Biochemical and Biophysical Research Communications 450 (2014) 782–787

Contents lists available at ScienceDirect

Biochemical and Biophysical Research Communications

journal homepage: www.elsevier.com/locate/ybbrc

Identification and mutagenesis of the TACE and γ-secretase cleavage sites in the colony-stimulating factor 1 receptor

Arrash Vahidi, Gary Glenn, Peter van der Geer *

Department of Chemistry and Biochemistry, San Diego State University, 5500 Campanile Dr., San Diego, CA 92182-1030, USA

ARTICLE INFO

Article history:
Received 4 June 2014
Available online 21 June 2014

Keywords:
Ectodomain shedding
Intramembrane proteolysis
Protein-tyrosine kinase
Signal transduction
Cleavage site selection

ABSTRACT

Stimulation of macrophages with phorbolesters, bacterial DNA, or lipopolysaccharides causes regulated intramembrane proteolysis or RIPping of the CSF-1 receptor. This process involves TACE-mediated cleavage in the extracellular domain, followed by γ-secretase-mediated cleavage within the transmembrane region. In the current study, we have identified the TACE cleavage site, which is present twelve residues from the carboxy-terminal end of the extracellular domain. Replacement of fourteen residues at the end of the extracellular domain blocked TACE cleavage. In addition, we identified the γ-secretase cleavage site, which is present four residues from the carboxy-terminal end of the transmembrane region. Replacement of six residues surrounding this site strongly reduced intramembrane cleavage. Our results provide new insights into the molecular physiology of the CSF-1 receptor and contribute to our understanding of substrate selection by TACE and γ-secretase.

1. Introduction

The CSF-1 receptor is a protein-tyrosine kinase that is expressed in a wide variety of cell types, including hematopoietic stem cells, monocytes, macrophages, smooth muscle cells, placental trophoblasts, and neurons [1–4]. Its function is best characterized in the monocyte/macrophage lineage, where it regulates proliferation, survival, differentiation, and activation [5]. The CSF-1 receptor is activated by binding to CSF-1 or IL-34 [6,7]. Ligand binding results in receptor dimerization, activation of the kinase domain, autophosphorylation on multiple tyrosine residues, and recruitment of cellular signaling proteins that bind to phosphotyrosine-containing recognition sites [8].

More recently, we observed that the CSF-1 receptor is also subject to regulated intramembrane proteolysis or RIPping [9]. RIPping often involves cell surface proteins with a single transmembrane region (Fig. 1). These proteins are first cleaved in the extracellular juxtamembrane region, which results in ectodomain shedding and production of a membrane-bound intracellular domain (mICD) [10]. Products of the first cleavage, integral membrane proteins with a short extracellular domain, are recognized by a second protease that cleaves within the transmembrane region, resulting in the release of a soluble intracellular domain (sICD) into the interior of the cell [11].

The CSF-1 receptor is cleaved in the extracellular juxtamembrane region by TACE [12,13]. TACE is a metalloprotease with a small intracellular region, a single transmembrane region, and an extracellular catalytic domain [14]. The membrane-bound cleavage product is then recognized by γ-secretase (Fig. 1), resulting in the release of the sICD into the interior of the cell [9]. γ-Secretase is an aspartyl protease composed of four subunits: the catalytic subunit presenilin, nicastrin, Aph-1, and Pen-2 [11]. γ-Secretase is best known for its role in the etiology of Alzheimer's disease [11]. While cleavage sites in sixteen of its substrates have been identified, it remains unclear exactly how γ-secretase recognizes these cleavage sites [15]. CSF-1 receptor RIPping occurs in response to various proinflammatory agents, including TPA, lipid A, lipoteichoic acid, polyI:polyC, and bacterial DNA [16]. This suggests that proteolytic processing of the CSF-1 receptor and release of its sICD into the interior of the cell provides a node in the signal transduction pathway that leads to macrophage activation.

2. Materials and methods

2.1. Reagents

Recombinant human CSF-1 was obtained from R&D Systems (Minneapolis, MN). A polyclonal antiserum was raised against the kinase insert domain of the murine CSF-1 receptor. 12-O-tetradecanoylphorbol-13-acetate (TPA) was purchased from Sigma (St. Louis, MO). The γ-secretase inhibitor L-685,458, S-protein agarose, and the anti-phosphotyrosine monoclonal antibody 4G10 were purchased from EMD Millipore (Billerica, MA). Protein A-horseradish peroxidase (HRP) was purchased from Biorad

* Corresponding author. Fax: +1 619 594 4634.
E-mail address: pvanderg@mail.sdsu.edu (P. van der Geer).

http://dx.doi.org/10.1016/j.bbrc.2014.06.061
0006-291X/

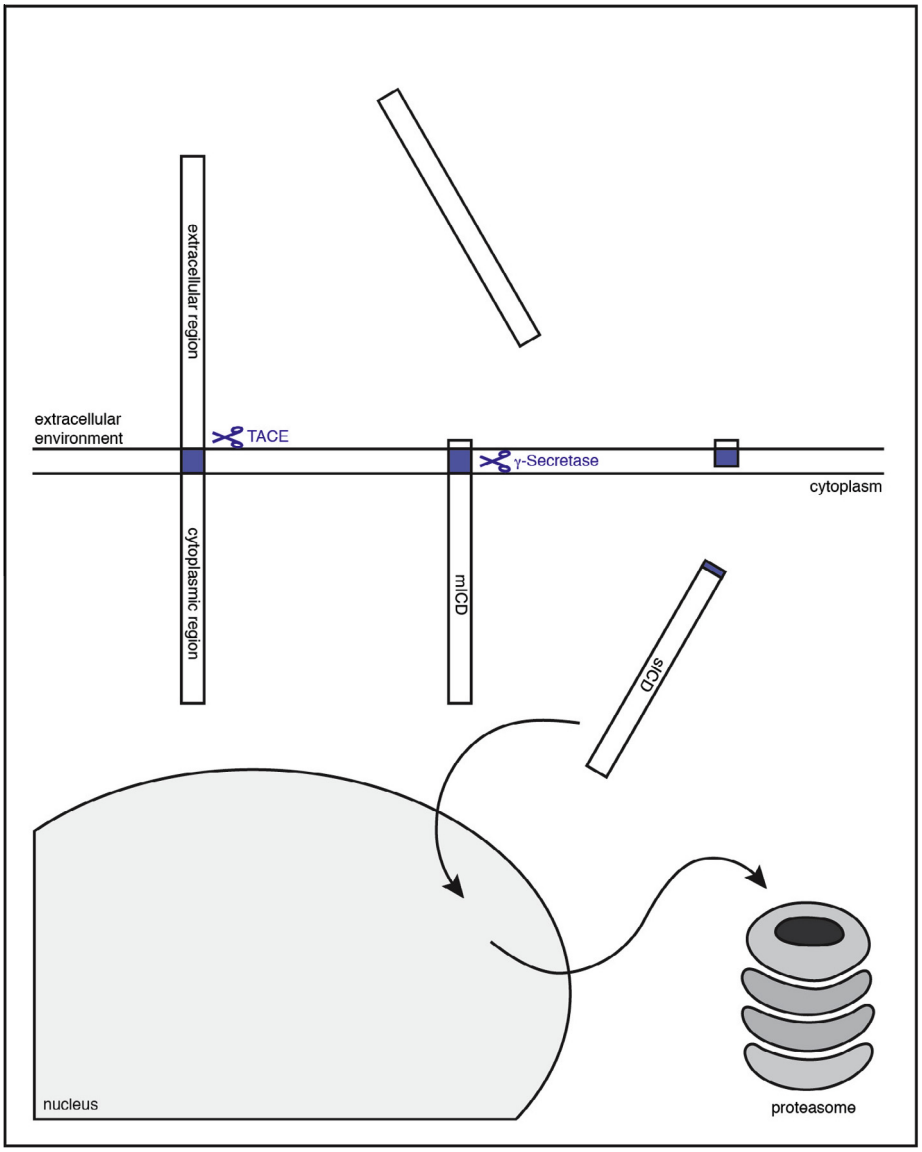

Fig. 1. Regulated intramembrane proteolysis of the CSF-1 receptor. The CSF-1 receptor undergoes RIPping in response to TPA, LPS, bacterial DNA, and other macrophage activators. RIPping is initiated by TACE-mediated cleavage in the extracellular juxtamembrane region, resulting in ectodomain shedding. The membrane associated intracellular domain (mICD) is recognized by γ-secretase, resulting in cleavage in the transmembrane region and release of the soluble intracellular domain (sICD) into the cytoplasm. We have preliminary results suggesting that the sICD localizes in part to the nucleus, where it is likely to be involved in the regulation of gene expression. The sICD has a short half-life and is degraded in the proteasome.

(Hercules, CA). Goat anti-mouse-HRP was purchased from GE Healthcare Biosciences (Piscataway, NJ). G418 was purchased from Life technologies (Grand Island, NY).

2.2. Cell lines

Tagged and chimeric receptor mutants were generated by PCR-mediated mutagenesis. PCR products were sequenced to ensure fidelity and cloned into the full-length cDNA contained in pcDNA3. pcDNA3 constructs were transfected into 293A cells by calcium phosphate precipitation and stable cell lines were selected and grown in DMEM, 10% FBS, and 400 μg/ml G418.

2.3. Whole cell lysates

Control cells or TPA-stimulated cells were rinsed twice with cold Tris-buffered saline (TBS) and lysed in 50 mM Hepes pH 7.5, 150 mM NaCl, 10% glycerol, 1% Triton X-100, 1.5 mM $MgCl_2$, 1 mM EGTA, 100 mM NaF, 10 mM pyrophosphate, 500 μM sodium orthovanadate, 1 mM PMSF, 10 μg/ml aprotinin, and 10 μg/ml leupeptin (PLC lysis buffer). Lysates were cleared by centrifugation for 10 min at 4 °C at 10,000 rpm in a microcentrifuge.

2.4. Cell fractionation

293A cells expressing wild type or chimeric receptors were grown to confluence on 10 cm tissue culture dishes. Control cells or cells stimulated with 100 ng/ml TPA were rinsed once with cold TBS, once with cold 20 mM Tris/Cl pH 7.4, 1 mM $MgCl_2$, 2 mM EGTA, 0.1 mM sodium vanadate, 10 μg/ml aprotinin and 10 μg/ml leupeptin (HLB) and incubated for 10 min at 4 °C in HLB (700 μl per 10 cm dish) followed by Dounce homogenization. Lysates were centrifuged for 45 min at 10,000 rpm in a microfuge at 4 °C to separate the membrane-bound and soluble fractions. Soluble fractions were mixed with 1 volume 2 × PLC lysis buffer. Membrane fractions were solubilized in 1.4 ml PLC lysis buffer and cleared by centrifugation for 10 min at 4 °C in a microcentrifuge.

2.5. S-protein affinity chromatography

293A cells stably expressing carboxy-terminally tagged CSF-1 receptors were grown to confluence on 15 cm issue culture dishes. For purification of the TACE cleavage product cells were pretreated for 1 h with 5 μM γ-secretase inhibitor L-685,458 and stimulated for 20 min with 100 ng/ml TPA. Cells were lysed by hypotonic lysis, the membrane fraction was isolated by centrifugation for 45 min at 10,000 rpm in a microcentrifuge at 4 °C, and the membranes were dissolved PLC lysis buffer. This fraction was cleared by centrifugation for 10 min at 10,000 rpm in a microcentrifuge at 4 °C and the membrane extract was incubated for 1 h on a rotator at 4 °C with S-protein agarose (20 μl bed volume per dish of cells). The agarose beads were washed 4 times with PLC lysis buffer, boiled in SDS-sample buffer, and loaded on a 10% polyacrylamide gel. For purification of the γ-secretase cleavage products, cells were stimulated with TPA in the presence of 3 mM hydrogen peroxide, the cells rinsed twice with TBS, lysed in PLC lysis buffer, and lysates were cleared by centrifugation at 10,000 rpm in a microfuge at 4 °C. Cleared lysates were incubated with S-protein agarose and washed as described above.

2.6. Edman degradation

Determination of the amino-terminal sequence of the TACE and γ-secretase cleavage products was carried out on PVDF membranes containing the cleavage products using an Applied Biosystems PROCISE 494HT Protein Sequenator at the UCSD Protein Sequencing Facility (La Jolla, CA).

2.7. Immunoblotting

Samples were resolved by SDS–PAGE and transferred to PVDF membranes by semi-dry transfer at 50 mA per gel for 50 min at room temperature. Membranes were blocked for 45 min at room temperature in 10 mM Tris/Cl pH 7.4, 150 mM NaCl, 0.2% Tween 20 (TBST) containing 5% milk and then incubated for 45 min at room temperature with a 1:200 dilution of the polyclonal anti-CSF-1 receptor serum raised against the kinase insert region. Blots were washed twice for 10 min in TBST and twice for 5 min in TBS. Membranes were then incubated for 30 min at room temperature with Protein A-HRP diluted 1:10,000 in TBST and washed as described above. For anti-P.Tyr blots the membranes were blocked in TBST containing 5% BSA for 45 min at room temperature and then incubated for 45 min at room temperature with the monoclonal antibody 4G10 diluted in TBST 5% BSA and washed as described above. Membranes were then incubated for 30 min at room temperature with goat anti-mouse-HRP and washed as described above. Reactive proteins were visualized by ECL.

3. Results

We have shown previously that the CSF-1 receptor undergoes regulated intramembrane proteolysis. During this process the receptor is cleaved in the extracellular juxtamembrane region followed by cleavage in or close to the transmembrane region (Fig. 1). Exact localization of cleavage sites requires isolation of the cleavage products, followed by amino-terminal sequencing. For routine analysis of processing, the CSF-1 receptor or its cleavage products are isolated by immunoprecipitation followed by SDS–PAGE. Unfortunately, the cleavage products to be analyzed co-migrate with the immunoglobulin heavy chain during electrophoresis. The presence of antibodies interferes with sequence analysis. To circumvent the use of antibodies during isolation, we engineered a CSF-1 receptor containing a His-tag, followed by the S-peptide, and a KT3 epitope at its carboxy-terminus (Fig. 2A). Tagged receptors were stably expressed in 293A cells. Cells were stimulated to initiate receptor processing and cleavage products were purified using batch-wise S-protein affinity chromatography [17]. Bound proteins were resolved by SDS–PAGE, transferred to PVDF membranes, and detected by immunoblotting or GelCode Blue staining (Fig. 2B).

The TPA-inducible TACE cleavage site was identified from 293A cells stably expressing the tagged CSF-1 receptor pretreated with the γ-secretase inhibitor, L-685,458, for 1 h, followed by stimulation with TPA for 20 min. The γ-secretase inhibitor was included to prevent the second cleavage and to optimize recovery of the TACE cleavage product. Cells were lysed by hypotonic lysis followed by Dounce homogenization. Cleavage products present in the particulate fraction were purified. Edman degradation yielded the following amino-terminal sequence, SKQLPDES, indicating that the CSF-1 receptor is cleaved by TACE between Gln^{503} and Ser^{504}, 12 amino acid residues amino-terminal to the start of the transmembrane region (Fig. 2C). The γ-secretase cleavage site was identified from cells that were induced for 20 min with TPA and H_2O_2. H_2O_2 was included because it inhibits degradation of the soluble intracellular domain. Cleavage products purified from control and stimulated cells were visualized by immunoblotting and GelCode Blue staining (Fig. 2B). Amino-terminal sequencing yielded a major and a minor sequence, LLLYKYKQKP and YKYKQKP respectively. This shows that the CSF-1 receptor contains a major γ-secretase cleavage site between Leu^{532} and Leu^{533} and a minor γ-secretase cleavage site between Leu^{535} and Tyr^{536} (Fig. 2C). Constitutive and CSF-1-induced processing yielded identical cleavage sites (results not shown).

To confirm the identification of the TACE cleavage site, two chimera were constructed, in which the 14 amino acid residues immediately amino-terminal to the transmembrane region were replaced with homologous sequences derived from the insulin

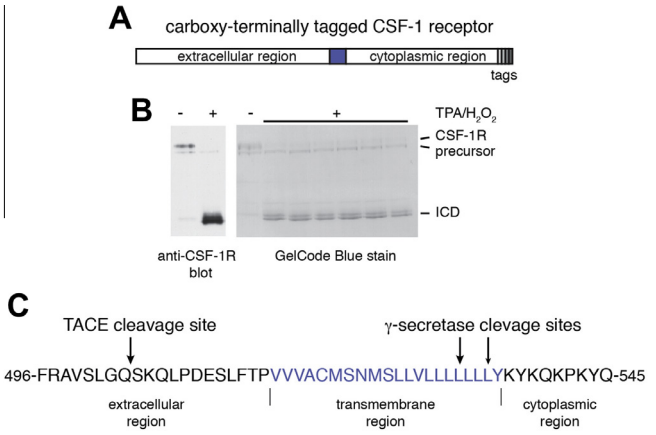

Fig. 2. Identification of TACE and γ-secretase cleavage sites in the CSF-1 receptor. (A) A CSF-1 receptor linked at its carboxy-terminus to a His-tag, followed by an S-tag and a KT3-tag was stably expressed in 293A cells. The transmembrane region is shown in blue, the carboxy-terminal tags are shown in various shades of gray. (B) To identify the γ-secretase cleavage products, cells expressing tagged CSF-1 receptors were stimulated with TPA in the presence of hydrogen peroxide. Unstimulated cells were analyzed in parallel as a control. Cell lysates were incubated with S-protein agarose, bound proteins were resolved by SDS–PAGE and visualized by anti-CSF-1 receptor immunoblotting or GelCode Blue staining. Similarly, TACE cleavage products were isolated from the membrane fraction of TPA-stimulated cells pretreated with the γ-secretase inhibitor L-685,458 (not shown). (C) Cleavage sites were identified by amino-terminal sequencing of the cleavage products. The cleavage sites are marked on a part of the receptor's amino acid sequence running from phenylalanine 496 to glutamine 545, numbering according to Rothwell and Rohrschneider [28]. Residues comprising the transmembrane region are shown in blue. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

receptor and α PDGF receptor (Fig. 3A). Wild type and chimeric receptors were stably expressed in 293A cells. To ensure that the chimera were functional and present on the cell surface, cells were stimulated with CSF-1 and cell lysates were analyzed by anti-P.Tyr and anti-CSF-1 receptor immunoblotting (Fig. 3B). The results show that both chimeric receptors can be activated by exposure of cells to CSF-1 (Fig. 3B). To test whether the chimera were able to undergo RIPping, the cells were stimulated with TPA for 20 and 60 min and cell lysates were analyzed for the presence of full-length receptors and cleavage products by anti-CSF-1 receptor immunoblotting (Fig. 3C). As expected, stimulation with TPA resulted in the disappearance of wild type receptors and the transient appearance of the 50 kDa ICD (Fig. 3C, lanes 1–3). In contrast, receptors containing the insulin receptor extracellular juxtamembrane region were unable to undergo cleavage; neither the disappearance of mature receptors nor the appearance of the ICD were observed following stimulation with TPA (Fig. 3C, lanes 4–6). Unexpectedly, receptors containing the α PDGF receptor extracellular juxtamembrane region were efficiently processed in response to TPA (Fig. 3C, lanes 7–9). These results confirm the identification of the TACE cleavage site and show that TACE-mediated cleavage of the CSF-1 receptor is dependent on sequences immediately amino-terminal to the transmembrane region.

To confirm the identification of the γ-secretase cleavage site in the transmembrane region, two chimera were analyzed for their ability to undergo intramembrane cleavage. In the first chimera the CSF-1 receptor transmembrane region was replaced with the transmembrane region of the insulin receptor (Fig. 4A, CSF-1R/IR_{tm}). In the second chimera the carboxy-terminal six residues of the transmembrane region were replaced with those present in the insulin receptor (Fig. 4A, CSF-$1R_{SIYLFL}$). To monitor stability of the ICD, 293A cells expressing wild type receptors or chimera were stimulated with TPA for 20 or 90 min and cell lysates were analyzed by anti-CSF-1 receptor immunoblotting. In cells expressing wild type receptors, low levels of the ICD were present in unstimulated cells. The ICD levels went up following stimulation with TPA, and returned to control levels by 90 min (Fig. 4B, lanes 1–3 and 10–12). When cells expressing the wild type receptor were stimulated with TPA in the presence of the γ-secretase inhibitor L-685,458, we observed stabilization of the ICD (Fig. 4B, lanes 4–6). Replacing the complete transmembrane region or the carboxy-terminal six residues of the transmembrane region with homologous sequences from the insulin receptor resulted in stabilization of the ICD, suggesting that these chimera are not subject to cleavage by γ-secretase (Fig. 4B, lanes 7–9 and 13–15). The ICD has to be released from the plasma membrane before it can be degraded by the proteasome. To investigate this further, 293A cells expressing wild type or chimeric receptors were stimulated with TPA for 20 or 90 min, lysed by hypotonic lysis followed by separation into a membrane-bound and a soluble fraction. Processing of wild type receptors resulted in the transient appearance of a membrane-bound ICD (Fig. 4C, lanes 1–3 and 13–15). Membrane-bound levels went down as the ICD was released into the soluble fraction, followed by its degradation (Fig. 4C, lanes 7–9 and 19–21). Replacement of the complete transmembrane region or the carboxy-terminal six amino acids of the transmembrane region by those of the insulin receptor did not affect the appearance of the ICD in the membrane-bound fraction (Fig. 4C, lanes 4–6 and 16–18). However, the ICD disappeared very slowly from the membrane-bound fraction and could not be detected in the soluble fraction (Fig. 4C, lanes 10–12 and 22–24). These results confirm the identification of the γ-secretase cleavage site and strongly suggest that cleavage is dependent of sequences surrounding the cleavage site.

4. Discussion

RIPping of the CSF-1 receptor is initiated through TACE-mediated cleavage in the extracellular juxtamembrane region [12,13]. In the current study we have determined that TACE cleaves the receptor between Gln^{503} and Ser^{504}. TACE was originally purified as the enzyme that releases tumor necrosis factor-α (TNFα)

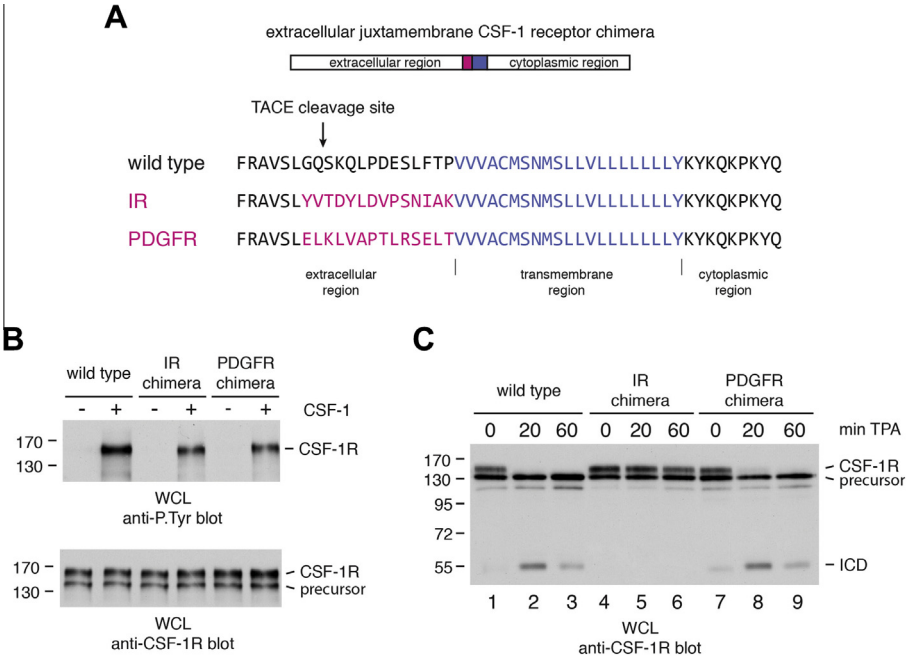

Fig. 3. The extracellular juxtamembrane region determines the sensitivity to TACE cleavage. (A) Schematic representation of CSF-1 receptor chimera and relevant sequences. In these chimera, 14 residues immediately amino-terminal to the transmembrane region of the CSF-1 receptor were replaced by those present in the insulin receptor or the α PDGF receptor. The transmembrane region is shown in blue, sequences from the insulin and α PDGF receptors are shown in magenta. (B) Wild type and chimeric receptors were stably expressed in 293A cells. Lysates from control and CSF-1-stimulated cells were analyzed by anti-CSF-1 receptor and anti-P.Tyr immunoblotting. (C) Lysates from control and TPA-stimulated cells expressing wild type and chimeric receptors were analyzed by anti-CSF-1 receptor immunoblotting. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

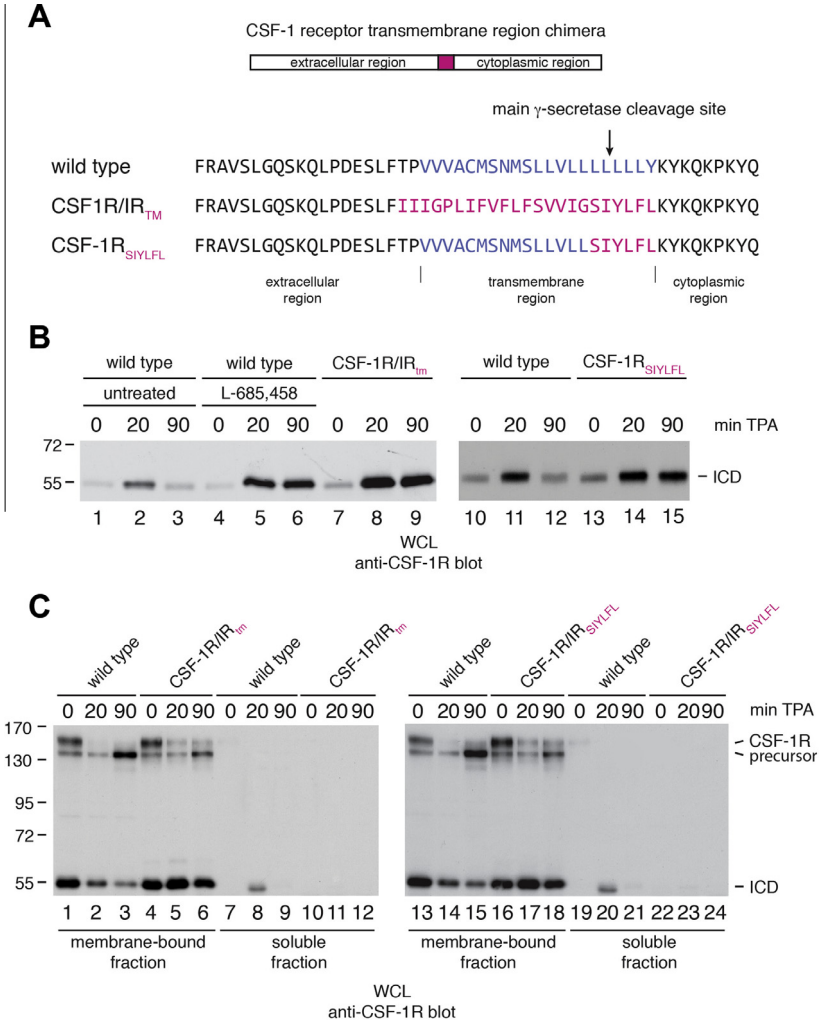

Fig. 4. The transmembrane sequence of the CSF-1 receptor determines its sensitivity to γ-secretase cleavage. (A) Schematic representation and relevant sequences of chimera in which amino acid sequences in the transmembrane region of the CSF-1 receptor were replaced with sequences derived from the insulin receptor. CSF-1 receptor transmembrane sequences are shown in blue, sequences derived from the insulin receptor are shown in magenta. (B) Lysates from control and TPA-stimulated cells expressing wild type or transmembrane chimera were analyzed for the presence of the ICD by anti-CSF-1 receptor immunoblotting. Cells expressing wild type receptors pretreated with the γ-secretase inhibitor L-685,458 were included as a control. (C) Control or TPA-stimulated cells expressing wild type receptors or transmembrane chimera were lysed by hypotonic lysis and separated into membrane-bound and soluble fractions. Both fractions were analyzed for the presence of the full-length receptor and the ICD by anti-CSF-1 receptor immunoblotting. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

from its membrane bound precursor [18]. In vitro cleavage studies using peptide substrates suggest that TACE prefers to cleave the Ala-Val site that is present in the TNFα precursor [19,20]. However, identification of additional TACE substrates suggests that TACE has a broader substrate specificity in vivo [21,22]. The presence of cleavage sites in amphiregulin and epiregulin, where TACE cleaves carboxy-terminal to Gln, and in L-selectin and the TNF receptor, where TACE cleaves amino-terminal to Ser, is consistent with our identification of a Gln-Ser cleavage site in the CSF-1 receptor [23–25].

A chimeric receptor in which 14 amino acids amino-terminal to the transmembrane region have been replaced with those present in the insulin receptor did not undergo cleavage, suggesting that the sequences in this region are important for the interaction with TACE. Interestingly, a chimeric receptor in which the same 14 residues were replaced with those present in the α PDGF receptor did undergo cleavage. This suggests the possibility that the α PDGF receptor, which is closely related to the CSF-1 receptor and to c-Kit, the stem cell receptor, could act as a substrate for TACE as well [26]. Finally, the wild type receptor and both chimera contain an Ala-Val site 18 amino acids amino-terminal to the transmembrane region (Fig. 3A). Our results indicate that this site is not being used, suggesting an important role for sequences adjacent to the cleavage site during the interaction with TACE. In addition, the distance between the cleavage site and the membrane may be important.

We have previously shown that release of the CSF-1 receptor ICD from the membrane can be inhibited using γ-secretase inhibitors [9]. Here we have identified a major and a minor γ-secretase cleavage site, between L^{532} and L^{533} and between Leu^{535} and Tyr^{536}, respectively. It is possible that γ-secretase cleaves once either carboxy-terminal to Leu^{532} or carboxy-terminal to Leu^{535}. Alternatively, γ-secretase could act processively, first cleaving carboxy-terminal to Leu^{532} and subsequently carboxy-terminal to Leu^{535}. Our observations are consistent with other studies reporting multiple cleavage sites in γ-secretase substrates [15].

Exactly how γ-secretase recognizes its substrates remains unresolved. Because of the heterogeneity of cleavage sites, some have proposed that cleavage is independent of the sequence and that substrates are recognized as type I integral membrane protein with a very short (average length of the extracellular domain is 15 amino acids) extracellular region. This idea is supported by the observation that nicastrin is involved in substrate selection by

binding to the amino-terminal amino group of substrate proteins [27]. Our results show that replacement of complete transmembrane region or six amino acids surrounding the cleavage site with those of the insulin receptor blocks efficient cleavage of the CSF-1 receptor by γ-secretase in cells. Thus, substrate recognition by γ-secretase involves the length of the extracellular region as well as the sequence of the transmembrane domain.

In summary, we have identified the TACE and γ-secretase cleavage sites in the CSF-1 receptor and we have created mutants that are resistant to cleavage. These observations contribute to our understanding of substrate selection by both TACE and γ-secretase and the mutants created here will be used to further investigate the biological function of CSF-1 receptor RIPping.

Acknowledgment

This work was supported in part by the California Metabolic Research Foundation.

References

[1] J.W. Pollard, A. Bartocci, R. Arceci, A. Orlofsky, M.B. Ladner, E.R. Stanley, Apparent role of the macrophage growth factor, CSF-1, in placental development, Nature 330 (1987) 484–486.
[2] Y. Wang, O. Berezovska, S. Fedoroff, Expression of colony stimulating factor-1 receptor (CSF-1R) by CNS neurons in mice, J. Neurosci. Res. 57 (1999) 616–632.
[3] T. Inaba, N. Yamada, T. Gotoda, H. Shimano, M. Shimada, K. Momomura, T. Kadowaki, K. Motoyoshi, T. Tsukada, N. Morisaki, et al., Expression of M-CSF receptor encoded by c-fms on smooth muscle cells derived from arteriosclerotic lesion, J. Biol. Chem. 267 (1992) 5693–5699.
[4] E. Sariban, T. Mitchell, D. Kufe, Expression of the c-fms proto-oncogene during human monocytic differentiation, Nature 316 (1985) 64–66.
[5] F.J. Pixley, E.R. Stanley, CSF-1 regulation of the wandering macrophage: complexity in action, Trends Cell Biol. 14 (2004) 628–638.
[6] C.J. Sherr, C.W. Rettenmier, R. Sacca, M.F. Roussel, A.T. Look, E.R. Stanley, The c-*fms* proto-oncogene product is related to the receptor for the mononuclear phagocyte growth factor, CSF-1, Cell 41 (1985) 665–676.
[7] H. Lin, E. Lee, K. Hestir, C. Leo, M. Huang, E. Bosch, R. Halenbeck, G. Wu, A. Zhou, D. Behrens, D. Hollenbaugh, T. Linnemann, M. Qin, J. Wong, K. Chu, S.K. Doberstein, L.T. Williams, Discovery of a cytokine and its receptor by functional screening of the extracellular proteome, Science 320 (2008) 807–811.
[8] K.A. Mouchemore, F.J. Pixley, CSF-1 signaling in macrophages: pleiotropy through phosphotyrosine-based signaling pathways, Crit. Rev. Clin. Lab. Sci. 49 (2012) 49–61.
[9] K. Wilhelmsen, P. van der Geer, Phorbol 12-myristate 13-acetate-induced release of the colony-stimulating factor 1 receptor cytoplasmic domain into the cytosol involves two separate cleavage events, Mol. Cell Biol. 24 (2004) 454–464.
[10] J. Arribas, A. Borroto, Protein ectodomain shedding, Chem. Rev. 102 (2002) 4627–4638.
[11] D.J. Selkoe, M.S. Wolfe, Presenilin: running with scissors in the membrane, Cell 131 (2007) 215–221.
[12] E. Rovida, A. Paccagnini, M. DelRosso, J. Peschon, P. DelloSbarba, TNF-alpha-converting enzyme cleaves the macrophage colony-stimulating factor receptor in macrophages undergoing activation, J. Immunol. 166 (2001) 1583–1589.
[13] G. Glenn, P. van der Geer, CSF-1 and TPA stimulate independent pathways leading to lysosomal degradation or regulated intramembrane proteolysis of the CSF-1 receptor, FEBS Lett. 581 (2007) 5377–5381.
[14] R.A. Black, Tumor necrosis factor-[alpha] converting enzyme, Int. J. Biochem. Cell Biol. 34 (2002) 1–5.
[15] A.J. Beel, C.R. Sanders, Substrate specificity of gamma-secretase and other intramembrane proteases, Cell. Mol. Life Sci. 65 (2008) 1311–1334.
[16] G. Glenn, P. van der Geer, Toll-like receptors stimulate regulated intramembrane proteolysis of the CSF-1 receptor through Erk activation, FEBS Lett. 582 (2008) 911–915.
[17] R.T. Raines, M. McCormick, T.R. Van Oosbree, R.C. Mierendorf, The S.Tag fusion system for protein purification, Methods enzymol. 326 (2000) 362–376.
[18] R.A. Black, C.T. Rauch, C.J. Kozlosky, J.J. Peschon, J.L. Slack, M.F. Wolfson, B.J. Castner, K.L. Stocking, P. Reddy, S. Srinivasan, N. Nelson, N. Boiani, K.A. Schooley, M. Gerhart, R. Davis, J.N. Fitzner, R.S. Johnson, R.J. Paxton, C.J. March, D.P. Cerretti, A metalloproteinase disintegrin that releases tumour-necrosis factor-alpha from cells, Nature 385 (1997) 729–733.
[19] R.A. Black, J.R. Doedens, R. Mahimkar, R. Johnson, L. Guo, A. Wallace, D. Virca, J. Eisenman, J. Slack, B. Castner, S.W. Sunnarborg, D.C. Lee, R. Cowling, G. Jin, K. Charrier, J.J. Peschon, R. Paxton, Substrate specificity and inducibility of TACE (tumour necrosis factor alpha-converting enzyme) revisited: the Ala-Val preference, and induced intrinsic activity, Biochem. Soc. Symp. (2003) 39–52.
[20] M.J. Mohan, T. Seaton, J. Mitchell, A. Howe, K. Blackburn, W. Burkhart, M. Moyer, I. Patel, G.M. Waitt, J.D. Becherer, M.L. Moss, M.E. Milla, The tumor necrosis factor-alpha converting enzyme (TACE): a unique metalloproteinase with highly defined substrate selectivity, Biochemistry 41 (2002) 9462–9469.
[21] C.I. Caescu, G.R. Jeschke, B.E. Turk, Active-site determinants of substrate recognition by the metalloproteinases TACE and ADAM10, Biochem. J. 424 (2009) 79–88.
[22] J. Scheller, A. Chalaris, C. Garbers, S. Rose-John, ADAM17: a molecular switch to control inflammation and tissue regeneration, Trends Immunol. 32 (2011) 380–387.
[23] C.L. Hinkle, S.W. Sunnarborg, D. Loiselle, C.E. Parker, M. Stevenson, W.E. Russell, D.C. Lee, Selective roles for tumor necrosis factor alpha-converting enzyme/ADAM17 in the shedding of the epidermal growth factor receptor ligand family: the juxtamembrane stalk determines cleavage efficiency, J. Biol. Chem. 279 (2004) 24179–24188.
[24] J. Kahn, R.H. Ingraham, F. Shirley, G.I. Migaki, T.K. Kishimoto, Membrane proximal cleavage of L-selectin: identification of the cleavage site and a 6-kD transmembrane peptide fragment of L-selectin, J. Cell Biol. 125 (1994) 461–470.
[25] S.W. Sunnarborg, C.L. Hinkle, M. Stevenson, W.E. Russell, C.S. Raska, J.J. Peschon, B.J. Castner, M.J. Gerhart, R.J. Paxton, R.A. Black, D.C. Lee, Tumor necrosis factor-alpha converting enzyme (TACE) regulates epidermal growth factor receptor ligand availability, J. Biol. Chem. 277 (2002) 12838–12845.
[26] Y. Yarden, J.A. Escobedo, W.-J. Kuang, T.L. Yang-Feng, T.O. Daniel, P.M. Tremble, E.Y. Chen, M.E. Ando, R.N. Harkins, U. Francke, V.A. Fried, A. Ullrich, L.T. Williams, Structure of the receptor for platelet-derived growth factor helps define a family of closely related growth factor receptors, Nature 323 (1986) 226–232.
[27] S. Shah, S.-F. Lee, K. Tabuchi, Y.-H. Hao, C. Yu, Q. LaPlant, H. Ball, C.E. Dannlii, T. Sdhof, G. Yu, Nicastrin functions as a [gamma]-secretase-substrate receptor, Cell 122 (2005) 435–447.
[28] V.M. Rothwell, L.R. Rohrschneider, Murine c-*fms* cDNA: cloning, sequence analysis and retroviral expression, Oncogene Res. 1 (1987) 311–324.