ADAM 17 endopeptidase 3.4.24.86

1 Nomenclature

EC number
3.4.24.86

Recommended name
ADAM 17 endopeptidase

Synonyms
(TACE/ADAM17/CD156q) <3> [29]
(TACE:ADAM17) <3> [19]
ADAM-17 <2, 3> [53, 54, 57]
ADAM17 <2, 3, 4> [44, 45, 55, 61]
ADAM17 proteinase
ADAM17/tumor necrosis factor-α (TNF-A)converting enzyme <3> [43]
H-TACE <3> [7]
TACE <1, 2, 3, 4, 5> [39, 41, 45, 46, 50, 54, 58, 60, 61]
TACE proteinase
TACE/ADAM17 <2, 3> [38, 42]
TNF-α convertase
TNF-α converting enzyme
TNF-α processing protease
human TACE B <3> [14]
metalloprotease TACE
metalloprotease-disintegrin tumour necrosis factor α convertase <3> [8]
metalloproteinase ADAM17
pro tumor necrosis factor cleavage enzyme
pro-tumor necrosis factor-α-processing enzyme
proteinase, pro-tumor necrosis factor (9CI)
sheddase <3> [12]
tumor necrosis factor α convertase
tumor necrosis factor α-converting enzyme
tumor necrosis factor-α converting enzyme <5> [41]
tumor necrosis factor-α-converting enzyme <1> [39]

CAS registry number
151769-16-3

2 Source Organism

<1> *Cricetulus griseus* (no sequence specified) [39, 51]
<2> *Mus musculus* (no sequence specified) [2, 3, 4, 6, 7, 10, 11, 14, 15, 17, 18, 23, 24, 25, 26, 27, 29, 33, 34, 35, 36, 38, 44, 50, 51, 53, 54, 55]
<3> *Homo sapiens* (no sequence specified) (<3> gene ACL5-1 [2, 4, 5, 7, 8, 9, 10, 11, 12]) [2, 4, 5, 7, 8, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 38, 42, 43, 44, 45, 46, 48, 49, 52, 57, 59, 60]
<4> *Rattus norvegicus* (no sequence specified) (<4> succinate dehydrogenase cytochrome B small subunit [3,23]) [3, 23, 56, 58, 59, 61]
<5> *Sus scrofa* (no sequence specified) (<5> fragment NCED52 [10, 28]) [10, 28, 40, 41]
<6> *Oryctolagus cuniculus* (no sequence specified) (<6> fragment of dihydropteroate synthase [18]) [18]
<7> *Cercopithecus aethiops* (no sequence specified) [17,34]
<8> *Homo sapiens* (UNIPROT accession number: P78536) [14]
<9> *Rattus norvegicus* (UNIPROT accession number: Q9Z1K9) [1]
<10> *Sus scrofa* (UNIPROT accession number: O77636) [37]
<11> *Cricetulus griseus* (UNIPROT accession number: Q923X3) [1]
<12> *Cricetulus griseus* (UNIPROT accession number: Q6W3F8) [47]
<13> *Cricetulus griseus* (UNIPROT accession number: Q6W3F7) [47]
<14> *Cricetulus griseus* (UNIPROT accession number: Q6W3F6) [47]

3 Reaction and Specificity

Catalyzed reaction

Narrow endopeptidase specificity. Cleaves Pro-Leu-Ala-Gln-AlaVal-Arg-Ser-Ser-Ser in the membrane-bound, 26-kDa form of tumor necrosis factor a (TNFa). Similarly cleaves other membrane-anchored, cell-surface proteins to "shed" the extracellular domains

Natural substrates and products

S Alzheimer's disease amyloid precursor protein + H_2O <3> (<3> TACE is involved in shedding of Alzheimers disease amyloid precursor protein [45]) (Reversibility: ?) [45]
P ?
S TNF-α + H_2O <2, 3> (<3> membrane-bound tumor necrosis factor α undergoes proteolysis [2]) (Reversibility: ?) [2, 5]
P soluble TNF-α
S α-chain of interleukin 15 receptor + H_2O <2> (<2> transmembrane α-chain of interleukin 15 receptor is constitutively converted into its soluble form by proteolytic cleavage that involves tumor necrosis factor-α-converting enzyme [50]) (Reversibility: ?) [50]
P soluble α-chain of interleukin 15 receptor
S amphiregulin + H_2O <2> (Reversibility: ?) [55]

P ?
S angiotensin-converting enzyme-2 + H_2O <2> (<2> ADAM-17 is responsible for the ACE2 shedding [53]) (Reversibility: ?) [53]
P ?
S epiregulin + H_2O <2> (Reversibility: ?) [55]
P ?
S glycoprotein Ibα + H_2O <2, 3> (<2,3> ADAM17 is the key enzyme mediating shedding of glycoprotein Ibα [44]) (Reversibility: ?) [44]
P ?
S growth factor α + H_2O <2> (Reversibility: ?) [55]
P ?
S heparin-binding EGF-like growth factor + H_2O <2> (Reversibility: ?) [55]
P ?
S intercellular adhesion molecule-1 + H_2O <2> (<2> ADAM-17 mediates shedding of intercellular adhesion molecule-1. The shedding of intercellular adhesion molecule-1 reduces the adhesive capacity of the cells. the cleavage site in the intercellular adhesion molecule-1 is not sequence-specific, but appears to be nonselective [54]) (Reversibility: ?) [54]
P ?
S p75 neurotrophin receptor + H_2O <1, 2> (<1,2> critical role of TACE in ectodomain shedding of the p75 neurotrophin receptor [51]) (Reversibility: ?) [51]
P ?
S preadipocyte factor 1 + H_2O <3> (<3> TACE is the major protease responsible for conversion of membrane-bound Pref-1 to the biologically active diffusible form [60]) (Reversibility: ?) [60]
P ?
S receptor tyrosine kinase c-Kit + H_2O <3> (<3> ADAM-17 controls mast cell survival by regulating shedding and surface expression of c-Kit [52]) (Reversibility: ?) [52]
P ?
S Additional information <3, 4> (<3> ectodomain shedding of the hypoxia-induced carbonic anhydrase IX is a metalloprotease-dependent process regulated by TACE/ADAM17 [42]; <3> TACE is not involved in shedding of angiotensin converting enzyme [45]; <3> TACE may have a role in phorbol myristate acetate-induced shedding of epiregulin [46]; <4> TACE-mediated ectodomain shedding of erbB ligands, epitomized by TGFα is a key component of the neuron-to-glia signaling mechanism used by excitatory amino acids to facilitate the advent of female puberty [58]) (Reversibility: ?) [42, 45, 46, 58]
P ?

Substrates and products

S 4',5'-dimethoxyfluoresceinyl-SPLAQAVRSSSR-cys(4-(3-succinimid-1-yl)-fluorescein)-NH_2 + H_2O <3> (Reversibility: ?) [30]
P ?
S 75kDaTNFR2 + H_2O <3, 5> (Reversibility: ?) [23, 28, 33, 36]

P ?
S Alzheimer's disease amyloid precursor protein + H_2O <3> (<3> TACE is involved in shedding of Alzheimers disease amyloid precursor protein [45]) (Reversibility: ?) [45]
P ?
S BTC + H_2O <2> (Reversibility: ?) [35]
P ?
S CD30 + H_2O <3> (Reversibility: ?) [33]
P ?
S EPR + H_2O <2> (Reversibility: ?) [35]
P ?
S GHR + H_2O <3> (Reversibility: ?) [33]
P ?
S HB-EGF heparin binding epidermal growth factor + H_2O <2> (Reversibility: ?) [35]
P ?
S HER-4 Jma + H_2O <3> (Reversibility: ?) [32]
P ?
S KL-1 + H_2O <3> (Reversibility: ?) [33]
P ?
S L-selectin + H_2O <2, 3> (<3> shedding [8]; <3> regulates plasma membrane composition and releases soluble signaling molecules and receptors from cells [12]) (Reversibility: ?) [8, 12, 14, 17, 32, 33, 36]
P ?
S LAQAVRSSSR + H_2O <3> (<3> fluorimetric assay for TACE, fluorogenic substrate, a 10-amino-acid peptide capped with an *o*-aminobenzoyl group on the N-terminal end and with a 3-(2,4-dinitrophenyl)-L-2,3-diaminopropionic amide group on the C-terminal end, enzymatic conversion of the substrate results in a fluorescence enhancement of 11fold [30]) (Reversibility: ?) [30]
P ?
S Mca-PLAQAV-N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl amide-RSSSR-NH_2 + H_2O <3> (Reversibility: ?) [30]
P ?
S NH_2-LAQAVRSSSR-OH + H_2O <3> (<3> uncapped counterpart of the fluorogenic substrate [30]) (Reversibility: ?) [30]
P ?
S RANKL + ? <3> (Reversibility: ?) [33]
P ?
S TNF-α + H_2O <2, 3> (<3> membrane-bound tumor necrosis factor α undergoes proteolysis [2]) (Reversibility: ?) [2, 5]
P soluble TNF-α
S TRANCE + H_2O <3> (Reversibility: ?) [33]
P ?
S α-chain of interleukin 15 receptor + H_2O <2> (<2> transmembrane α-chain of interleukin 15 receptor is constitutively converted into its soluble

form by proteolytic cleavage that involves tumor necrosis factor-α-converting enzyme [50]) (Reversibility: ?) [50]
P soluble α-chain of interleukin 15 receptor
S amphiregulin + H_2O <2> (Reversibility: ?) [55]
P ?
S angiotensin-converting enzyme-2 + H_2O <2> (<2> ADAM-17 is responsible for the ACE2 shedding [53]) (Reversibility: ?) [53]
P ?
S β-amyloid precursor protein + H_2O <2, 3> (<3> shedding [8]; <3> Alzheimer amyloid precursor protein [24,25,29,33,34,36]; <3> α-secretase processing [12]; <3> APP [25,33]) (Reversibility: ?) [8, 12, 17, 24, 25, 29, 33, 34, 36]
P ?
S c-KLR + H_2O <3> (Reversibility: ?) [33]
P ?
S cellular prion protein PrPc + H_2O <3> (Reversibility: ?) [27, 33]
P ?
S epiregulin + H_2O <2> (Reversibility: ?) [55]
P ?
S erbB4/HER4 + H_2O <2> (<2> epidermal growth factor, essential function in heart and neural development, TACE is essential for regulated shedding of the HER4 JM-a receptor [15]) (Reversibility: ?) [15]
P ?
S fractalkine + H_2O <3> (<3> FK, CX3CL1 [19,26,33]) (Reversibility: ?) [19, 26, 32, 33]
P ?
S glycoprotein Ibα + H_2O <2, 3> (<2,3> ADAM17 is the key enzyme mediating shedding of glycoprotein Ibα [44]) (Reversibility: ?) [44]
P ?
S growth factor α + H_2O <2> (Reversibility: ?) [55]
P ?
S growth hormone binding protein + H_2O <2> (<2> shedding, TACE is critical for PMA-induced GH receptor proteolysis and GHBP generation [18]) (Reversibility: ?) [18]
P ?
S growth hormone receptor + H_2O <1> (<1> growth hormone receptor/TACE interaction precedes proteolysis and is transient [39]) (Reversibility: ?) [39]
P ?
S heparin-binding EGF-like growth factor + H_2O <2> (Reversibility: ?) [55]
P ?
S intercellular adhesion molecule-1 + H_2O <2> (<2> ADAM-17 mediates shedding of intercellular adhesion molecule-1. The shedding of intercellular adhesion molecule-1 reduces the adhesive capacity of the cells. The cleavage site in the intercellular adhesion molecule-1 is not sequence-specific, but appears to be nonselective [54]) (Reversibility: ?) [54]
P ?

S interleukin (IL)-1R-II + H_2O <2, 3> (Reversibility: ?) [14, 29]
P ?
S interleukin-6-receptor + H_2O <3> (Reversibility: ?) [19, 32, 33]
P ?
S macrophage colony-stimulating factor receptor M-CSFR + H_2O <3> (Reversibility: ?) [24, 33]
P ?
S notch 1 receptor + H_2O <3> (Reversibility: ?) [33]
P ?
S *o*-aminobenzoyl-LAQAFRSSSR-N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl amide + H_2O <3> (<3> enzymatic cleavage 22% [30]) (Reversibility: ?) [30]
P ?
S *o*-aminobenzoyl-LAQAIRSSSR-N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl amide + H_2O <3> (<3> enzymatic cleavage 66% [30]) (Reversibility: ?) [30]
P ?
S *o*-aminobenzoyl-LAQALRSSSR-N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl amide + H_2O <3> (<3> enzymatic cleavage 92% [30]) (Reversibility: ?) [30]
P ?
S *o*-aminobenzoyl-LAQAVRSSSR-N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl amide + H_2O <3> (<3> enzymatic cleavage 90% [30]) (Reversibility: ?) [30]
P ?
S *o*-aminobenzoyl-LAQFVRSSSR-N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl amide + H_2O <3> (<3> enzymatic cleavage 39% [30]) (Reversibility: ?) [30]
P ?
S *o*-aminobenzoyl-LAQGVRSSSR-N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl amide + H_2O <3> (<3> enzymatic cleavage 11% [30]) (Reversibility: ?) [30]
P ?
S *o*-aminobenzoyl-LAQLVRSSSR-N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl amide + H_2O <3> (<3> enzymatic cleavage 34% [30]) (Reversibility: ?) [30]
P ?
S *o*-aminobenzoyl-LAQVARSSSR-N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl amide + H_2O <3> (<3> enzymatic cleavage 19% [30]) (Reversibility: ?) [30]
P ?
S p55 TNFR1 + H_2O <2, 3, 5> (Reversibility: ?) [14, 23, 28, 29, 33]
P ?
S p75 neurotrophin receptor + H_2O <1, 2> (<1,2> critical role of TACE in ectodomain shedding of the p75 neurotrophin receptor [51]) (Reversibility: ?) [51]
P ?

S p75 tumour necrosis factor receptor + H_2O <2, 3, 5> (<2,3> shedding [8,14]) (Reversibility: ?) [8, 14, 17, 28]
P ?
S preadipocyte factor 1 + H_2O <3> (<3> TACE is the major protease responsible for conversion of membrane-bound Pref-1 to the biologically active diffusible form [60]) (Reversibility: ?) [60]
P ?
S pro amphiregulin + H_2O <3> (<3> TACE is capable of cleaving both N- and C-terminal sites in the pro-amphiregulin ectodomain [46]) (Reversibility: ?) [46]
P
S pro heparin-binding epidermal growth factor + H_2O <3> (<3> purified soluble TACE cleaves a single site in the juxtamembrane stalk of pro heparin-binding epidermal growth factor [46]) (Reversibility: ?) [46]
P ?
S pro-TGF-α + H_2O <2> (Reversibility: ?) [35]
P mature growth factor
S proTNF-α + H_2O <2, 3> (<3> membrane-bound tumor necrosis factor α undergoes proteolysis [2]) (Reversibility: ?) [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36]
P soluble TNF-α <3> (<3> release of proTNFα from cellular membranes [5]; <3> release of membrane-bound TNF-α [4]) [4, 5]
S receptor tyrosine kinase c-Kit + H_2O <3> (<3> ADAM-17 controls mast cell survival by regulating shedding and surface expression of c-Kit [52]) (Reversibility: ?) [52]
P ?
S transforming growth factor α + H_2O <2, 3, 4, 5, 6, 7> (<3> TGF α shedding [8]) (Reversibility: ?) [2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36]
P ?
S Additional information <2, 3, 4> (<3> TACE is a multidomain, type I transmembrane protein, contains a pro-domain which is removed by proteolysis to generate the active enzyme and a zinc-dependent metalloprotease catalytic domain, TACE cleaves peptides containing the sequence of the processing site at the physiolocically relevant peptide bond [14]; <3> *o*-aminobenzoyl-LAQVARSSSR-N-3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl diaminopropionic amide is no substrate [30]; <3> 4-dinitrophenyl)-L-2,3-diaminopropionyl diaminopropionic amide-PChaGC(-Me)HK(NMA)-NH_2 is not cleaved at all by TACE [33]; <3> amphiregulin is no substrate [35]; <2> angiotensin converting enzyme is not cleaved by TACE [17]; <3> TACE is the only enzyme confirmed to process TNF-α in vitro and in vivo [36]; <3> ectodomain shedding of the hypoxia-induced carbonic anhydrase IX is a metalloprotease-dependent process regulated by TACE/ADAM17 [42]; <3> TACE is not involved in shedding of angiotensin converting enzyme [45]; <3> TACE may have a role in phorbol myristate acetate-induced shedding of epiregulin [46]; <4> TACE-

mediated ectodomain shedding of erbB ligands, epitomized by TGFα is a key component of the neuron-to-glia signaling mechanism used by excitatory amino acids to facilitate the advent of female puberty [58]; <3> a comparison of the binding sites of matrix metalloproteinases and tumor necrosis factor-α converting enzyme [57]) (Reversibility: ?) [14, 17, 30, 33, 35, 36, 42, 45, 46, 57, 58]

P ?

Inhibitors

(2R)-5-nitroguanyl-2-([(2R,3S)-2-(cyclohexylmethyl)-3-cyclopropyl-3-[formyl(hydroxy)amino]propanoyl]-amino)-N-(1,3-thiazol-2-yl)pentanamide <2, 3> [23]

(2R,3S)-N-[(1S)-4-(2-pyridylsulfonyl)guanyl-1-[(1,3-thiazol-2-ylamino)-carbonyl]butyl]-3-[formyl(hydroxy)amino]-2-[(4-methylcyclohexyl)-methyl]-hexanamide <2, 3> [23]

(2R,3S)-N-[(1S)-4-(2-pyridylsulfonyl)guanyl-1-[(1,3-thiazol-2-ylamino)-carbonyl]butyl]-3-[formyl(hydroxy)amino]-2-[(5-methyl-2-thienyl)methyl]hexanamide <2, 3> [23]

(2R,3S)-N-[(1S)-4-(2-pyridylsulfonyl)guanyl-1-[(1,3-thiazol-2-ylamino)-carbonyl]butyl]-3-[formyl(hydroxy)amino]-2-isobutylhexanamide <2, 3> [23]

(2R,3S)-N-[(1S)-4-(2-pyridylsulfonyl)guanyl-1-[(1,3-thiazol-2-ylamino)-carbonyl]butyl]-3-[formyl(hydroxy)amino]-4-methyl-2-[(4-methylcyclohexyl)-methyl]pentanamide <2, 3> [23]

(2R,3S)-N-[(1S)-4-methanesulfonylguanyl-1-[(1,3-thiazol-2-ylamino)carbonyl]butyl]-3-[formyl(hydroxy)amino]-2-isobutyl-4-methylpentanamide <2, 3> [23]

(2R,3S)-N-[(1S)-4-methanesulfonylguanyl-1-[(1,3-thiazol-2-ylamino)carbonyl]butyl]-3-[formyl(hydroxy)amino]-2-isobutylhexanamide <2, 3> [23]

(2R,3S)-N-[(1S)-4-methanesulfonylguanyl-1-[(1,3-thiazol-2-ylamino)carbonyl]butyl]-3-[formyl(hydroxy)amino]-4-methyl-2-[(4-methylcyclohexyl)-methyl]pentanamide <2, 3> [23]

(2R,3S)-N-[(1S)-4-methanesulfonylguanyl-2-methyl-1-[(1,3-thiazol-2-ylamino)carbonyl]butyl]-3-[formyl-(hydroxy)amino]-2-isobutyl-4-methylpentanamide <2, 3> [23]

(2R,3S)-N-[(1S)-4-methanesulfonylguanyl-2-methyl-1-[(1,3-thiazol-2-ylamino)carbonyl]butyl]-3-[formyl-(hydroxy)amino]-2-isobutylhexanamide <2, 3> [23]

(2R,3S)-N-[(1S)-4-methanesulfonylguanyl-2-methyl-1-[(1,3-thiazol-2-ylamino)carbonyl]butyl]-6,6,6-trifluoro-3-[formyl(hydroxy)amino]-2-isobutylhexanamide <2, 3> [23]

(2R,3S)-N-[(1S)-4-nitroguanyl-1-[(1,3-thiazol-2-ylamino)carbonyl]butyl]-2-(cyclohexylmethyl)-3-[formyl(hydroxy)amino]hexanamide <2, 3> [23]

(2R,3S)-N-[(1S)-4-nitroguanyl-1-[(1,3-thiazol-2-ylamino)carbonyl]butyl]-2-(cyclohexylmethyl)-6,6,6-trifluoro-3-[formyl(hydroxy)amino]hexanamide <2, 3> [23]

(2R,3S)-N-[(1S)-4-nitroguanyl-1-[(1,3-thiazol-2-ylamino)carbonyl]butyl]-2-[(1S)-1-[formyl(hydroxy)amino]-2-phenylethyl]-4-methylpentanamide <2, 3> [23]
(2R,3S)-N-[(1S)-4-nitroguanyl-1-[(1,3-thiazol-2-ylamino)carbonyl]butyl]-3-[formyl(hydroxy)amino]-2-[5-methyl-2-thienylmethyl]hexanamide <2, 3> [23]
(2R,3S)-N-[(1S)-4-nitroguanyl-1-[(1,3-thiazol-2-ylamino)carbonyl]butyl]-3-[formyl(hydroxy)amino]-4-methyl-2-[(4-methylcyclohexyl)methyl]hexanamide <2, 3> [23]
(2R,3S)-N-[(1S)-4-nitroguanyl-1-[(1,3-thiazol-2-ylamino)carbonyl]butyl]-3-[formyl(hydroxy)amino]-4-methyl-2-[(4-methylcyclohexyl)methyl]pentanamide <2, 3> [23]
(2R,3S)-N-[(1S,2R)-4-nitroguanyl-2-methyl-1-[(1,3-thiazol-2-ylamino)carbonyl]butyl]-3-[formyl(hydroxy)amino]-2-isobutylhexanamide <2, 3> [23]
(2R,3S)-N-{(1R)-4-nitroguanyl-1-[(1,3-thiazol-2-ylamino)carbonyl]butyl}-3-[formyl(hydroxy)amino]-2-isobutylhexanamide <2, 3> [23]
(2S)-2-[(tert-butoxycarbonyl)amino]-5-({(Z)-(methyl-sulfanyl)[(methylsulfonyl)imino]methyl}amino)pentanoic acid <2, 3> [23]
(2S)-2-amino-5-({(E)-amino[(methylsulfonyl)imino]-methyl}amino)-N-(1,3-thiazol-2-yl)pentanamide hydrochloride <2, 3> [23]
(2S,3R)-2-[(tert-butoxycarbonyl)amino]-5-{[imino(2-oxido-2-oxohydrazino)-methyl]amino}-3-methylpentanoic acid (3R) N^{α}-boc-Nγ-nitro-3-methyl L-arginine <2, 3> [23]
(2S,3R)-2-{[(benzyloxy)carbonyl]amino}-3-methyl-5-({(Z)-(methylsulfanyl)[(methylsulfonyl)imino]methyl}-amino)pentanoic acid <2, 3> [23]
(2S,3R)-5-methanesulfonylguanyl-2-[((2R)-2-[(1S)-1-[formyl(hydroxy)amino]ethyl]-4-methylpentanoyl)amino]-3-methyl-N-(1,3-thiazol-2-yl)pentanamide <2, 3> [23]
(2S,3R)-5-nitroguanyl-2-[((2R)-2-[(1S)-1-[formyl(hydroxy)amino]ethyl]-4-methylpentanoyl)amino]-3-methyl-N-(1,3-thiazol-2-yl)pentanamide <2, 3> [23]
(4-bromobut-2-enyloxymethyl)benzene <3> [31]
(4-methoxyphenyl)acetic acid 4-benzyloxybut-2-enyl ester <3> [31]
1,10-phenanthroline <2, 3, 7> [11, 17, 24, 27]
1-[4-[(2-methylquinolin-4-yl)methoxy]benzyl]-1,3,5-triazinane-2,4,6-trione <5> (<5> IC50: 0.0073 mM [40]) [40]
2(R)-benzyloxymethyl-N-(2,2-dimethyl-1(S)-methyl-carbamoylpropyl)-3-(S)-(4-methoxyphenyl)succinamic acid <3> [31]
2-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]-N-[(5-methyl-2,4,6-trioxohexahydropyrimidin-5-yl)methyl]acetamide <5> (<5> IC50: above 0.1 mM [41]) [41]
3(R)-benzyloxymethyl-2-(S)-(4-methoxyphenyl)pent-4-enoic acid <3> [31]
3(R)-benzyloxymethyl-2-(S)-(4-methoxyphenyl)pent-4-enoic acid (2,2-dimethyl-1-(S)-methylcarbamoylpropyl)amide <3> [31]
4-[(2-methylquinolin-4-yl)methoxy]-N-(1,3,5-trioxo-2,4-diazaspiro[5.5]undec-7-yl)benzamide <5> (<5> IC50: 0.000138 mM [41]) [41]

4-[(2-methylquinolin-4-yl)methoxy]-N-(5-methyl-2,4,6-trioxohexahydropyrimidin-5-yl)benzamide <5> (<5> IC50: above 0.1 mM [41]) [41]
4-[(2-methylquinolin-4-yl)methoxy]-N-(6,8,10-trioxo-2-oxa-7,9-diazaspiro[4.5]dec-4-yl)benzamide <5> (<5> IC50: 0.000044 mM [41]) [41]
4-[(2-methylquinolin-4-yl)methoxy]-N-(6,8,10-trioxo-7,9-diazaspiro[4.5]dec-1-yl)benzamide <5> (<5> IC50: 0.000024 mM [41]) [41]
4-[(2-methylquinolin-4-yl)methoxy]-N-([2,4,6-trioxo-5-[1-(tetrahydro-2H-pyran-4-yl)piperidin-4-yl]hexahydropyrimidin-5-yl]methyl)benzamide <5> (<5> IC50: 0.000031 mM [41]) [41]
4-[(2-methylquinolin-4-yl)methoxy]-N-([2,4,6-trioxo-5-[4-(pyridin-3-ylcarbonyl)piperazin-1-yl]hexahydropyrimidin-5-yl]methyl)benzamide <5> (<5> IC50: 0.00001 mM [41]) [41]
4-[(2-methylquinolin-4-yl)methoxy]-N-([5-[1-(methylsulfonyl)piperidin-4-yl]-2,4,6-trioxohexahydropyrimidin-5-yl]methyl)benzamide <5> (<5> IC50: 0.000029 mM [41]) [41]
4-[(2-methylquinolin-4-yl)methoxy]-N-([5-[4-(methylsulfonyl)piperazin-1-yl]-2,4,6-trioxohexahydropyrimidin-5-yl]methyl)benzamide <5> (<5> IC50: 0.000002 mM [41]) [41]
4-[(2-methylquinolin-4-yl)methoxy]-N-[(2,4,6-trioxo-5-piperidin-4-ylhexahydropyrimidin-5-yl)methyl]benzamide <5> (<5> IC50: 0.000055 mM [41]) [41]
4-[(2-methylquinolin-4-yl)methoxy]-N-[(5-methyl-2,4,6-trioxohexahydropyrimidin-5-yl)(pyridin-4-yl)methyl]benzamide <5> (<5> IC50: 0.00236 mM [41]) [41]
4-[(2-methylquinolin-4-yl)methoxy]-N-[(5-methyl-2,4,6-trioxohexahydropyrimidin-5-yl)methyl]benzamide <5> (<5> IC50: 0.000026 mM [41]) [41]
4-[(2-methylquinolin-4-yl)methoxy]-N-[2-(methylsulfonyl)-6,8,10-trioxo-2,7,9-triazaspiro[4.5]dec-4-yl]benzamide <5> (<5> IC50: 0.000036 mM [41]) [41]
4-[(2-methylquinolin-4-yl)methoxy]-N-[6,8,10-trioxo-2-(pyridin-3-ylcarbonyl)-2,7,9-triazaspiro[4.5]dec-4-yl]benzamide <5> (<5> IC50: 0.000029 mM [41]) [41]
4-[[4-(2-butynyloxy)phenyl]sulfonyl]-N-hydroxy-2,2-dimethyl-(3S)-thiomorpholinecarboxamide <2, 3> (<2> IC50: 0.05 mM [44]; <3> IC50: 0.009 mM [44]) [44]
5-(4-acetylpiperazin-1-yl)-5-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.00062 mM [40]) [40]
5-(4-benzylpiperazin-1-yl)-5-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]-pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.000195 mM [40]) [40]
5-(4-hexylpiperazin-1-yl)-5-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.000081 mM [40]) [40]
5-(4-methylpiperazin-1-yl)-5-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]-pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.000091 mM [40]) [40]
5-[4-(1-methylethyl)piperazin-1-yl]-5-[4-[(2-methylquinolin-4-yl)methoxy]-phenyl]pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.000096 mM [40]) [40]

5-[4-(2,2-dimethylpropanoyl)piperazin-1-yl]-5-[4-[(2-methylquinolin-4-yl)-methoxy]phenyl]pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.00054 mM [40]) [40]
5-[4-(2,2-dimethylpropyl)piperazin-1-yl]-5-[4-[(2-methylquinolin-4-yl)-methoxy]phenyl]pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.00016 mM [40]) [40]
5-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]-5-(pyridin-3-ylcarbonyl)pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.000535 mM [40]) [40]
5-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]-5-[4-(2-phenylethyl)piperazin-1-yl]pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.000084 mM [40]) [40]
5-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]-5-[4-(3-phenylpropyl)piperazin-1-yl]pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.00011 mM [40]) [40]
5-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]-5-[4-(4-nitrophenyl)piperazin-1-yl]pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.0028 mM [40]) [40]
5-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]-5-[4-(methylsulfonyl)piperazin-1-yl]pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.000275 mM [40]) [40]
5-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]-5-piperazin-1-ylpyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.0011 mM [40]) [40]
5-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]-5-piperidin-1-ylpyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.000855 mM [40]) [40]
5-methyl-5-(2-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]ethyl)pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.049 mM [41]) [41]
5-methyl-5-(3-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]-3-oxopropyl)pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.0008 mM [41]) [41]
5-methyl-5-(3-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]prop-2-en-1-yl)-pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.011 mM [41]) [41]
5-methyl-5-(3-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]propyl)pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: above 0.1 mM [41]) [41]
5-methyl-5-[4-[(2-methylquinolin-4-yl)methoxy]benzyl]pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.0022 mM [41]) [41]
5-methyl-5-[4-[(2-methylquinolin-4-yl)methoxy]phenoxy]pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.0013 mM [41]) [41]
5-methyl-5-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]dihydropyrimidine-2,4(1H,3H)-dione <5> (<5> IC50: 0.0037 mM [40]) [40]
5-methyl-5-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]pyrimidine-2,4,6(1H,3H,5H)-trione <5> (<5> IC50: 0.00103 mM [40,41]) [40, 41]
APMA <3> (<3> inhibits TACE completely [5]) [5]
BB 1101 <3> [10]
BB 1433 <3> [10]
BB 16 <3> [10]
BB 2116 <3> [10, 24]
BB 2516 <3> [10]
BB 94 <2, 3, 7> [10, 17]

BB2275 <2> [24]
BB2284 <2> [24]
BB3103 <3, 4> [3, 24, 27]
CGS 27023 <3> [10]
CT 572 <3> [10]
DPH-067517 <4> [61]
Dithiothreitol <3> [11]
EDTA <3, 4> [3, 4, 11]
EndoH <2, 3, 7> (<2,3,7> full-length TACE is sensitive to EndoH, mature TACE is resistant [17]) [17]
GI 129471 <3> [10]
GM 6001 <3> [10]
GW 3333 <3> (<3> N-hydroxyformamide TACE inhibitor [23]) [10, 23]
GW1988 <3> [7]
GW280264X <2> [53]
GW9471 <2, 3> (<3> hydroxamic acid competitive inhibitor that totally blocks TACE activity [5]) [5, 7, 10]
hydroxamate <2, 3, 7> [10, 17, 24, 34]
IC-3 <3> (<3> protects TACE from degradation by inhibiting either TACE itself or another metalloprotease [12]) [12]
Immunex compound 3 <3> [2]
KB-R7785 <3> [10]
L-N^{γ}-(2-pyridylsulfonyl)arginine2-aminothiazole amide hydochloride <2, 3> [23]
L-N^{γ}-nitroarginine 2-aminothiazole amide dihydrochloride <2, 3> [23]
MMP-1 <3> [20]
MMP-2 <3> [20]
N(R)-[2-(hydroxyaminocarbonyl)methyl]-4-methylpentanoyl-L-alanine amide <2, 3> (<3> IC50: about 0.11 mM [44]; <2> IC50: about 0.7 mM [44]) [44]
N-(2-acetyl-6,8,10-trioxo-2,7,9-triazaspiro[4.5]dec-4-yl)-4-[(2-methylquinolin-4-yl)methoxy]benzamide <5> (<5> IC50: 0.000055 mM [41]) [41]
N-([5-[1-(1-methylethyl)piperidin-4-yl]-2,4,6-trioxohexahydropyrimidin-5-yl]methyl)-4-[(2-methylquinolin-4-yl)methoxy]benzamide <5> (<5> IC50: 0.000052 mM [41]) [41]
N-([5-[1-(2,2-dimethylpropanoyl)piperidin-4-yl]-2,4,6-trioxohexahydropyrimidin-5-yl]methyl)-4-[(2-methylquinolin-4-yl)methoxy]benzamide <5> (<5> IC50: 0.000013 mM [41]) [41]
N-([5-[4-(1-methylethyl)piperazin-1-yl]-2,4,6-trioxohexahydropyrimidin-5-yl]methyl)-4-[(2-methylquinolin-4-yl)methoxy]benzamide <5> (<5> IC50: 0.000007 mM [41]) [41]
N-([5-[4-(2,2-dimethylpropanoyl)piperazin-1-yl]-2,4,6-trioxohexahydropyrimidin-5-yl]methyl)-4-[(2-methylquinolin-4-yl)methoxy]benzamide <5> (<5> IC50: 0.000029 mM [41]) [41]
N-[(5-benzyl-2,4,6-trioxohexahydropyrimidin-5-yl)methyl]-4-[(2-methylquinolin-4-yl)methoxy]benzamide <5> (<5> IC50: 0.000018 mM [41]) [41]

N-[(5-ethyl-2,4,6-trioxohexahydropyrimidin-5-yl)methyl]-4-[(2-methylquinolin-4-yl)methoxy]benzamide <5> (<5> IC50: 0.000016 mM [41]) [41]
N-[2-(2,2-dimethylpropanoyl)-6,8,10-trioxo-2,7,9-triazaspiro[4.5]dec-4-yl]-4-[(2-methylquinolin-4-yl)methoxy]benzamide <5> (<5> IC50: 0.000111 mM [41]) [41]
N-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]-2-(5-methyl-2,4,6-trioxohexahydropyrimidin-5-yl)acetamide <5> (<5> IC50: 0.012 mM [41]) [41]
N-[DL-[2-(hydroxyamino-carbonyl)methyl]-4-methylpentanoyl]-L-3-(tert-butyl)glycyl-L-alanine,2-aminoethylamide <3> [30]
N-[[5-(1-methylethyl)-2,4,6-trioxohexahydropyrimidin-5-yl]methyl]-4-[(2-methylquinolin-4-yl)methoxy]benzamide <5> (<5> IC50: 0.000019 mM [41]) [41]
N-[[5-(1-methylpiperidin-4-yl)-2,4,6-trioxohexahydropyrimidin-5-yl]-methyl]-4-[(2-methylquinolin-4-yl)methoxy]benzamide <5> (<5> IC50: 0.000057 mM [41]) [41]
N-[[5-(4-acetylpiperazin-1-yl)-2,4,6-trioxohexahydropyrimidin-5-yl]methyl]-4-[(2-methylquinolin-4-yl)methoxy]benzamide <5> (<5> IC50: 0.000005 mM [41]) [41]
N-[[5-(4-benzylpiperazin-1-yl)-2,4,6-trioxohexahydropyrimidin-5-yl]-methyl]-4-[(2-methylquinolin-4-yl)methoxy]benzamide <5> (<5> IC50: 0.000014 mM [41]) [41]
N-[[5-(4-ethynylpiperazin-1-yl)-2,4,6-trioxohexahydropyrimidin-5-yl]-methyl]-4-[(2-methylquinolin-4-yl)methoxy]benzamide <5> (<5> IC50: 0.000062 mM [41]) [41]
N-[[5-(4-methylpiperazin-1-yl)-2,4,6-trioxohexahydropyrimidin-5-yl]-methyl]-4-[(2-methylquinolin-4-yl)methoxy]benzamide <5> (<5> IC50: 0.000058 mM [41]) [41]
N^1-benzyloxy-2(R)-benzyloxymethyl-N^4-(2,2-dimethyl-1(S)-methylcarbamoylpropyl)-3(S)-(4-methoxyphenyl)-succinamide <3> [31]
N^4-(2,2-dimethyl-1(S)-methylcarbamoylpropyl)-N^1-hydroxy-2(R)-hydroxymethyl-3(R)-(isobutyl)succinamide <3> [31]
N^4-(2,2-dimethyl-1(S)-methylcarbamoylpropyl)-N^1-hydroxy-2(R)-hydroxymethyl-3(S)-(4-methoxyphenyl)succinamide <3> [31]
N^4-(2,2-dimethyl-1(S)-methylcarbamoylpropyl)-N^1-hydroxy-2(R)-hydroxymethyl-3(S)-*p*-tolylsuccinamide <3> [31]
N^4-(2,2-dimethyl-1(S)-methylcarbamoylpropyl)-N^1-hydroxy-2(R)-hydroxymethyl-3(S)-phenylsuccinamide <3> [31]
NaCl <3> (<3> dramatic inhibitory effect on the activity of TACE [5]) [5]
Ro 31-9790 <3> [10]
SC 903 <3> [10]
SE 205 <3> [10]
Succinate <3> [31]
TACE-pro domain <2, 3> (<3> pro domain is an inhibitor of the catalytic domain [5,17]) [5, 17]
TAPI <3> (<3> hydroxamic acid-based broad-spectrum inhibitor of zinc metalloproteinases [4]) [4, 10, 27]

TAPI-2 <2, 3, 4> (<3> hydroxamate-based inhibitor of matrix metalloproteases that has high activity against TACE [26]) [3, 26]
TIMP-3 <3> (<3> tissue inhibitor of metalloproteases-3, CAS: 147783-68-4, 171039-15-9, 13037-60-4 [12,21,29,32]) [12, 21, 29, 32]
[((3R,4S)-4-{[(benzyloxy)carbonyl]}-4-carboxy-3-methylbutyl)amino](imino)methanaminium nitrate (3R) 3-methyl L-arginine nitric acid salt <2, 3> [23]
benzyl (1S,2R)-4-({(E)-amino[(methylsulfonyl)imino]-methyl}amino)-2-methyl-1-[(1,3-thiazol-2-ylamino)carbonyl]butylcarbamate <2, 3> [23]
macrocyclic hydroxamic acid <3, 5> [20, 28]
methyl 4-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]-2,5-dioxoimidazolidine-4-carboxylate <5> (<5> IC50: 0.0047 mM [40]) [40]
peptide hydroxamate <3> [29]
peptidomimetic hydroxamate <3> [10]
succinyl hydroxamate <3> [10]
sulfonamide hydroxamate <3> [10]
tert-butyl (1S,2R)-4-{[imino(2-oxido-2-oxohydrazino)-methyl]amino}-2-methyl-1-[1,3-thiazol-2-ylaminocarbonyl]butylcarbamate <2, 3> [23]
tert-butyl (2S,3R)-2-{[(benzyloxy)carbonyl]amino}-3-methyl-4-pentenoate <2, 3> [23]
tert-butyl (2S,3R)-2-{[(benzyloxy)carbonyl]amino}-5-amino-3-methylpentanoate <2, 3> [23]
tert-butyl (2S,3R)-2-{[(benzyloxy)carbonyl]amino}-5-azido-3-methylpentanoate <2, 3> [23]
tert-butyl (2S,3R)-2-{[(benzyloxy)carbonyl]amino}-5-hydroxy-3-methylpentanoate <2, 3> [23]
tert-butyl (5-[[([4-[(2-methylquinolin-4-yl)methoxy]phenyl]carbonyl)amino]methyl]-2,4,6-trioxohexahydropyrimidin-5-yl)carbamate <5> (<5> IC50: 0.000013 mM [41]) [41]
tert-butyl 4-(5-[4-[(2-methylquinolin-4-yl)methoxy]phenyl]-2,4,6-trioxohexahydropyrimidin-5-yl)piperazine-1-carboxylate <5> (<5> IC50: 0.00016 mM [40]) [40]
tert-butyl 4-(5-[[([4-[(2-methylquinolin-4-yl)methoxy]phenyl]carbonyl)amino]methyl]-2,4,6-trioxohexahydropyrimidin-5-yl)piperidine-1-carboxylate <5> (<5> IC50: 0.000047 mM [41]) [41]
tert-butyl 4-[([4-[(2-methylquinolin-4-yl)methoxy]phenyl]carbonyl)amino]-6,8,10-trioxo-2,7,9-triazaspiro[4.5]decane-2-carboxylate <5> (<5> IC50: 0.000128 mM [41]) [41]
tert-butyl(1S)-4-({(Z)-(methylsulfanyl)[(methylsulfonyl)-imino]methyl}amino)-1-[(1,3-thiazol-2-ylamino)carbonyl]butylcarbamate <2, 3> [23]
tumor necrosis factor-α protease inhibitor <3> [43]
tumor necrosis factor-α-converting enzyme pro domain <3> (<3> inhibition of the tumor necrosis factor-α-converting enzyme by its isolated pro domain, IC50: 70 nM [48]) [48]

Activating compounds

lipopolysaccharide <3> [8, 12, 25]
phorbol 12-myristate-13-acetate <2, 3> (<3> PMA [12]) [12, 15]
phorbol ester <2, 3> (<3> stimulates the TACE-mediated release of TNF-α from cells [8]) [8, 12, 15, 17, 18, 25, 27, 29, 34]

Metals, ions

Zinc <3> (<3> pronounced diversity in electronic and chemical properties between the catalytic zinc sites of tumor necrosis factor-α-converting enzyme and matrix metalloproteinases despite their high structural similarity [49]) [49]
Zn^{2+} <2, 3> (<2,3> zinc metalloprotease [7,14,17,32]; <3> zinc-dependent catalytic domain [29]) [7, 14, 17, 29, 32, 33]

K_m-Value (mM)

1.3 <3> (NH_2-LAQAVRSSSR-OH) [30]

K_i-Value (mM)

2.8e-006 <4> (DPH-067517) [61]
5 <3> (NaCl) [5]

4 Enzyme Structure

Molecular weight

80000 <2, 3, 7> (<2,3,7> migrates as a 80 kDa protein under non-reducing conditions, immunoprecipitation [17]) [17]
80000-100000 <2> (<2> sucrose density gradient centrifugation [7]) [7]
85000 <2> (<2> SDS-PAGE [4]; <2> glycerol gradient, gel filtration [7]; <2> proteolytically mature TACE, immunoblotting [25]) [4, 7, 25]
100000 <2, 3> (<2,3> 100 kDa reduced form represents mature TACE lacking the prodomain, immunoprecipitation [17]) [17]
110000 <2> (<2> pro TACE, immunoblotting [25]) [25]
120000 <2, 3, 7> (<2,3,7> full length form of TACE migrates as a 120 kDa protein under reducing conditions, immunoprecipitation [17]) [17]
160000 <7> (<7> identified with prodomain antibody in COS-7 membrane preparations [17]) [17]

5 Isolation/Preparation/Mutation/Application

Source/tissue

CHO cell <1, 12, 13, 14> (<12,13,14> mutated sublines M1 and M2. M1 contains only one expressible TACE allele encoding an M435I point mutation in the catalytic center of the protease, and M2 cells produce two TACE variants with distinct point mutations in the catalytic domain (C22Y) and the cysteine-rich/disintegrin domain (C600Y) [47]) [47, 51]
HT-29 cell <3> [42]

HeLa cell <3> [42]
SH-SY5Y cell <3> [45]
SiHa cell <3> [42]
T-cell <4> (<4> primary cellular source of ADAM-17 in inflamed peripheral nervous system (experimental autoimmune neuritis). Not all T lymphocytes within the inflamed peripheral nervous system express ADAM-17. No ADAM-17 expressing cells are found in nerves from control animals [59]) [59]
adipocyte <3> (<3> adipose tissue [36]) [36]
astrocyte <2> [25]
atherosclerotic lesion <2, 3> (<2,3> atherosclerotic lesions of apolipoprotein E-deficient mice [38]) [38]
blood <2, 3> (<2,3> peripheral blood T-cells [4]) [4, 23, 28, 34]
blood platelet <2, 3> [44]
bone marrow <2, 3> [4, 11, 24]
brain <2, 3, 4> (<2> fetal brain [4]; <3> neocortex, cerebellum, pyramidal neurons of the cerebral cortex and granular cell layer neurons in the hippocampus [25]) [4, 25, 27, 61]
embryo <2, 3> [2, 15, 25, 27, 29, 34]
embryonic fibroblast <2> [55]
endothelium <2, 3> [4, 19, 23, 26]
epithelium <3> (<3> glandular epithelial cells [13]) [13, 26]
fibroblast <2, 3> (<3> dermal fibroblasts [19]) [2, 11, 14, 15, 18, 19, 24, 26, 27, 29, 34, 35, 51]
gastric mucosa <4> [3]
heart <2> [4]
hypothalamus <4> (<4> within the hypothalamus, TACE is most abundantly expressed in astrocytes of the median eminence, specific changes in TACE activity are required for the normal timimg of puberty. TACE is a component of the neuron-to-glia signaling process used by glutamatergic neurons to control female sexual development [58]) [58]
kidney <2, 3, 7> [4, 17, 27, 34]
leukocyte <3> [14]
liver <2> [4, 10, 18]
lung <2, 3> (<3> adenocarcinoma cells [32]) [4, 32]
macrophage <2, 3> [3, 24, 25, 36]
microglial cell <2> [25]
monocyte <2, 3> [4, 5, 7, 10, 11, 12, 25]
muscle <2, 3> (<2> skeletal muscle, smooth muscle cells [4]) [4, 36]
myocyte <3> [16]
nerve <3> (<3> sural nerve biopsies from Guillain-Barre syndrome patients. ADAM-17-expressing T cells can be localized primarily within the epi- and perineurium, whereas in control sections from patients with non-inflammatory neuropathies, no axpression can be depected. The enzyme may contribute to the pathogenesis of inflammatory demyelination of the peripheral nervous system [59]) [59]
neuron <2, 3> [25, 26]
neutrophil <2> [4]

oligodendrocyte <2> [25]
ovary <2> [4]
pancreas <2, 3> (<3> ADAM17/TACE mRNA is expressed in 3 of 10 normal pancreatic tissues, 6 of 8 samples from patients with chronic pancreatitis [43]) [4, 43]
pancreatic cancer cell line <3> (<3> ADAM17/TACE mRNA is expressed in 10 of 10 PDAC tissues. ADAM17/TACE mRNA expression is down-regulated in pancreatic cancer cells arrested in G2 -M phase. Critical involvement of ADAM17/TACE in the invasion behavior of pancreatic cancer cells [43]) [43]
pancreatic ductal adenocarcinoma cell <3> (<3> ADAM17/TACE mRNA is expressed in 10 of 10 PDAC tissues. ADAM17/TACE expression is a later event in progression of pancreatic intraepithelial neoplasia to pancreatic ductal adenocarcinoma [43]) [43]
placenta <2> [4]
prostate <2> [4]
small intestine <2> [4]
spleen <2> [4, 7, 24]
subventricular zone neural progenitor cell <4> [56]
testis <2> [4]
thymocyte <2, 3> [36]
thymus <2> [4]

Localization

Golgi apparatus <2, 3, 7> (<2,3,7> proximal Golgi [17]) [17, 25, 29]
cell surface <2, 3> [12, 17, 18, 26, 29]
cytoplasm <2, 3, 7> (<2,3,7> cytoplasmic tail [7,8,10,17]) [7, 8, 10, 12, 14, 17, 25, 29]
cytosol <3> (<3> cytosolic tail of TACE precedes TACE activation [5]) [5]
endoplasmic reticulum <2, 3, 7> [17]
endosome <1> [39]
extracellular <5> (<5> disintegrin and protease regions [28]) [28]
membrane <2, 3, 5, 7> (<2, 3, 5> membrane-bound [10, 13, 14, 17, 19, 23, 28, 29, 35, 36]; <3> microsomal membrane, transmembrane domain [7]) [2, 5, 7, 10, 13, 14, 17, 19, 23, 28, 29, 33, 35, 36]
microsome <3> [33]
perinuclear space <2> [17]
plasma membrane <1, 2, 3> [36, 39]

Purification

<2> [7, 35]
<3> [4, 5, 9, 10, 11, 12, 14, 30, 33]
<3> (recombinant enzyme) [17]
<5> [10]

Crystallization

<3> [10, 28, 29]
<3> (X-ray crystal structure of the catalytic domain of TACE) [30]
<5> [10, 28]

Cloning

<2> [18, 34]
<2> (TACE transfected CHO cells) [25]
<2> (bone marrow cultures infected with a retrovirus expressing murine TACE cDNA) [11]
<2> (cDNA encoding mouse TACE, transfection of COS-7 cells) [15]
<2> (isolation of cDNA clones encoding TACE by PCR) [4]
<2> (mouse TACE complete cDNA cloned) [6]
<2> (overexpression in COS-7 cells) [50]
<2> (reconstitution of TNF shedding in TACE-deficient cells by TACE cDNA transfection) [14]
<2> (transfection of TACE into TACE deficient cells) [35]
<3> [9, 10, 29, 33, 34]
<3> (PCR used or quantification of TACE-mRNA in fresh tissue) [13]
<3> (cDNA clones coding for various segments of the TACE cytotail) [8]
<3> (cDNA encoding TACE, full-length human TACE, inefficiently expressed in insect cells, baculovirus particles in Sf9 cell line from Spodoptera frugiperda) [5, 7]
<3> (cDNA fragment coding for the prodomain of human TACE, expressed and purified from a baculoviral expression system) [17]
<3> (cloned with retroviral expression plasmids) [19]
<3> (human embryonic kidney 293 transfectants overexpressing TACE) [27]
<3> (recombinantly expressed human TACE in plasmid transfected chinese hamster ovary cells) [12]
<5> (recombinant TACE expressed in insect cells) [10]

Engineering

C225Y <12, 13, 14> (<12,13,14> overexpression of C225 and C600Y TACE by transient transfection largely compensates for maturation defects in the variants but fails to restore TNF-α and TGF-α release in the shedding-defective CHO cell lines and fibroblasts derived from TACE-null mouse embryos [47]) [47]
C600Y <12, 13, 14> (<12,13,14> overexpression of C225 and C600Y TACE by transient transfection largely compensates for maturation defects in the variants but fails to restore TNF-α and TGF-α release in the shedding-defective CHO cell lines and fibroblasts derived from TACE-null mouse embryos [47]) [47]

Application

medicine <3, 4> (<3> over-expression of TNF-α has been implicated in diseases such as rheumatoid arthritis, Crohns disease, septic shock, AIDS, insulin resistance, cachexia and cancer [20]; <4> TACE inhibitors prevent TNFα release and protect against TNFα-mediated disease [3]; <3> tumor necrosis factor α converting enzyme is involved in regulated α-secretase cleavage of the Alzheimer amyloid protein precursor, activating TACE by pharmacological manipulation might prove beneficial in Alzheimers disease [2,11]; <3> targeting this key enzyme for therapeutic intervention in inflammatory diseases, cancer and AIDS [5,33]; <3> TACE plays a role in the pathogenesis of

endometriosis, a benign gynecologic disorder [13]; <3> TACE as target for drug discovery, potential therapeutic target in the areas of arthritis, cancer, diabetes and HIV cachexia [22]; <3> pharmaceutical industry is attempting to design specific TACE inhibitors to treat inflammatory diseases, may also be beneficial in treating certain cancers [29]; <3> isolation of TACE facilitates the development of therapeutically useful inhibitors of TNF-α release [4]; <3> putative cellular targets of a therapeutic strategy in neurodegenerative prion diseases [27]; <3> TNF-α thought to be a selective anti-tumor agent and a contributor to cachexia in cancer patients, clinical trials for cancer [10]; <3> therapeutic potential of TACE inhibitors benefit in treating autoimmune diseases like Crohns disease or rheumatoid arthritis [28]; <3> implicated in the pathogenesis of dilated cardiomyopathy [9]; <3> TACE has implications in the pathogenesis of myocarditis and may have influence on advanced cardiac dysfunction in myocarditis [16]; <3,4> ADAM-17 is a putative target for treatment of neuroinflammatory diseases [59]; <3> ADAM17/TACE might be an important therapeutic target. The blocking of ADAM17/TACE expression and/or the evaluation and development of specific TACE inhibitors might have therapeutic potential even in later stages of cancer. Furthermore, ADAM17/TACE might be useful as a diagnostic marker of pancreatic cancer to distinguish between PDAC and chronic pancreatitis. Aberrant ADAM17/TACE expression might be a diagnostic and therapeutic target in human pancreatic ductal adenocarcinoma [43]; <4> inhibition of TACE might be a potential therapeutic strategy for neuroprotection after focal ischemic stroke [61]; <4> TACE proteolysis is a promoter of stroke-induced SVZ progenitor cell neurogenesis, and suggest this protease activity may represent an attractive therapeutic target for stroke recovery [56]) [2, 3, 4, 5, 9, 10, 11, 13, 16, 20, 22, 27, 28, 29, 33, 43, 56, 59, 61]

6 Stability

General stability information

<3>, TACE appears quite stable in untreated cells [12]

<3>, extreme salt sensitivity [5]

<3>, in absence of cell activators the enzyme is long-lived, with a half-life of more than 8h [29]

<3>, surface-biotinylated TACE is stable in Jurkat cells with a half-life of at least 8h [12]

Storage stability

<3>, -70°C, TACE stored in small aliquots prevents self-degradation [32]

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