ADAM-10

A Disintegrin and metalloproteinase domain-containing protein 10, also known as ADAM10 or CDw156 or CD156c is a protein that in humans is encoded by the ADAM10 gene.

Members of the ADAM family are cell surface proteins with a unique structure possessing both potential adhesion and protease domains. Sheddase, a generic name for the ADAM metallopeptidase, functions primarily to cleave membrane proteins at the cellular surface. Once cleaved, the sheddases release soluble ectodomains with an altered location and function.

Although a single sheddase may “shed” a variety of substances, multiple sheddases can cleave the same substrate resulting in different consequences.This gene encodes an ADAM family member that cleaves many proteins including TNF-alpha and E-cadherin.

Disintegrin and metalloproteinases (ADAMs) 10 and 17 can release the extracellular part of a variety of membrane-bound proteins via ectodomain shedding important for many biological functions. So far, substrate identification focused exclusively on membrane-anchored ADAM10 and ADAM17. However, besides known shedding of ADAM10, we identified ADAM8 as a protease capable of releasing the ADAM17 ectodomain. Therefore, we investigated whether the soluble ectodomains of ADAM10/17 (sADAM10/17) exhibit an altered substrate spectrum compared to their membrane-bound counterparts. A mass spectrometry-based N-terminomics approach identified 134 protein cleavage events in total and 45 common substrates for sADAM10/17 within the secretome of murine cardiomyocytes. Analysis of these cleavage sites confirmed previously identified amino acid preferences. Further in vitro studies verified fibronectin, cystatin C, sN-cadherin, PCPE-1 as well as sAPP as direct substrates of sADAM10 and/or sADAM17. Overall, we present the first degradome study for sADAM10/17, thereby introducing a new mode of proteolytic activity within the protease web [1)].

In a study, Sanz et al. identified a metalloproteinase-dependent mechanism necessary to promote growth in embryonic dorsal root ganglion cells (DRGs). Treatment of embryonic DRG neurons with pan-metalloproteinase inhibitors, tissue inhibitor of metalloproteinase-3, or an inhibitor of ADAM Metallopeptidase Domain 10 (ADAM10) reduces outgrowth from DRG neurons indicating that metalloproteinase activity is important for outgrowth.

The IgLON family members Neurotrimin (NTM) and Limbic System-Associated Membrane Protein (LSAMP) were identified as ADAM10 substrates that are shed from the cell surface of Dorsal root ganglion (DRG) neurons. Overexpression of LSAMP and NTM suppresses outgrowth from DRG neurons. Furthermore, LSAMP loss of function decreases the outgrowth sensitivity to an ADAM10 inhibitor. Together this findings support a role for ADAM-dependent shedding of cell surface LSAMP in promoting outgrowth from DRG neurons [2)].

1)
Scharfenberg F, Helbig A, Sammel M, Benzel J, Schlomann U, Peters F, Wichert R, Bettendorff M, Schmidt-Arras D, Rose-John S, Moali C, Lichtenthaler SF, Pietrzik CU, Bartsch JW, Tholey A, Becker-Pauly C. Degradome of soluble ADAM10 and ADAM17 metalloproteases. Cell Mol Life Sci. 2019 Jun 17. doi: 10.1007/s00018-019-03184-4. [Epub ahead of print] PubMed PMID: 31209506.
2)
Sanz RL, Ferraro GB, Girouard MP, Fournier AE. Ectodomain shedding of Limbic System-Associated

Membrane Protein (LSAMP) by ADAM Metallopeptidases promotes neurite outgrowth in DRG neurons. Sci Rep. 2017 Aug 11;7(1):7961. doi: 10.1038/s41598-017-08315-0. PubMed PMID: 28801670.

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