-mediated cleavage events do not involve a defined sequence or cleavage site in the substrate, it seems that longer stalk regions in substrates may simply permit accessibility of the protease. Interestingly, the stalk region in Jm-b is much shorter (6 residues) than the corresponding region of Jm-a (16 residues) and ErbB-1, -2 and -3 also have relatively short stalk regions (6–9 residues) and are not subject to a significant level

of metalloprotease mediated ectodomain cleavage [7]. Hence the unique sensitivity of the Jm-a ErbB-4 isoform to secretase-dependent processing and signaling seem likely due to the length of its stalk region.

It seems probable, though not formally demonstrated, that the shed ErbB-4 ectodomain may function to block receptor activation by binding neuregulin. The function of the m80 fragment, however, is known. The capacity of γ -secretase to cleave substrates requires that the substrate have a short ectodomain region of 50 or fewer residues [13]. Hence, the ADAM-mediated removal of a large portion of the ErbB-4 ectodomain is a prerequisite step for subsequent γ -secretase cleavage of the m80 fragment [14].

γ -Secretase is a complex of at least four distinct transmembrane proteins of which presenilin is the catalytic protease [15]. It has been shown that the nicastrin subunit of the γ -secretase complex recognizes transmembrane proteins with shortened or nub-like ectodomains and thereby acts as a targeting subunit for intramembrane cleavage by presenilin [16]. This would predict that nicastrin recognition of the ErbB-4 m80 fragment initiates intramembraneous cleavage. As shown in Figure 1, presenilin activity converts the ErbB-4 m80 fragment to a soluble s80 or ICD fragment that is found in the cytoplasm, nucleus and, in one report, mitochondria [17,14].

The C-terminus of ErbB-4 encodes a PDZ domain recognition motif, which is required for presenilin cleavage of the m80 fragment [18]. Deletion of this motif (TVV) does not influence ectodomain cleavage, but does abrogate presenilin association with the m80 fragment and production of the ICD fragment. Presenilin also contains a PDZ domain recognition motif, and, it is possible that a scaffold of PDZ domain containing proteins may be required for γ -secretase cleavage. Proteins that recognize the PDZ domain recognition motifs in ErbB-4 [149,150] and presenilin [151,152] have been reported.

Presenilin cleavage of substrates occurs within the transmembrane domain and, based on APP and Notch processing, this may occur at multiple sites, producing several species of ICD fragments that may have differing levels of metabolic stability based on the N-end rule [19]. Hence, mutation within the transmembrane domain can diminish cleavage and/or alter the metabolic stability of the ICD fragments. This is shown in the case of Notch where a transmembrane mutation appears to prevent cleavage, but actually results in a new ICD fragment that is very rapidly degraded due to the presence of a metabolically destabilizing N-terminal residue [20].

It has been reported that the Val675Ala [21] or Val673Ile [22] mutations within the ErbB-4 transmembrane domain abrogate γ -secretase cleavage, as judged by the inability to detect the ICD fragment. In view of the Notch mutagenesis data, it is not clear whether these mutations actually prevent cleavage or result in a less stable ICD fragment. Given the low level of ICD fragment normally detectable, a modest change in stability may render the fragment undetectable by the same methodology.

In terms of the physiological relevance of the ErbB-4 ICD, it is now clear that endogenous generation of the ICD by γ -secretase is required for control of astrogenesis in the developing mouse [23]. In this system the ICD fragment interacts with TAB2, an adaptor protein, and thereby with N-CoR, a co-repressor, and chaperones this complex into the nucleus. A similar chaperone mechanism between the ErbB-4 ICD and STAT5 has been proposed to be operative in mammary differentiation in vitro [24] and it is clear that ErbB-4 is functionally involved in mammary development in the animal [25]. While ErbB-4 nuclear localization has been observed in normal and tumor mammary tissue and exogenous ICD expression provokes differentiation events, it has not yet been demonstrated that ErbB-4 cleavage is physiologically relevant in this tissue. Also, in line with a role of the ErbB-4 ICD fragment in various cell

differentiation systems, is the report that γ -secretase inhibition prevents neuregulin generation of the nuclear ErbB-4 ICD in oligodendrocytes and maturation of this cell type [26].

In addition to STAT 5 and the TAB 2:N-CoR complex mentioned above, several other proteins (Eto-2 [27], YAP [28,29], WWOX [30], ER [31], Mdm 2 [32], AIP4/Itch [33]) have been reported to associate with the ErbB-4 ICD. Eto-2, YAP and ER are transcription factors/co-activators and the ICD may regulate their nuclear localization similar to STAT 5 and N-CoR. WWOX is a cytoplasmic protein and its interaction with the ICD attenuates nuclear translocation of the ICD, while AIP4/Itch is a cytoplasmic ubiquitin ligase that modulates the levels of intact ErbB-4 and the ICD. The ICD is an active tyrosine kinase [34] that phosphorylates Mdm2, a regulator of p53, which is predominantly localized in the nucleus [32].

As mentioned above, the ErbB-4 ICD has also been localized in mitochondria and in that location may function as a proapoptotic protein. This is based on the capacity of the ICD to induce cell death, the presence of a BH3 domain in the ICD, the loss of apoptotic capacity following mutagenesis of this domain, and detection of an interaction with the antiapoptotic protein BCL-2, which, when over-expressed, abrogated ICD-induced cell death [17]. This and other aspects of the ErbB-4 ICD are reviewed elsewhere [25].

Ephrin Receptor—Addition of the ephrin receptor ligand ephrin provokes secretase cleavages of the receptor releasing the ectodomain fragment and an ICD fragment [35]. The cleavage events are also stimutable by ionomycin or activation of the NMDA receptor, agents that mediate Ca^{2+} influx into cells. In this system, ephrin-mediated cleavage events require endocytosis, while cleavage mediated by ionomycin in NMDA receptor activation occurs on the cell surface. A similar endocytosis relationship between neuregulin and TPA mediated cleavage of ErbB-4 was noted [8]. To date it is unclear whether the receptor ICD fragment is translocated from the cytoplasm to another organelle and there is no data related to a physiological function in mediating ligand cell responsiveness.

CSF-1 Receptor—Secretase cleavage of the CSF-1R can be stimulated by CSF-1, LPS and TPA [36–38]. LPS is a ligand for the Toll4 receptor and agonists for other Toll-like receptors also stimulate cleavage of CSF-1R. This heterologous stimulation of CSF-1R cleavage may be related to the fact that in macrophages both receptor systems are thought to be involved in producing innate immune responses. While the CSF-1 ICD fragment does appear in both cytoplasm and nucleus, a physiologic function has not been identified.

VEGF Receptor 1—Pigment epithelium-derived factor (PEDF) binds to an unknown receptor and promotes an anti-angiogenic response and can oppose the capacity of VEGF to promote endothelial cell proliferation. The addition of PEDF to endothelial cells promotes the γ -secretase mediated cleavage of VEGFR1 with release of its ICD fragment [39]. This ICD fragment was only present when cells were treated simultaneously with PEDF and VEGF and the fragment was detected in the cytoplasm, but not in the nucleus. In this system, the intact VEGFR1 molecule is found in the nucleus following the addition of VEGF (see below) and PEDF reduces VEGF-induced angiogenesis and the nuclear level of intact VEGFR in a manner dependent on γ -secretase activity. This implies that the PEDF stimulated production of the VEGFR1 ICD fragment negatively regulates intact VEGFR1 levels in the nucleus and VEGF-induced angiogenesis, based on the action of γ -secretase inhibitors. However, other signaling systems (Notch, etc.) will also be blocked by pharmacologic γ -secretase inhibitors.

Tie 1—Tie 1 is an orphan receptor that forms a hetero-oligomeric complex with Tie 2, the receptor for angiopoietin 1 (Ang 1). Addition of Ang 1 activates Tie 2 and provokes tyrosine phosphorylation of Tie 1. In this system ectodomain cleavage of Tie 1 is stimulated by a variety

of agents (TPA, VEGF, TNF α , shear stress) and increases Ang 1 activation of Tie 2, apparently by allowing greater access of the ligand to its Tie 2 binding site. Following ectodomain release, the Tie1 cell-associated cleavage fragment (45 kDa) is processed by γ -secretase to produce a 42 kDa cytoplasmic ICD fragment [40]. In this receptor system, the ectodomain secretase action is physiologically important; however, the significance of γ -secretase activity may be simply to remove the highly tyrosine phosphorylated 45 kDa fragment. While the addition of Ang 1 promotes rapid endocytosis and degradation of Tie 2, Tie1 is not cleared from the cell surface by this same route. Therefore, a secretase mechanism may provide the means by which Ang1-phosphorylated Tie 1 is inactivated.

IGF-1 and Insulin Receptors—In preliminary reports, it has been demonstrated that the insulin and IGF-1 receptors can be cleaved by secretase action to produce ICD fragments [41,42]. However, while TPA stimulates formation of the ICD fragments neither cognate ligand was demonstrated to do so.

Non-Secretase Formation of RTK ICD Fragments

In the case of several RTKs (ErbB-2 [43–45], Ret [46], ALK [47], TrkC [48], Met [49–51]) there is evidence that caspases cleave the cytoplasmic domain to produce an ICD fragment. Since the fragment is often produced by two cleavage events within the cytoplasmic domain, the fragment is often considerably smaller than that produced by intramembrane proteolysis. In no reported case are these caspase cleavages stimulated by ligand binding or by TPA and in some studies the presence of the cognate ligand prevents cleavage. In the above RTKs the formation of caspase ICD fragments is functionally associated with the induction of apoptosis and in one instance [44] the fragment has been localized to the mitochondria. Thus, this group of RTKs can be added to the list of dependence receptors in which the receptor mediates opposing cellular responses (apoptosis, cell proliferation) depending on the absence or presence of ligand.

Trafficking of Intact Receptors to the Nucleus

An accounting of recently published reports demonstrating the appearance of intact RTKs and other cell surface receptors in the nucleus is presented in Table 3. In a few instances the data relies on immuno-histochemistry alone and it is not clear that intact receptor is distinguishable from an ICD fragment. In nearly all cases, however, it does appear that the receptor is present in the nucleoplasm and not the nuclear envelope. The presence of a transmembrane protein in a non-membranous environment requires a mechanism to extract the intact receptor from the surrounding lipid bilayer. Such a mechanism has recently been reported and is described below and illustrated in Figure 2.. Whether this trafficking route can be applied to other receptors listed in Table 3 remains to be seen.

ErbB-1 and Translocon –Mediated Trafficking—The capacity of EGF to induce trafficking of the intact EGF receptor (ErbB-1) to the nucleus was first reported in 2001 and a nuclear function was also identified [52]. The nuclear receptor was reported to recognize the promoter of cyclin D1 and to transactivate this promoter in a reporter system. Subsequently, the same group established the following points: 1) other promoters are also recognized by the ErbB-1 (though direct binding to any promoter remains to be shown [53–55]), 2) importin β is required for ErbB-1 nuclear localization [56], 3) a nuclear localization sequence is present in the ErbB-1 sequence [57], and 4) the nuclear receptor associates with PCNA in the nucleus and modifies its stability [58]. The nuclear receptor was identified by both biochemical fractionation and morphological methods and shown to be in a non-membranous environment. Furthermore, the ligand (EGF) was reported to also be present in the nucleus [52].

While no RTK trafficking system was known to extract the transmembrane receptor from its lipid bilayer, another group suggested that a protein translocon could provide such a step [59]. Specifically, the Sec 61 translocon located in the endoplasmic reticulum was known to mediate the trafficking of certain extracellular toxins from the cell surface to the cytoplasm and also, as part of the ERAD pathway, to retrotranslocate misfolded transmembrane proteins from the endoplasmic reticulum to the cytoplasm. Subsequent testing of this possibility showed that EGF induced trafficking of ErbB-1 to the endoplasmic reticulum where it interacted with the Sec61 translocon that then mediated receptor retrotranslocation to the cytoplasm and import into the nucleus [60]. The data showed that knock-down of a Sec61 subunit abrogates both EGF nuclear localization of ErbB-1 and EGF induction of cyclin D1. This trafficking pathway is depicted in Figure 2. HSP 70 has been shown to be essential in the *in vitro* retrotranslocation process [60] and likely functions by interacting with the receptor transmembrane domain and thereby maintaining the receptor in a soluble state following extraction from the ER membrane. The route by which the receptor is trafficked from the cell surface to the endoplasmic reticulum was not determined, but precedent exists with both toxins [153,154] and the SV40 virus [155]. In the former case, the Golgi serves as an intermediate, while in the latter caveosomes translocate virus to the endoplasmic reticulum.

The translocon pathway described above for ErbB-1 is distinguished from the endocytic pathways leading to lysosomal degradation or recycling to the cell surface on the basis of time and quantity of receptors involved. The translocon pathway is relatively slow and involves a smaller fraction of the receptor population [60]. Therefore it is not clear whether the translocon pathway represents a third destination for receptors internalized through clathrin-coated pits or whether receptors destined for the translocon and nucleus are internalized by a separate cell surface mechanism.

There are several examples of ligand/receptor pairs that translocate to the nucleus, perhaps as a complex. However, this has not been convincingly demonstrated. The interested reader is referred to recent reviews that address the issue of ligand trafficking to the nucleus [61–63].

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Figure 1. Secretase-mediated trafficking of ErbB-4 from the cell surface to intracellular compartments. Following ligand binding and receptor activation and dimerization, ErbB-4 is subject to ectodomain cleavage by ADAM17(TACE) with release of the ectodomain fragment into the media. The cell-associated fragment m80 is then cleaved by γ -secretase to produce an ICD fragment also termed s80. The ICD fragment is translocated to intracellular organelles. In the case of nuclear translocation, transcription factors are reported to be chaperoned into the nucleus with the ICD.

Figure 2. Translocon-mediated trafficking of ErbB-1 (EGF receptor) from the cell surface to the nucleus. Following ligand binding and receptor activation and dimerization, the receptor is internalized and trafficked to the endoplasmic reticulum (ER). Interaction with the Sec 61 translocon mediates extraction from the lipid bilayer, interaction with chaperones, such as Hsp 70, and extrusion into the cytoplasm. Subsequent association with importin- β leads to nuclear import.

Table 1

Receptor Tyrosine Kinases Subject to Intramembrane Proteolysis*

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

* References are in the text.

Cell Surface Transmembrane Protein Subject to Intramembrane Proteolysis

Table 2

Category	Protein	Stimulating Ligand	ICD		References
			Localization	Functional Evidence	
Ligands	TNF α	none	cytoplasm	yes	[64,65]
	NRG1 Type III	ErbB-4	cytoplasm, nucleus	yes	[66,67]
	Delta, Jagged	Notch	cytoplasm, nucleus	yes	[68-70]
	Ephrin	Eph, TPA	cytoplasm, nucleus	yes	[71,72]
PTPases	RPTP $_{\alpha/\beta}$	High cell density, antibody	cytoplasm, nucleus	yes	[73]
	LAR	TPA	cytoplasm, nucleus	yes	[74]
Ligand Receptor	Notch	Delta, Serrate	cytoplasm, nucleus	yes	[4](ref therein)
	p75	BDNF, TPA	cytoplasm, nucleus	no	[75-81]
	IL-1R2	TPA	cytoplasm	no	[82]
	Growth Hormone Receptor	TPA	cytoplasm, nucleus	no	[83]
	GluR3	none	ICD not produced	yes	[84]
	LDLRs	TPA	cytoplasm, nucleus	yes	[85-90]
	CXCL1&16	none	cytoplasm	none	[91]
	IFN α 2	IFN- α , TPA	cytoplasm, nucleus	yes	[92-94]
	Na channel- β 2	none	cytoplasm	no	[95-97]
	CD44	Ionomycin, TPA	cytoplasm, nucleus	yes	[98-101]
Channels Adhesion	Cadherins	Apoptosis, Ca influx, toxin	cytoplasm	yes	[102-108]
	DCC	none	cytoplasm	yes	[109]
	Syndecan 3	TPA, bFGF	cytoplasm	yes	[110]
	L1	none	cytoplasm	no	[111]
	APP	TPA	cytoplasm, nucleus	yes	[112](ref therein)
	TMEFF2	TPA	cytoplasm	no	[113]
	CD43	none	cytoplasm, nucleus	yes	[114,115]
	CD74	none	cytoplasm, nucleus	yes	[116]
	SorLA	none	cytoplasm, nucleus	yes	[117]
	Fibrocystin	Ca+2 mobilization	cytoplasm, nucleus	no	[118]
Miscellaneous	RAGE receptor	ionomycin	cytoplasm, nucleus	no	[119]
	HLA-A2	TPA	cytoplasm	no	[120]

Category	Protein	Stimulating Ligand	ICD		References
			Localization	Functional Evidence	
	Brl 2	none	cytoplasm	no	[121]
	Nectin-1 α	TPA	cytoplasm	no	[122]
	Neogenin	none	cytoplasm, nucleus	yes	[123]
	NRADD	none	cytoplasm	no	[124]
	Tyrosinase	none	cytoplasm	no	[125]
	Gnt-V	none	cytoplasm	no	[126]

Table 3
Intact Receptors Trafficked to Nucleus or Mitochondria

Receptor Tyrosine Kinase	Stimulating Ligand	Organelle	Functional Evidence	References
ErbB-1	EGF	nucleus	yes	[53,57,127,60,52,56,54,55,58]
ErbB-1	Src	mitochondria	no	[128]
ErbB-1 vIII	none	nucleus	yes	[129]
ErbB-2	over-expression	nucleus	yes	[130,131]
ErbB-3	none	nucleus	no	[132]
FGF-R1, R2	FGF	nucleus	yes	[133,134](ref therein)
IFN- γ R1	IFN- γ	nucleus	yes	[135–137]
TrkA	NGF, LPS	nucleus	no	[138,139]
TGF- β	TGF- β	nucleus	no	[140]
GH	Growth hormone	nucleus	yes	[141–143]
IL-15R2	IL-15	nucleus	no	[144]
VEGFR1/FLT1	VEGF	nucleus	no	[145–147]
Met	HGF	nucleus	no	[148]