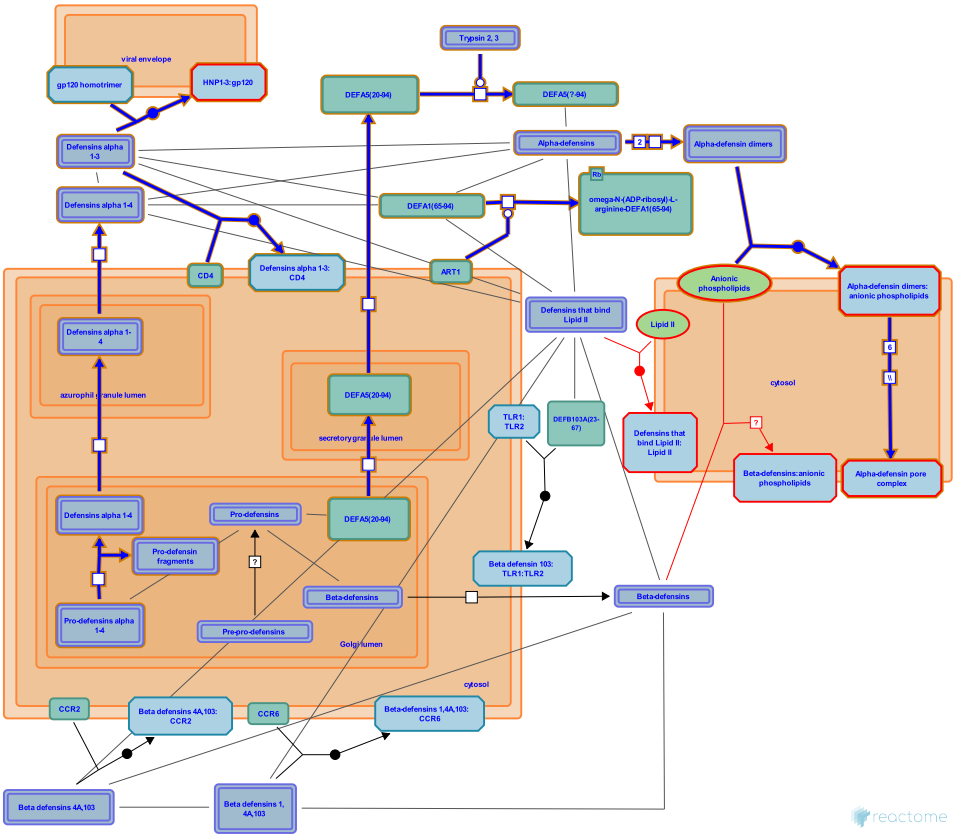
Alpha-defensins



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07/05/2024

Introduction

Reactome is open-source, open access, manually curated and peer-reviewed pathway database. Pathway annotations are authored by expert biologists, in collaboration with Reactome editorial staff and cross-referenced to many bioinformatics databases. A system of evidence tracking ensures that all assertions are backed up by the primary literature. Reactome is used by clinicians, geneticists, genomics researchers, and molecular biologists to interpret the results of high-throughput experimental studies, by bioinformaticians seeking to develop novel algorithms for mining knowledge from genomic studies, and by systems biologists building predictive models of normal and disease variant pathways.
The development of Reactome is supported by grants from the US National Institutes of Health (P41 HG003751), University of Toronto (CFREF Medicine by Design), European Union (EU STRP, EMI-CD), and the European Molecular Biology Laboratory (EBI Industry program).

Literature references

Fabregat, A., Sidiropoulos, K., Viteri, G., Forner, O., Marin-Garcia, P., Arnau, V. et al. (2017). Reactome pathway analysis: a high-performance in-memory approach. *BMC bioinformatics, 18*, 142. ↗

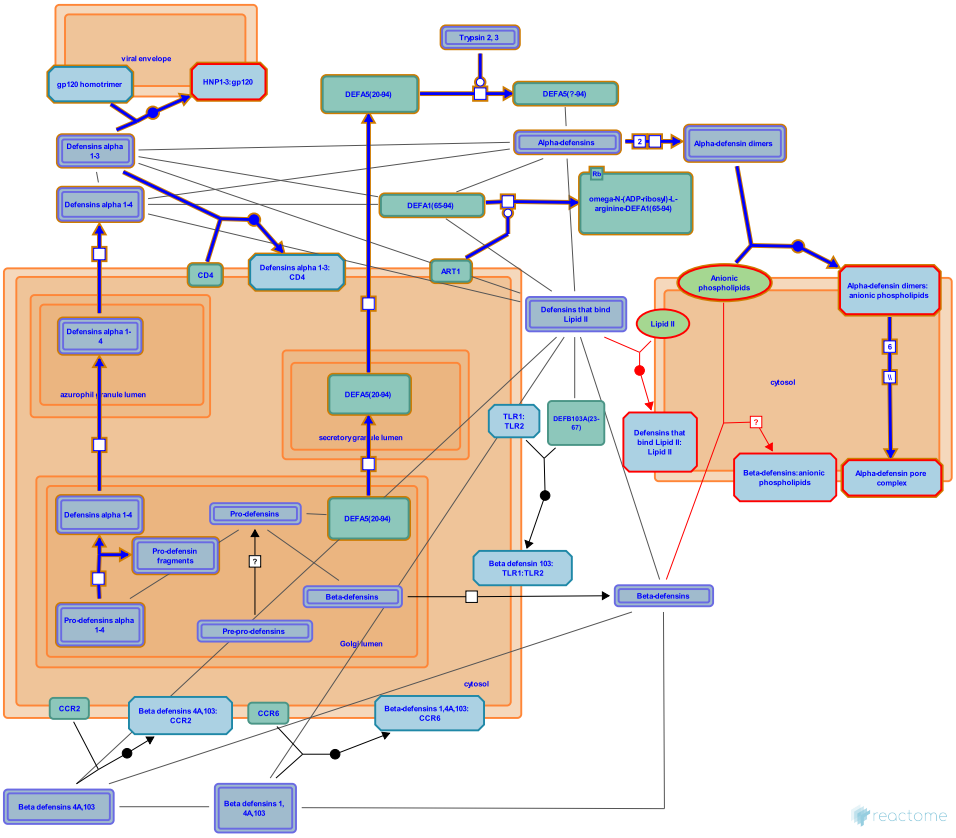
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

Fabregat, A., Jupe, S., Matthews, L., Sidiropoulos, K., Gillespie, M., Garapati, P. et al. (2018). The Reactome Pathway Knowledgebase. *Nucleic Acids Res, 46*, D649-D655. ↗

Fabregat, A., Korninger, F., Viteri, G., Sidiropoulos, K., Marin-Garcia, P., Ping, P. et al. (2018). Reactome graph database: Efficient access to complex pathway data. *PLoS computational biology, 14*, e1005968. ↗

Alpha-defensins ↗

Stable identifier: R-HSA-1462054



Humans have 7 alpha defensin genes plus 5 pseudogenes (see HGNC at http://www.genenames.org/genefamilies/DEFA). Alpha-defensins have six cysteines linked 1-6, 2-4, 3-5. The canonical sequence of alpha-defensins in humans is x1-2CXCRx2-3Cx3Ex3GxCx3Gx5CCx1-4, where x represents any amino acid residue.
Human alpha-defensins 1-4 are often called human neutrophil peptides (HNP1-4) as they were initially identified in neutrophil primary (azurophilic) granules. Alpha-defensins 5 and 6 (HD5, HD6) are products of Paneth cells. HNP-1 and -3 peptides are 30 residues long, differing only in the first amino acid. They are encoded by the genes DEFA1 and DEFA3 respectively. These exhibit copy number polymorphism, with some individuals having 4-14 copies per diploid genome, while 10-37% of individuals have no copies of DEFA3 (Aldred et al. 2005, Linzmier & Ganz 2005, Ballana et al. 2007). HNP-4, encoded by DEFA4, is 33 amino acids long of which 22 differ from the other HNPs (Wilde et al. 1989). It is a minor component of neutrophil granules compared to HNP1-3. In contrast to DEFA1 and DEFA3, the genes for HNP-4, HD-5 and HD-6 are only found as two copies per diploid genome (Linzmeier & Ganz 2005). HNP-2 is 29 amino acids in length and is the proteolytic product of cleavage of the N-terminal amino acid from either HNP-1 and/or HNP-3 (Selsted et al. 1985).

Literature references

Ganz, T. (2003). Defensins: antimicrobial peptides of innate immunity. *Nat Rev Immunol, 3*, 710-20. ↗

Editions

2011-04-28	Authored	Jupe, S.
2011-07-27	Edited	Jupe, S.
2011-11-03	Reviewed	McDermott, AM.

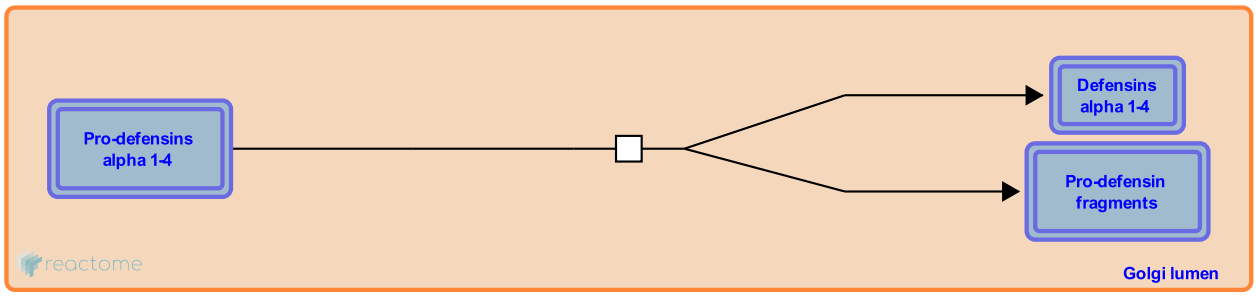
Pro-HNP1-4 are cleaved to biologically active defensin ↗

Location: Alpha-defensins

Stable identifier: R-HSA-1462039

Type: transition

Compartments: Golgi lumen



Synthesis of alpha defensins takes place in neutrophil precursor cells, the promyelocytes, in the bone marrow. Pro HNP1-4 are cleaved in the Golgi body, with HNP-2 being derived from cleavage of the N-terminal amino acid from HNP-1 or HNP-3. The defensin propiece is not only important for correct sub-cellular trafficking and sorting but also inhibits HNP activity (Valore et al. 1996, Wu et al. 2007). The resulting mature peptides are sorted to primary neutrophil (azurophil) granules for storage (Valore & Ganz 1992, Harwig et al. 1992, Cowland & Borregaard).

Followed by: HNP1-4 are stored in primary neutrophil granules

Literature references

Harwig, SS., Lehrer, RI., Park, AS. (1992). Characterization of defensin precursors in mature human neutrophils. *Blood, 79*, 1532-7. ↗

Ganz, T., Valore, EV. (1992). Posttranslational processing of defensins in immature human myeloid cells. *Blood, 79*, 1538-44. ↗

Editions

2011-04-28	Authored	Jupe, S.
2011-07-27	Edited	Jupe, S.
2011-11-03	Reviewed	McDermott, AM.

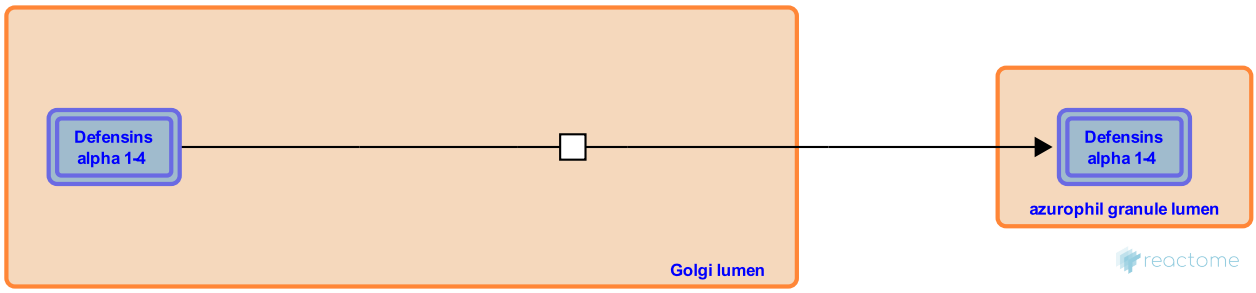
HNP1-4 are stored in primary neutrophil granules ↗

Location: Alpha-defensins

Stable identifier: R-HSA-1462003

Type: transition

Compartments: Golgi lumen, azurophil granule lumen



Alpha defensins HNP1-4, the neutrophil defensins, are stored in biologically active form in neutrophil primary (azurophil) granules, where they make up 5-10% of total cellular protein in these cells (Lehrere et al. 1993). The relative amounts of peptide for HNP-1 to -3 are 2:2:1 with HNP-4 being only a minor component.

Preceded by: Pro-HNP1-4 are cleaved to biologically active defensin

Followed by: HNP1-4 are released into phagocytic vacuoles

Literature references

Marra, MN., Griffith, JE., Wilde, CG., Snable, JL., Scott, RW. (1989). Purification and characterization of human neutrophil peptide 4, a novel member of the defensin family. *J Biol Chem, 264*, 11200-3. ↗

Daher, K., Ganz, T., Szklarek, D., Selsted, ME., Bainton, DF., Harwig, SS. et al. (1985). Defensins. Natural peptide antibiotics of human neutrophils. *J Clin Invest, 76*, 1427-35. ↗

Editions

2011-04-28	Authored	Jupe, S.
2011-07-27	Edited	Jupe, S.
2011-11-03	Reviewed	McDermott, AM.

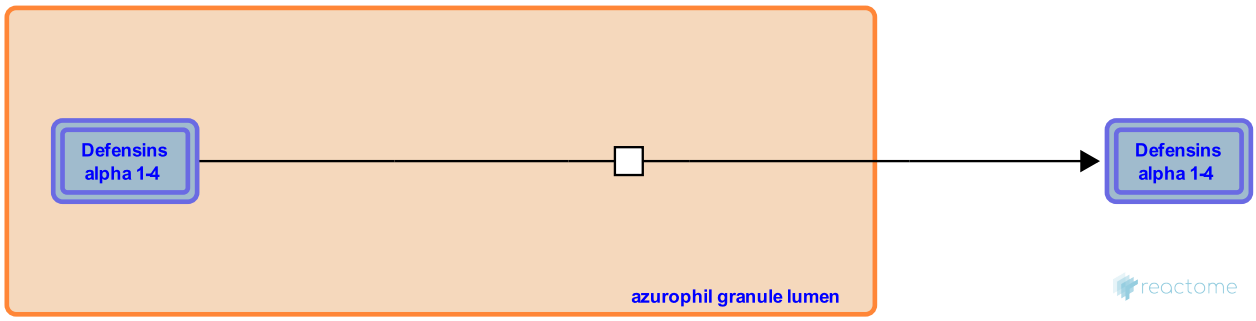
HNP1-4 are released into phagocytic vacuoles ↗

Location: Alpha-defensins

Stable identifier: R-HSA-1462041

Type: transition

Compartments: azurophil granule lumen, extracellular region



Human neutrophils contain thousands of cytoplasmic granules. These membrane-bound organelles act as storage compartments destined for secretion or in the case of azurophil granules, destined for fusion with phagosomes. A small amount of defensin, but perhaps not enough for antimicrobial activity, may be released extracellularly by neutrophils (Ganz 1987).

Preceded by: HNP1-4 are stored in primary neutrophil granules

Followed by: ADP-Ribosylation of HNP-1, HNP1-3 bind gp120, Alpha-defensins form biologically active dimers, HNP1-3 bind CD4

Literature references

Ganz, T., Lehrer, RI. (1992). Defensins: endogenous antibiotic peptides from human leukocytes. *Ciba Found Symp, 171*, 276-90; discussion 290-3. ↗

Gullberg, U., Lindmark, A., Bülow, E., Olsson, I., Bengtsson, N., Garwicz, D. (1999). Processing and targeting of granule proteins in human neutrophils. *J Immunol Methods, 232*, 201-10. ↗

Ganz, T., Valore, EV., Oren, A., Liu, L. (1993). Posttranslational processing and targeting of transgenic human defensin in murine granulocyte, macrophage, fibroblast, and pituitary adenoma cell lines. *Blood, 82*, 641-50. ↗

Editions

2011-04-28	Authored	Jupe, S.
2011-07-27	Edited	Jupe, S.
2011-11-03	Reviewed	McDermott, AM.

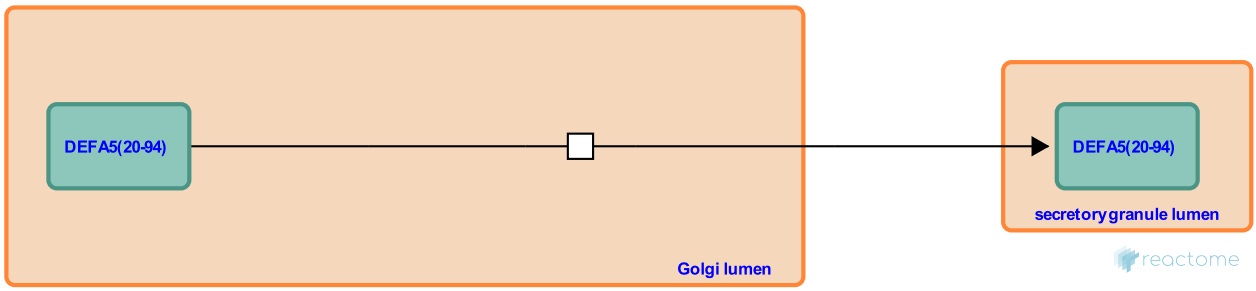
pro-defensin alpha 5 is stored in Paneth cell granules ↗

Location: Alpha-defensins

Stable identifier: R-HSA-1461995

Type: transition

Compartments: Golgi lumen, secretory granule lumen



Pro-defensin alpha 5 is stored in the granules of Paneth cells in the small intestine (Porter et al. 1997). This pro-peptide has some antimicrobial activity but is not as effective as the mature peptide (Ghosh et al. 2002).

Followed by: pro-defensin alpha 5 is secreted

Literature references

Anton, PA., Ganz, T., Oren, A., Liu, L., Porter, EM. (1997). Localization of human intestinal defensin 5 in Paneth cell granules. *Infect Immun, 65*, 2389-95. ↗

Editions

2011-04-28	Authored	Jupe, S.
2011-07-27	Edited	Jupe, S.
2011-11-03	Reviewed	McDermott, AM.

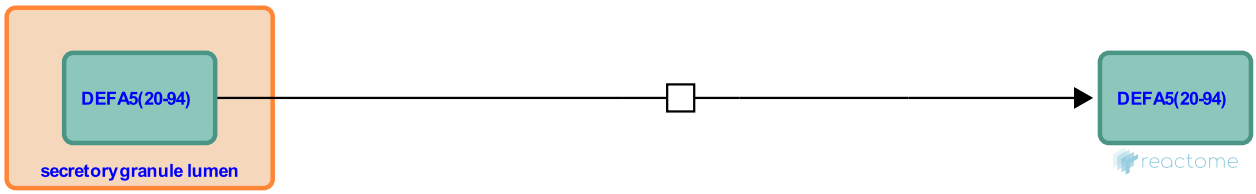
pro-defensin alpha 5 is secreted ↗

Location: Alpha-defensins

Stable identifier: R-HSA-1462005

Type: transition

Compartments: extracellular region, secretory granule lumen



Pro defensin alpha 5 is secreted from the storage granules of Paneth cells in the small intestine (Porter et al. 1997).

Preceded by: pro-defensin alpha 5 is stored in Paneth cell granules

Followed by: pro-HD5 is cleaved by trypsin

Literature references

Anton, PA., Ganz, T., Oren, A., Liu, L., Porter, EM. (1997). Localization of human intestinal defensin 5 in Paneth cell granules. *Infect Immun, 65*, 2389-95. ↗

Editions

2011-04-28	Authored	Jupe, S.
2011-07-27	Edited	Jupe, S.
2011-11-03	Reviewed	McDermott, AM.

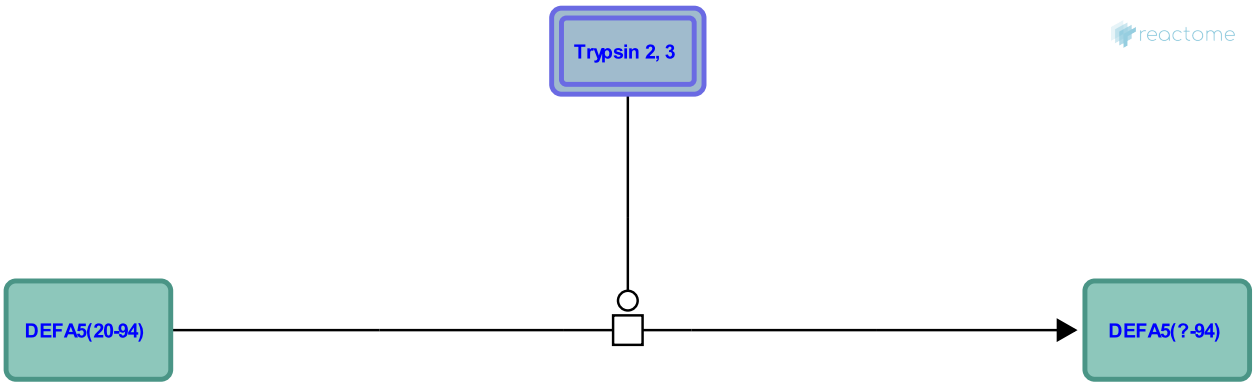
pro-HD5 is cleaved by trypsin ↗

Location: Alpha-defensins

Stable identifier: R-HSA-1461993

Type: transition

Compartments: extracellular region



Pro HD5 is stored and secreted from granules of Paneth cells in the small intestine (Porter et al. 1997, Cunliffe et al. 2001). The serine protease tryspin colocalizes to these granules as the inactive zymogen trypsinogen. Removal of the defensin propiece occurs extracellularly after release in to the crypt lumen, and is mediated by trypsin 2 (anionic trypsin) and/or trypsin-3 (mesotrypsin) which are converted to their active forms by enteroprotease like enzymes or by autoactivation (Ghosh et al. 2002, Ouelette 2011).

Preceded by: pro-defensin alpha 5 is secreted

Followed by: Alpha-defensins form biologically active dimers

Literature references

Crabb, JW., Ganz, T., Drazba, J., Porter, E., Wilk, D., Yadav, SP. et al. (2002). Paneth cell trypsin is the processing enzyme for human defensin-5. *Nat Immunol, 3*, 583-90. ↗

Editions

2011-04-28	Authored	Jupe, S.
2011-07-27	Edited	Jupe, S.
2011-11-03	Reviewed	McDermott, AM.

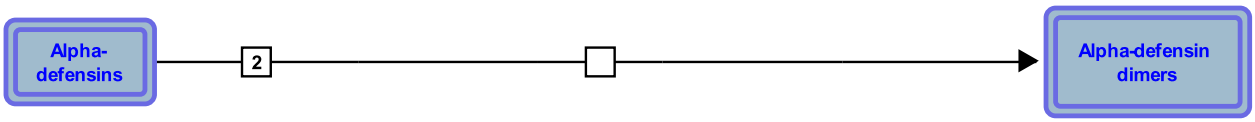
Alpha-defensins form biologically active dimers ↗

Location: Alpha-defensins

Stable identifier: R-HSA-1462014

Type: transition

Compartments: extracellular region



The crystal structure of human alpha-defensin HNP-3 revealed that it forms a dimer containing a six-stranded beta-sheet region (Hill et al. 1991). NMR studies indicate that HNP-1 can also form dimers or higher-order aggregates in solution and artificial lipid bilayers (Zhang et al. 1992, 2010a, 2010b). Models of alpha and beta defensins suggest that dimerization and/or higher order structures are characteristic, though not univeral or required for the biological effects of some beta-defensins (Suresh & Verma 2006, Pazgier et al. 2006).

Preceded by: pro-HD5 is cleaved by trypsin, HNP1-4 are released into phagocytic vacuoles

Followed by: Alpha-defensin dimers adsorb onto microbial membrane anionic phospholipids

Literature references

Lubkowski, J., Yang, D., Wu, Z., Tucker, K., Lu, W., Szyk, A. (2006). Crystal structures of human alpha-defensins HNP4, HD5, and HD6. *Protein Sci, 15*, 2749-60. ↗

Zhang, XL., Selsted, ME., Pardi, A. (1992). NMR studies of defensin antimicrobial peptides. 1. Resonance assignment and secondary structure determination of rabbit NP-2 and human HNP-1. *Biochemistry, 31*, 11348-56. ↗

Eisenberg, D., Yee, J., Selsted, ME., Hill, CP. (1991). Crystal structure of defensin HNP-3, an amphiphilic dimer: mechanisms of membrane permeabilization. *Science, 251*, 1481-5. ↗

Editions

2011-04-28	Authored	Jupe, S.
2011-07-27	Edited	Jupe, S.
2011-11-03	Reviewed	McDermott, AM.

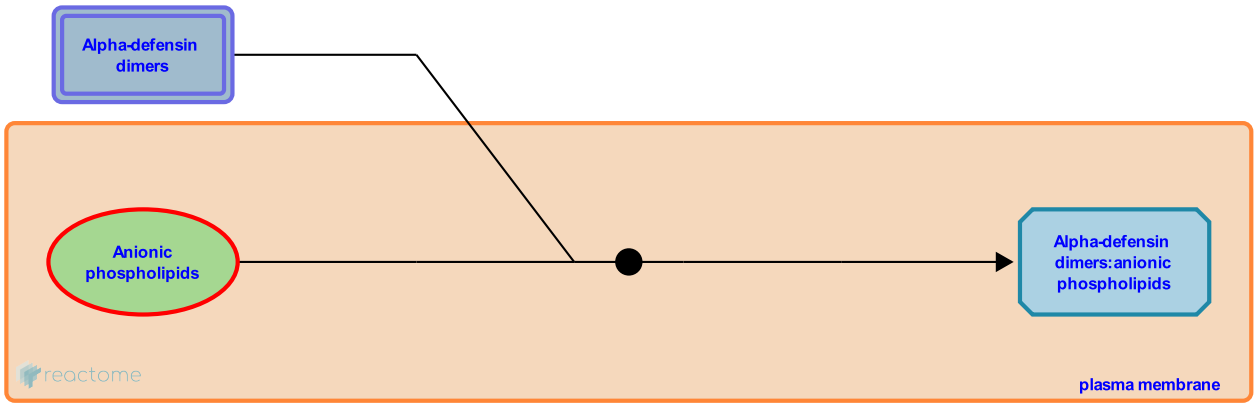
Alpha-defensin dimers adsorb onto microbial membrane anionic phospholipids ↗

Location: Alpha-defensins

Stable identifier: R-HSA-1461971

Type: binding

Compartments: plasma membrane, extracellular region



The alpha-defensin dimers adsorb onto microbial membrane anionic phospholipids, represented here as a complex of alpha-defensin dimers and a representative set of phospholipid molecules 'membrane anionic phospholipids'. The polar topology of defensins, with their spatially separated charged and hydrophobic regions, allows them to insert into microbial cell membranes, which contains more negatively charged phospholipids than mammalian cell membranes (Lohner et al. 1997). Defensins permeabilize membrane vesicles (Lehrer et al. 1989) with a greater effect on vesicles rich in negatively charged phospholipids (Fuji et al. 1993, Wimley et al. 1994).

Preceded by: Alpha-defensins form biologically active dimers

Followed by: Alpha-defensin dimers multimerize to form a pore complex

Literature references

Daher, KA., Ganz, T., Selsted, ME., Harwig, SS., Barton, A., Lehrer, RI. (1989). Interaction of human defensins with Escherichia coli. Mechanism of bactericidal activity. *J Clin Invest, 84*, 553-61. ↗

Hadjicharalambous, C., Ouellette, AJ., Gizeli, E., Sheynis, T., Shanahan, MT., Jelinek, R. (2008). Mechanisms of alpha-defensin bactericidal action: comparative membrane disruption by Cryptdin-4 and its disulfide-null analogue. *Biochemistry, 47*, 12626-34. ↗

Wimley, WC., White, SH., Selsted, ME. (1994). Interactions between human defensins and lipid bilayers: evidence for formation of multimeric pores. *Protein Sci, 3*, 1362-73. ↗

Editions

2011-04-28	Authored	Jupe, S.
2011-07-27	Edited	Jupe, S.
2011-11-03	Reviewed	McDermott, AM.

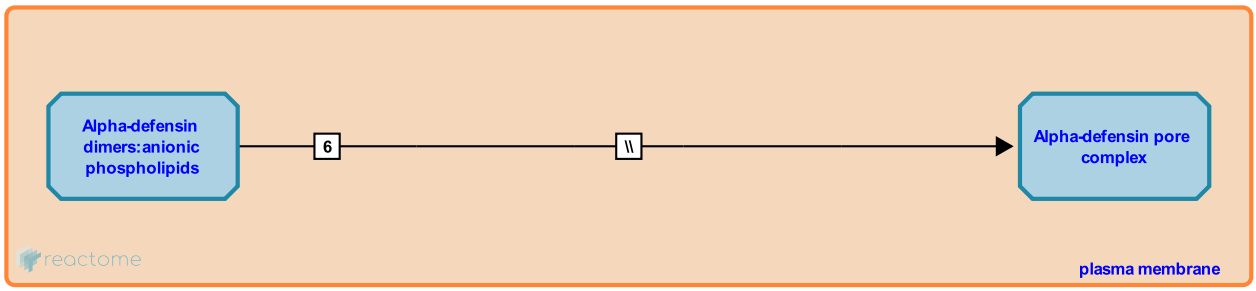
Alpha-defensin dimers multimerize to form a pore complex ↗

Location: Alpha-defensins

Stable identifier: R-HSA-1461982

Type: omitted

Compartments: plasma membrane



Once adsorbed/inserted into the membrane, alpha defensins are believed to aggregate into pore forming structures. Based on vesicle leakage and dextran permeability experiments, Wimley et al. (1994) proposed a multimeric pore model consisting of 6-8 defensin dimers which come together to form a large pore with inner diameter of 2-2.5nm. More recently using solid-state NMR and artificial lipid bilayers, Zhang et al. (2010) provide evidence of a dimer pore model in which the polar top of the dimer lines an aqueous pore while the hydrophobic bottom faces the lipid chains. Regardless of the exact conformation, the resulting pores then allow the efflux of essential microbial cell components.

Preceded by: Alpha-defensin dimers adsorb onto microbial membrane anionic phospholipids

Literature references

Wimley, WC., White, SH., Selsted, ME. (1994). Interactions between human defensins and lipid bilayers: evidence for formation of multimeric pores. *Protein Sci, 3*, 1362-73. ↗

Editions

2011-04-28	Authored	Jupe, S.
2011-07-27	Edited	Jupe, S.
2011-11-03	Reviewed	McDermott, AM.

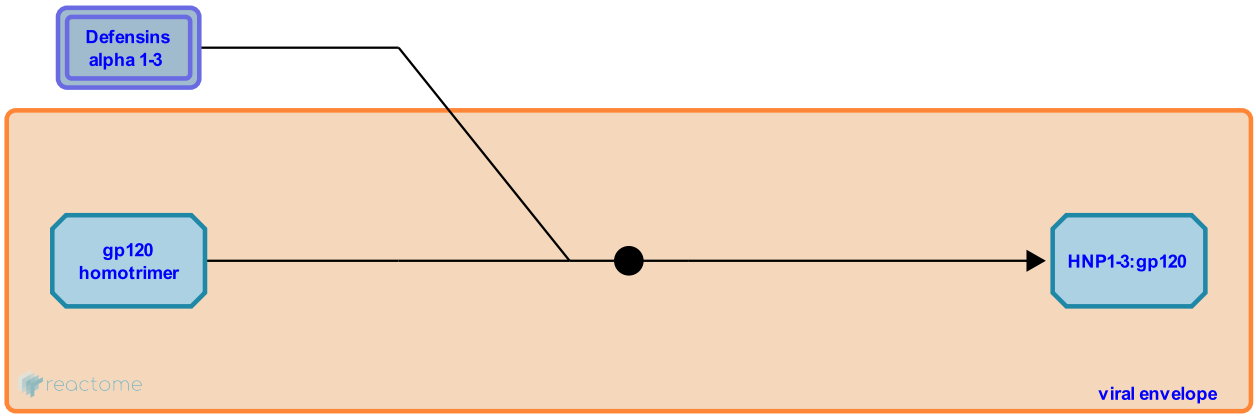
HNP1-3 bind gp120 ↗

Location: Alpha-defensins

Stable identifier: R-HSA-1471354

Type: binding

Compartments: viral envelope, extracellular region



Alpha-defensins, theta-defensins and their synthetic analogues the retrocyclins have been shown in numerous studies to have anti-HIV-1 activity (Chang & Klotman 2004). This appears to be mediated via multiple mechanisms including direct viral inactivation and down regulation of host-cell target co-receptors important for viral entry (Furci et al. 2007, Seidel et al. 2010). HNP1-3 act as lectins, binding with relatively high affinity to gp120 (KD range, 15.8-52.8 nM) on the HIV-1 envelope and CD4 (KD range, 8.0-34.9 nM) on host target cells, both important molecules for viral entry (Wang et al. 2004). Retrocyclins, artificial theta defensins predicted from human defensin pseudogenes, bind with even higher affinity whereas HNP-4 binding is much weaker (Wu et al. 2005). Alpha defensins have been demonstrated to inhibit the binding of gp120 to CD4 thus blocking HIV-1 fusion with its target cells (Furci et al. 2007).

Preceded by: HNP1-4 are released into phagocytic vacuoles

Literature references

Waring, AJ., Lal, RB., Hong, T., Cole, AM., Owen, SM., Wang, W. et al. (2004). Activity of alpha- and theta-defensins against primary isolates of HIV-1. *J Immunol, 173*, 515-20. ↗

Editions

2011-04-28	Authored	Jupe, S.
2011-07-27	Edited	Jupe, S.
2011-11-03	Reviewed	McDermott, AM.

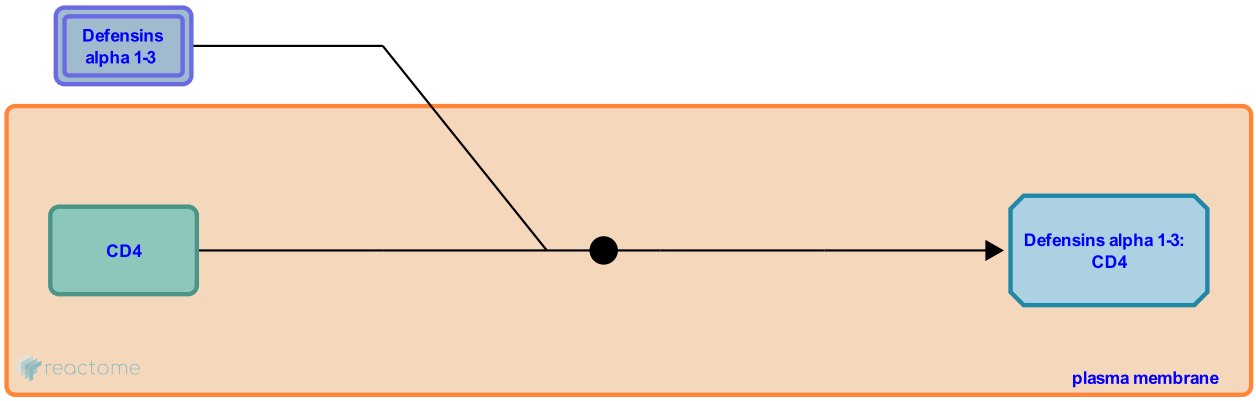
HNP1-3 bind CD4 ↗

Location: Alpha-defensins

Stable identifier: R-HSA-1471314

Type: binding

Compartments: plasma membrane, extracellular region



Alpha-defensins, theta-defensins and their synthetic analogues the retrocyclins have been shown in numerous studies to have anti-HIV-1 activity (Chang & Klotman 2004). This appears to be mediated via multiple mechanisms including direct viral inactivation and down regulation of host-cell target co-receptors important for viral entry (Furci et al. 2007, Seidel et al. 2010). Further, HNPs 1 3, act as lectins and bind with relatively high affinity to gp120 (KD range, 15.8-52.8 nM) on the HIV-1 envelope and CD4 (KD range, 8.0-34.9 nM) on host target cells, both important molecules for viral entry (Wang et al. 2004). Artificial theta defensins, the retrocyclins, predicted from the human pseudogenes bind with even higher affinity whereas HNP-4 binding is much weaker (Wu et al. 2005). Alpha defensins have been demonstrated to inhibit the binding of gp120 to CD4 thus blocking HIV-1 fusion with its target cells (Furci et al. 2007).

Preceded by: HNP1-4 are released into phagocytic vacuoles

Literature references

Waring, AJ., Lal, RB., Hong, T., Cole, AM., Owen, SM., Wang, W. et al. (2004). Activity of alpha- and theta-defensins against primary isolates of HIV-1. *J Immunol, 173*, 515-20. ↗

Editions

2011-04-28	Authored	Jupe, S.
2011-07-27	Edited	Jupe, S.
2011-11-03	Reviewed	McDermott, AM.

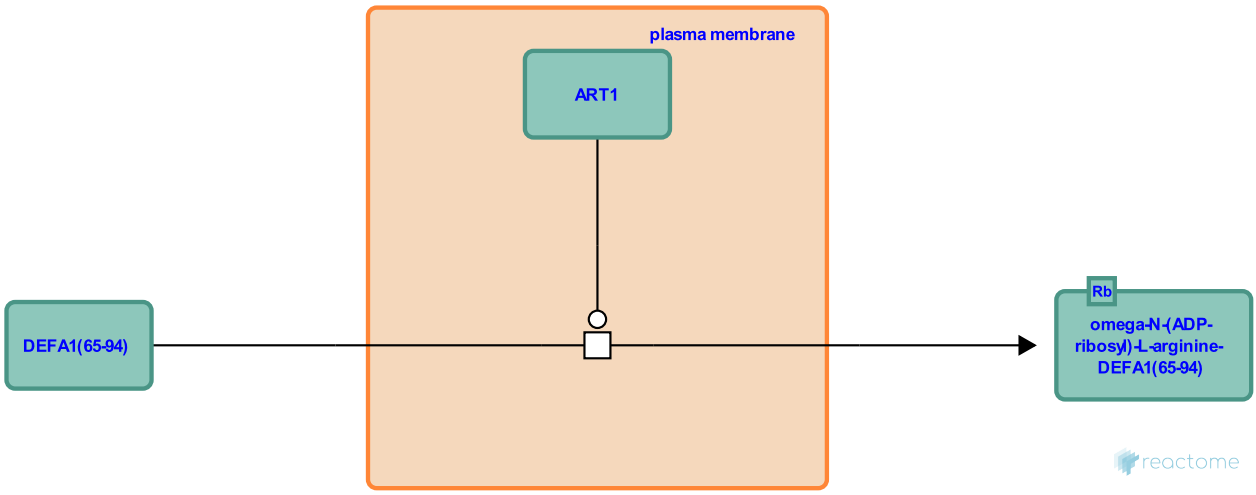
ADP-Ribosylation of HNP-1 ↗

Location: Alpha-defensins

Stable identifier: R-HSA-1972385

Type: transition

Compartments: plasma membrane, extracellular region



HNP-1 is recognized as a substrate by arginine-specific ADP-ribosyltransferase-1 which ribosylates Arg-14 of the peptide. The modified defensin has reduced antimicrobial and cytotoxic activities but its chemotactic properties remain unchanged whilst its ability to induced the chemokine IL-8 is enhanced.

Preceded by: HNP1-4 are released into phagocytic vacuoles

Literature references

Moss, J., Wada, A., Paone, G., Hirayama, T., Matin, A., Stevens, LA. et al. (2002). ADP ribosylation of human neutrophil peptide-1 regulates its biological properties. *Proc Natl Acad Sci U S A, 99*, 8231-5. ↗

Editions

2011-11-03	Reviewed	McDermott, AM.
2011-11-04	Authored, Edited	Jupe, S.

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