Receptor Tyrosine Kinases in the Nucleus

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To date, 18 distinct receptor tyrosine kinases (RTKs) are reported to be trafficked from the cell surface to the nucleus in response to ligand binding or heterologous agonist exposure. In most cases, an intracellular domain (ICD) fragment of the receptor is generated at the cell surface and translocated to the nucleus, whereas for a few others the intact receptor is translocated to the nucleus. ICD fragments are generated by several mechanisms, including proteolysis, internal translation initiation, and messenger RNA (mRNA) splicing. The most prevalent mechanism is intramembrane cleavage by γ -secretase. In some cases, more than one mechanism has been reported for the nuclear localization of a specific RTK. The generation and use of RTK ICD fragments to directly communicate with the nucleus and influence gene expression parallels the production of ICD fragments by a number of non-RTK cell-surface molecules that also influence cell proliferation. This review will be focused on the individual RTKs and to a lesser extent on other growth-related cell-surface transmembrane proteins.

The localization of receptor tyrosine kinases (RTKs) in the nucleus is perhaps 20 years old and was for some time limited by the available techniques to descriptive experiments that suffered from potential artifacts. With improved technical approaches and clearer understanding of subcellular compartments more convincing and mechanistic data have appeared. The authors have previously reviewed this topic (Carpenter and Liao 2009) and will, therefore, concentrate on more recent and mechanistic advances.

Although there are several mechanisms involved in this trafficking pathway, the role of secretase-dependent processing of cell-surface molecules to the nucleus is the most clear and convincing in the case of Notch (Bray 2006). In that 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 remaining 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 cellular responses to the ligand. The Notch scenario is recapitulated to different extents by numerous RTKs, as indicated in Table 1, and other growth-related molecules as shown in Table 2.

In reviewing intramembraneous cleavage of RTKs, two points are emphasized. First, is the cleavage process or nuclear localization of the ICD fragment stimulated by a ligand? Although a number of receptors and other cell-surface molecules are cleaved following the addition of

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Table 1. Receptor tyrosine kinase in the nucleus

RTK ^a	Mechanism
CSF-1	γ -Secretase-generated ICD
Eph B2	γ -Secretase-generated ICD
ErbB-1	Holoreceptor, mRNA splicing: rhomboid-generated ICD
ErbB-2	Holoreceptor, CTF
ErbB-3	Holoreceptor, RNA splicing
ErbB-4	γ -Secretase-generated ICD
FGFR1	Holoreceptor, granzyme-generated ICD
FGFR2	Holoreceptor
FGFR3	γ -Secretase-generated ICD
IGF-1	Holoreceptor, ICD
Insulin	ICD
Met	Holoreceptor, secretase- or caspase- generated ICD
PTK7	γ -Secretase-generated ICD
Ret	γ -Secretase-generated ICD
Ron	γ -Secretase-generated ICD
Ryk	γ -Secretase-generated ICD
Tie1	γ -Secretase-generated ICD
VEGFR1	γ -Secretase-generated ICD, holoreceptor
VEGFR2	γ -Secretase-generated ICD, holoreceptor

ICD, intracellular domain; CTF, carboxy-terminal fragment.

^aReferences can be found in the text or in Carpenter and Liao (2009).

protein kinase C agonists, such as phorbol esters, it remains to be shown in those cases whether natural receptor ligands also influence receptor trafficking to the nucleus. 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 presents a barrier to other proteolytic systems (Small 2002; Kopan and Ilagan 2004). These are not, however, necessarily mutually exclusive interpretations. For example, α - or β -secretase release of an ectodomain fragment may be biologically important, whereas 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, then it seems very likely that the nuclear trafficking also represents a signal

transduction mechanism. Although the nuclear function(s) of ICD fragments is unknown in many cases, the lessons of ErbB-4 and Notch indicate that ICDs may activate transcription by transporting transcription factors from the cytoplasm to the nucleus.

SECRETASE PROCESSING OF RTKs

ErbB-4 Receptor

Within the family of RTKs that are processed to the nucleus, ErbB-4 is the most completely understood in terms of mechanism and biological function and will be discussed in more detail as a model for the secretase cleavage of other RTKs (Fig. 1). Ectodomain proteolytic processing of ErbB-4 includes a basal level, which can be increased by 12-O-tetradecanoylphorbol-13-acetate (TPA) in all cells or by the addition of its cognate ligand, neuregulin (heregulin), to certain cells (Vecchi et al. 1996; Zhou and Carpenter 2000). 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 or CTF (carboxy-terminal fragment). 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 (Rio et al. 2000; Cheng et al. 2003). 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 as shown for the selectins (Migaki et al. 1995). There are two ErbB-4 isoforms termed Jm-a, in which the ectodomain is sensitive to cleavage, and Jm-b, which is not cleavable (Elenius et al. 1997). The presence of these two isoforms is unique to ErbB-4. Because 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 (six residues) than the corresponding region of Jm-a (16 residues), and ErbB-1, -2,

Table 2. Growth-related cell-surface molecules in the nucleus

Molecules	Mechanism	References ^a
ADAM10	γ -Secretase-generated ICD	Tousseyn et al. 2009
ADAM13	γ -Secretase-generated ICD	Cousin et al. 2011
CD44	γ -Secretase-generated ICD	Janiszewska et al. 2010; Milette-González et al. 2012
EpCAM	γ -Secretase-generated ICD	Denzel et al. 2009; Maetzel et al. 2009; Ralhan et al. 2010; Huang et al. 2011b; Chaves-Pérez et al. 2013
Frizzled	γ -Secretase-generated ICD	Mathew et al. 2005
Growth hormone receptor	γ -Secretase-generated ICD	Wang et al. 2011a
IL-2R	γ -Secretase-generated ICD	Montes de Oca et al. 2010
Klotho	γ -Secretase-generated ICD	Bloch et al. 2009
LRP1	γ -Secretase-generated ICD	Rebeck 2009
Neogenin (DDC)	γ -Secretase-generated ICD	Goldschneider et al. 2008; Bai et al. 2011
p75NTR	γ -Secretase-generated ICD	Ceni et al. 2010; Parkhurst et al. 2010; Wang et al. 2010a; Le Moan et al. 2011
Patched	γ -Secretase-generated ICD	Kagawa et al. 2011
Pre- β -cellulin	γ -Secretase-generated ICD	Stoeck et al. 2010
Protocadherin	γ -Secretase-generated ICD	Buchanan et al. 2010
PTP μ	γ -Secretase-generated ICD	Burgoyne et al. 2009
T β RI	γ -Secretase-generated ICD, holoreceptor	Mu et al. 2011; Chandra et al. 2012
Ephrin B2	γ -Secretase-generated ICD	Tomita et al. 2006; Georgakopoulos et al. 2011
Notch	γ -Secretase-generated ICD	Fortini 2009

^aEarlier references can be found in Carpenter and Liao (2009).

and -3 also have relatively short stalk regions (6–9 residues) and are not subject to a significant level of metalloprotease-mediated ectodomain cleavage (Vecchi et al. 1996). Hence the unique sensitivity of the Jm-a ErbB-4 isoform to secretase-dependent processing and signaling seems likely owing to the length of its stalk region.

It seems probable 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 (Struhl and Adachi 2000). 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 (Ni et al. 2001).

γ -Secretase is a complex of at least four distinct transmembrane proteins of which presenilin is the catalytic protease (Selkoe and Wolfe 2007). The nicastrin subunit of this complex recognizes transmembrane proteins with short-

ened or nublike ectodomains and thereby acts as a targeting subunit for intramembrane cleavage by presenilin (Shah et al. 2005). Presenilin activity converts the ErbB-4 m80 fragment to a soluble s80 or ICD fragment that is found in the cytoplasm, nucleus, and mitochondria (Ni et al. 2001; Naresh et al. 2006). Recently, a fifth protein (GASP) has been added to the γ -secretase complex (He et al. 2010). GASP, which was first identified as a target of the tyrosine kinase inhibitor imatinib, is a 16 kDa protein that is required for efficient γ -secretase cleavage of the cell-surface protein APP. This raises the issue of whether a similar targeting protein may participate in the cleavage of other γ -secretase substrates.

The carboxyl terminus of ErbB-4 encodes a PDZ domain recognition motif, which is required for presenilin cleavage of the m80 fragment (Ni et al. 2003). Deletion of this motif (TVV) does not influence ectodomain cleavage, but does attenuate presenilin association with the m80 fragment and production of the ICD

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Figure 1. Depicted is the general mechanism for generation and nuclear localization of RTK ICD fragments. Included are examples of canonical signal transduction pathways to the nucleus (i.e., MAPK and STAT pathways) as contrasted to the noncanonical ICD mechanism.

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.

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 (Varshavsky 1997). Mutation within the transmembrane domain, which is often used to identify a cleavage site based on the lack of detectable ICD formation, can 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 owing to the presence of a metabolically destabilizing amino-terminal residue (Tagami et al. 2008).

It has been reported that the Val675Ala (Muraoka-Cook et al. 2006) or Val673Ile (Vidal et al. 2005) mutations within the ErbB-4 transmembrane domain abrogate γ -secretase cleav-

age, 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. Additional splice variants of ErbB-4 (Veikkolainen et al. 2011) produce two isoforms of the ICD fragment, CYT-1 and CYT-2. The two isoforms differ by 16 consecutive residues that are present in CYT-1, but absent in the CYT-2, and provide the CYT-1 isoform with overlapping docking sites for PI3 kinase and proteins containing WW domains. In a comparative study using Madin-Darby canine kidney (MDCK) cells, one group has shown that the CYT-1 ICD is less metabolically stable than the CYT-2 ICD (Zeng et al. 2009) and that the CYT-2 ICD is more readily detected in the nucleus (Zeng et al. 2007). These differences were due, at least in part, to association of the ubiquitin ligase Nedd4, a WW-domain-containing protein, with selective sequence motifs present in the CYT-1 isoform.

Using different cell backgrounds, similar results have been reported by others (Omerovic et al. 2007; Feng et al. 2009).

In terms of the physiological relevance, it is now clear that endogenous generation of the ErbB-4 ICD by γ -secretase is required for control of astrogenesis in the developing mouse (Sardi et al. 2006). In this system, the ICD fragment interacts with TAB2, an adaptor protein, and thereby with N-CoR, a corepressor, and chaperones this complex into the nucleus. A similar chaperone mechanism between the ErbB-4 ICD and STAT5 has been proposed to be operative during mammary differentiation (Williams et al. 2004). Also, the nuclear interaction of the ErbB-4 ICD with HIF-1 α is reported to attenuate metabolic degradation of HIF-1 α and thereby promote gene expression in mammary tissue (Paatero et al. 2012).

It is clear that ErbB-4 is functionally involved in mammary development in the animal (Jones 2008). ErbB-4 nuclear localization has been observed in normal and tumor mammary tissue and exogenous ICD expression provokes differentiation events (Muraoka-Cook et al. 2006). However, as a cautionary note studies using exogenous expression of the Notch ICD have shown that different levels of expression can provoke distinct biologic responses (Mazzone et al. 2010; Han et al. 2011). Nevertheless, analysis of an ErbB-4 noncleavable mutant (Rokicki et al. 2010) and the intracellular distribution of the ICD fragment in breast tumor tissue (Thor et al. 2009) are consistent with the conclusion that endogenous ErbB-4 cleavage is physiologically relevant to differentiation in this tissue and a positive factor for breast cancer patients.

Also, consistent with a role of the ErbB-4 ICD fragment in various differentiation systems is the report that γ -secretase inhibition prevents neuregulin generation of the ErbB-4 ICD in oligodendrocytes and maturation of this cell type (Lai and Feng 2004). Interestingly, there is a genetic correlation between ErbB-4 and schizophrenia (Pan et al. 2011) and the involvement of the ICD fragment in controlling gene expression in relevant cell types has been reported (Wong and Weickert 2009; Allison et al. 2011). Also, the maturation of fetal lung cells is report-

ed to be dependent on secretase processing of ErbB-4 and ICD association with the transcription factors YAP (Hoeing et al. 2011), STAT 5a (Zscheppang et al. 2011a), and ER β (Zscheppang et al. 2011b). It is suggested that these interactions allow ErbB-4 to regulate transcription of surfactant protein B and thereby promote lung maturation.

As mentioned above, the ErbB-4 ICD also has 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 overexpressed, abrogated ICD-induced cell death (Naresh et al. 2006).

Ephrin-B2

Addition of the ligand ephrin-B2 (Eph-B2) provokes the secretase cleavage of the EphB2 receptor releasing ectodomain and ICD fragments (Litterst et al. 2007; Lin et al. 2008). The cleavage events are also stimulated by ionomycin or by activation of the *N*-methyl-D-aspartate (NMDA) receptor, agents that mediate Ca²⁺ influx into cells. In this system, ephrin-mediated cleavage events require endocytosis, whereas cleavage mediated by ionomycin or NMDA receptor activation occurs on the cell surface. A similar endocytosis relationship between neuregulin- or TPA-mediated cleavage of ErbB-4 was noted (Zhou and Carpenter 2000). To date, it is unclear whether the Eph receptor ICD fragment is translocated from the cytoplasm to another organelle and there is no data related to its physiological function in mediating ligand responsiveness.

Colony Stimulating Factor-1 Receptor

Secretase cleavage of the colony-stimulating factor-1 receptor (CSF-1R) can be stimulated by CSF-1, LPS, or TPA (Wilhelmsen and van der Geer 2004; Glenn and van der Geer 2007, 2008). Lipopolysaccharide (LPS) is a ligand for the

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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. Although the CSF-1 ICD fragment does appear in both cytoplasm and nucleus, a physiologic function has not been identified.

Vascular Endothelial Growth Factor-1

Pigment epithelium-derived factor (PEDF) binds to an unknown receptor and promotes an antiangiogenic response that can oppose the capacity of vascular endothelial growth factor (VEGF) to promote endothelial cell proliferation. The addition of PEDF to endothelial cells promotes the γ -secretase-mediated cleavage of VEGFR1 (Flt1) with release of its ICD fragment (Cai et al. 2006, 2011a; Rahimi et al. 2009). The ICD fragment is only present when cells are 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 sensitivity to γ -secretase inhibitors, it is reported that the capacity of PEDF to prevent VEGF-induced changes in vascular permeability requires production of the VEGFR1 ICD fragment (Cai et al. 2011b). In contrast, Ablonczy et al. (2009) report that it is VEGFR2 that is cleaved by γ -secretase in this system.

Tie 1

Tie 1 is an orphan receptor that forms a heterooligomeric 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. 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 Tie 1 cell-associated 45-kDa cleavage fragment is processed by γ -secretase to produce a 42-kDa cytoplasmic ICD fragment (Marron et al. 2007). 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. Although the addition of Ang 1 promotes rapid endocytosis and degradation of Tie 2, Tie 1 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.

Insulin-like Growth Factor-1 and Insulin Receptors

In preliminary reports, it has been shown that the insulin and IGF-1 receptors can be cleaved by secretase action to produce ICD fragments (Kasuga et al. 2007; McElroy et al. 2007). However, although TPA stimulated formation of the ICD fragments neither cognate ligand was shown to do so.

Ryk

Wnt proliferative signaling is mainly mediated by Frizzled receptors and low-density lipoprotein-related proteins (LRP) through a canonical pathway involving β -catenin and T-cell factor (TCF). However, it is known that Ryk, a receptor tyrosine kinase that lacks kinase activity, binds Wnt and participates in Wnt signaling in certain biologic contexts. Evidence has appeared demonstrating that γ -secretase cleavage of Ryk is required for Wnt 3-dependent neuronal differentiation (Lyu et al. 2008). Release of the Ryk ICD fragment does not require Wnt, but nuclear translocation of the ICD does require Wnt. Because the Ryk ICD lacks a nuclear localization signal, the mechanism for nuclear translocation is unclear. Cdc 37, a cochaperone of Hsp 90, interacts with the Ryk ICD, attenuates metabolic

degradation, and promotes nuclear ICD levels (Lyu et al. 2009). Because this interaction has not been shown to be a result of Wnt signaling, the mechanism by which Wnt promotes nuclear translocation of the ICD fragment is not known. It is interesting to note that in *Drosophila*, Wnt binding induces the γ -secretase cleavage of D Frizzled, a heptahelical receptor, with nuclear localization of a CTF (Mathew et al. 2005). Also, the RTKs Ror1/2 participate in signaling by certain Wnt ligands (Grumolato et al. 2010), but it is not known whether ICD fragments are produced.

Fibroblast Growth Factor 3

Activation of the fibroblast growth factor receptor 3 (FGFR3) by FGF-1 leads to an ErbB-4-like cleavage pathway (Degnin et al. 2011). Both FGFR3 and ErbB-4 can undergo regulated intramembrane proteolysis following addition of the homologous ligand or TPA, but in the former case autophosphorylation and endocytosis are required. Although internalized ErbB-4 is first cleaved by a metalloprotease, ectodomain cleavage of FGFR3 is catalyzed by a cathepsin protease. Subsequently, γ -secretase cleavage liberates a FGFR3 ICD fragment that translocates to the nucleus.

Met

Ligand-independent constitutive γ -secretase cleavage of Met in several cell types has been described (Foveau et al. 2009). Interestingly, an inhibitory antibody to Met (DN30), which induces receptor degradation and biologic activity of overexpressed Met, promotes the formation of Met ICD. The intracellular localization of this ICD fragment, however, was not reported.

Protein Tyrosine Kinase 7

Protein tyrosine kinase 7 (PRK7), a pseudokinase, is constitutively cleaved by ADAM metalloprotease and γ -secretase to produce an ICD fragment that can be found in the nucleus (Golubkov and Strongin 2012; Na et al. 2012). In these studies, exogenous expression of the ICD

fragment promoted cell proliferation, migration, and colony formation. Although PTK7 functions as a coreceptor in the Wnt pathway, it has been implicated in a broad range of biologic processes. Whether the PTK7 ICD fragment has a role in these events is not known.

NONSECRETASE FORMATION OF RTK ICD FRAGMENTS

Caspase-Dependent Fragments

In the case of several RTKs (ErbB-2 [Tikhomirov and Carpenter 2001; Benoit et al. 2004; Strohacker et al. 2008], Ret [Bordeaux et al. 2000; Cabrera et al. 2011], ALK [Mourali et al. 2006; Racaud-Sultan et al. 2006], TrkC [Tauszig-Delamasure et al. 2007], and Met [Tulasne et al. 2004; Pozner-Moulis et al. 2006; Foveau et al. 2007; Deheuninck et al. 2009]) there is evidence that caspase activity cleaves the cytoplasmic domain to produce an ICD fragment. Because 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 proteolytic events stimulated by ligand binding or by TPA, and in some studies the presence of the cognate ligand prevents cleavage. The formation of caspase ICD fragments is functionally associated with the induction of apoptosis and in one instance (Strohacker et al. 2008) the fragment has been localized to the mitochondria.

Translation-Dependent Fragments

Metalloprotease activity (Codony-Servat et al. 1999) or internal translation initiation of ErbB-2 mRNA (Anido et al. 2006) leads to the production of ErbB-2 CTFs. The CTFs, which are generated at three methionine residues located on either side of the transmembrane domain, are found in the nucleus (Anido et al. 2006; Xia et al. 2011). These fragments promote cell migration (García-Castillo et al. 2009) and are reported to be oncogenic (Pedersen et al. 2009). Because two of the CTFs include the transmembrane domain, a mechanism for translocation

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of these CTFs to the nucleus is not clear. ErbB-2 is a major therapeutic target in breast cancer and the therapeutic agent used is an antibody to the ectodomain. Therefore the presence of these biologically active CTFs in tumor tissue represents a potential therapeutic problem (Arribas et al. 2011).

Splicing-Dependent Fragments

Another group has identified a spliced product of the epidermal growth factor (EGF) receptor (ErbB-1) that represents the splicing of exon 1 of the ectodomain to exon 23 of the cytoplasmic domain (Piccione et al. 2012). Hence, sequences required for ligand binding and tyrosine kinase activity are deleted. This variant, termed mLEEK, is constitutively produced in a variety of cell lines and tumor tissues, is present in the nucleus, and displays transcriptional activity. Because mLEEK retains a signal sequence and may be secreted, it remains to be shown how nuclear localization is achieved. Splicing of ErbB-3 produces at least 14 variants and a few of these encode sequences corresponding to an ICD. One of these encodes an ICD sequence encoding a protein 80 kDa, which is localized to the nucleus (Andrique et al. 2012). Data have been presented to implicate this protein in the regulation of cyclin D1 transcription. Another nuclear ErbB-3 variant has been reported to associate with active promoters in Schwann cells (Adilakshmi et al. 2011).

Granzyme-Dependent Fragments

The generation of an ICD fragment from FGFR1 in an FGF-dependent manner has been reported (Chioni and Grose 2012). The ICD fragment is localized to the nucleus and evidence is presented to argue that this fragment increases cell migration. Unexplained, however, was the mechanism by which the ICD fragment could be generated by granzyme B, a serine protease localized within cytoplasmic granules.

Rhomboid-Dependent Fragments

Rhomboids are intramembrane serine proteases that are best known for the regulation of the

ectodomain shedding of transmembrane proteins, such as the precursor for TGF- α . The intramembrane cleavage of ErbB-1 (EGF receptor) by rhomboid activity has now been reported (Liao and Carpenter 2012). This cleavage is EGF-stimulated and produces an ICD-like fragment that is localized to membrane and nuclear fractions, but is not found in the cytosol. Because rhomboid cleavage occurs close to the ectodomain side of the transmembrane domain, this fragment may retain transmembrane domain residues at its amino terminus and therefore remain membrane associated.

INTACT RECEPTORS IN THE NUCLEUS

Listed in Table 1 are several receptors for which the data show that the intact or holoreceptor is present in the nucleus. That the nuclear species is the holoreceptor and not an ICD fragment is based on a nuclear fraction M_r value indicative of the mature receptor, which is significantly distinct from the size of an ICD fragment. Because cell fractionation can produce contamination of organelle preparations, this is a source of concern when nuclear extracts are used for size analysis. However, most localization studies are supplemented with imaging data of intact cells. In a few instances the data relies on immunohistochemistry alone and in those cases it is not clear that intact receptor is distinguishable from an ICD fragment unless both ectodomain and cytoplasmic domain antibodies are used. In nearly all cases, however, it does appear that the receptor is present in the nucleoplasm and not the nuclear envelope.

ErbB-1

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 target was identified (Lin et al. 2001). The nuclear receptor is reported to recognize the promoter of cyclin D1 and to transactivate this promoter in a reporter system. Other promoters are also reported to be recognized by the EGF receptor (Lo et al. 2005, 2010; Tao et al. 2005; Hanada et al. 2006). However, direct and specific binding to

any promoter remains to be shown. Also, the nuclear receptor associates with proliferating cell nuclear antigen (PCNA) in the nucleus, modifying its stability (Wang et al. 2006), and with polynucleotide phosphorylase, increasing cellular radioresistance (Yu et al. 2012).

Trafficking from the cell surface to the nucleus requires receptor internalization through clathrin-coated pits (De Angelis Campos et al. 2011); retrograde transport from the Golgi to the endoplasmic reticulum (ER) (Wang et al. 2011b); phosphorylation of Ser 229, an ectodomain residue, by Akt (Huang et al. 2011a); phosphorylation of Thr 654 (Dittmann et al. 2010), a known cytoplasmic domain protein kinase C (PKC) phosphorylation site; and function of the lipid kinase PIKfyve (Kim et al. 2007). Importin β is required for ErbB-1 nuclear entry (Lo et al. 2006) and a nuclear localization sequence to facilitate this interaction is present in the cytoplasmic juxtamembrane region of the EGF receptor (Hsu and Hung 2007). The nuclear receptor has been identified by biochemical fractionation, immunohistochemistry, and live cell imaging methods and shown to be in a nonmembranous nuclear environment, based on its extractability with a high salt aqueous buffer.

The above trafficking steps, perhaps with the exception of Ser 229 phosphorylation, are reasonable given what is known about intracellular trafficking in general and more specifically about other molecules (e.g., bacterial toxins) (Sandvig and van Deurs 2002; Bonifacino and Rojas 2006), that are trafficked from the cell surface to the ER. The toxins are soluble molecules and after reaching the ER are translocated to the cytoplasm where they exert their biological activity. Therefore, a mechanism is required to facilitate movement of the membrane-bound EGF receptor in the ER to the nucleus as a non-membrane localized molecule. Although no endocytic trafficking system was known to extract a transmembrane receptor from its lipid bilayer, it was suggested that an ER protein translocon could provide such a step (Carpenter 2003). The Sec61 translocon located in the ER is known to mediate the trafficking of extracellular toxins from the cell surface to the cytoplasm

and, as part of the ERAD pathway, to retrotranslocate misfolded transmembrane proteins in the ER to the cytoplasm. Subsequent experiments showed that EGF induced trafficking of the EGF receptor to the ER where it interacted with the Sec61 translocon that mediated receptor retrotranslocation to the cytoplasm and import into the nucleus (Liao and Carpenter 2007). Experimental data showed that knockdown of a Sec61 subunit attenuated both EGF nuclear localization of the EGF receptor and EGF induction of cyclin D1. This trafficking pathway is depicted in Figure 2. A subsequent report has confirmed the role of the Sec61 translocon in this pathway, but places the interaction between the EGF receptor and the translocon at the inner nuclear membrane (Wang et al. 2010b, 2012).

Additional reports have shown that nuclear localization of the EGF receptor is provoked by radiation (Dittmann et al. 2005; Liccardi et al. 2011) or treatment with the receptor antibody C225/Cetuximab (Liao and Carpenter 2009). The nuclear receptor is reported to interact with MUC1 and increase the level of chromatin-bound EGF receptor (Bitler et al. 2010; Merlin et al. 2011). MUC1 is a cell-surface protein that is known to interact with the receptor and promote receptor internalization. It is also known to be trafficked to the nucleus (Carson 2008).

ErbB-2 and ErbB-3

Using methodologies similar to those used to localize the EGF receptor to the nucleus (Lin et al. 2001), the same group showed that the intact ErbB-2 molecule translocated from the cell surface to the nucleus and thereby facilitates the expression of the Cox-2 mRNA (Wang et al. 2004; Giri et al. 2005) and ribosomal RNA (Li et al. 2011). The mechanism of ErbB-2 trafficking to the nucleus is reported to include a Sec61-dependent step analogous to that of ErbB-1 (Wang et al. 2012). Because ErbB-2 does not bind a known ligand, the studies represent a constitutive pathway. Progesterone, however, transactivates ErbB-2 and thereby initiates ErbB-2 translocation to the nucleus

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Figure 2. Illustrated is the Sec61-dependent trafficking pathway for intact RTKs, such as the EGF receptor, to translocate from the cell surface to the nucleus.

(Béguelin et al. 2010). This translocation of ErbB-2 chaperones STAT3 into the nucleus where the complex, together with the progesterone receptor, interacts with the cyclin D promoter to bring about progesterone-induced cyclin D expression. Less is known about the nuclear form of ErbB-3 (Offterdinger et al. 2002).

IGF-1

An initial report of intact IGF-1 receptors present in the nucleus (Chen and Roy 1996) has been confirmed and extended in recent reports from two groups (Aleksic et al. 2010; Deng et al. 2010; Sehat et al. 2010). Both groups indicate that this relocation from plasma membrane to nucleus is IGF-1 dependent and that the nuclear receptor may function as a transcriptional coactivator. One report showed that nuclear lo-

calization and the capacity to increase transcription in reporter assays require sumoylation at three lysine residues in the β chain of the receptor. Chromatin-immunoprecipitation (ChIP) assays indicated the nuclear IGF-1R interacts with DNA sequences identified as predominately intergenic, with characteristics of enhancers and having the capacity to increase luciferase transcription in reporter assays.

Ron

Nuclear localization of the Ron RTK is reported to occur in bladder cancer cells and is not stimutable by the Ron ligand MSP (Liu et al. 2010). Rather nuclear levels of Ron are increased during serum starvation. Interestingly, the increase in nuclear Ron requires the EGF receptor as a heterodimerization partner. ChIP assays have

identified potential gene targets, including a number of stress-responsive genes.

Met

Nuclear localization of Met ICD fragments produced by either secretase or caspase cleavage are discussed above. One group has reported that the intact Met receptor is very rapidly translocated from the cell surface to the nucleus following the addition of HGF, and this translocation event is required for HGF induction of a nuclear Ca^{2+} signal (Gomes et al. 2008).

FGFR1 and 2

There is a large background of published reports describing the ligand-dependent translocation of intact FGFR1 to the nucleus (reviewed in Stachowiak et al 2007). There is a report detailing the dynamics of nuclear FGFR1 movement among receptor populations having different motilities taken to represent free receptor or receptor associated with chromatin or nuclear matrix (Dunham-Ems et al. 2009). The interaction of FGFR1 and the transcription factor Nurr1 in the nucleus of dopaminergic neurons has been described (Baron et al. 2012). Morphologic studies have recognized FGFR2 in the nucleus of tissue samples (Lu et al. 2004; Schmahl et al. 2004; Giulianelli et al. 2008; Martin et al. 2011), but without analysis of the size it is not possible to distinguish whether this represents an intact receptor or a receptor fragment.

VEGFR1 and R2

Two reports have identified intact VEGFR1 in the nucleus and one indicates that the localization is increased by ligand (Cai et al. 2006; Lee et al. 2007). Several studies have found that intact VEGFR2 (KDR) is localized in the nucleus and in some reports this is ligand sensitive (Stewart et al. 2003; Fox et al. 2004; Santos and Dias 2004; Zhang et al. 2005; Santos et al. 2007). Domingues et al. (2001) conclude that nuclear VEGFR2 regulates its own transcription.

NUCLEAR LOCALIZATION OF OTHER GROWTH-REGULATING RECEPTORS

Although Notch is an obvious example of a cell-surface receptor that uses nuclear localization of the receptor to affect its biologic activity, there are a number of other examples for growth-related cell-surface proteins and these are presented in Table 2. This list is limited to recent additions; a more comprehensive list was previously published and should be consulted for earlier references (Carpenter and Liao 2009).

CONCLUDING REMARKS

The role of regulated intramembrane proteolysis in signal transduction by activated RTKs is reasonably well established biochemically and biologically. One open question revolves around the role of tyrosine kinase activity within the nuclear compartment. Are there nuclear substrates or does kinase activity not have a role in ICD function? A second issue is whether any ICD, regardless of its source, actually forms a direct and biologically important contact with DNA. To date, there is no convincing data to resolve either of those questions.

It might be important to note that the ligand-dependent trafficking of any RTK or its ICD to the nucleus would represent a noncanonical signaling pathway for that particular ligand. This would be unique as other signaling elements are canonical (i.e., common to multiple ligand–receptor systems).

Last, the reader is referred to other recent reviews on this topic (Ancot et al. 2009; Borlido et al. 2009; McCarthy et al. 2009; De Strooper and Annaert 2010; López-Otin and Hunter 2010; Wang et al. 2010c; Lal and Caplan 2011; Lemberg 2011).

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