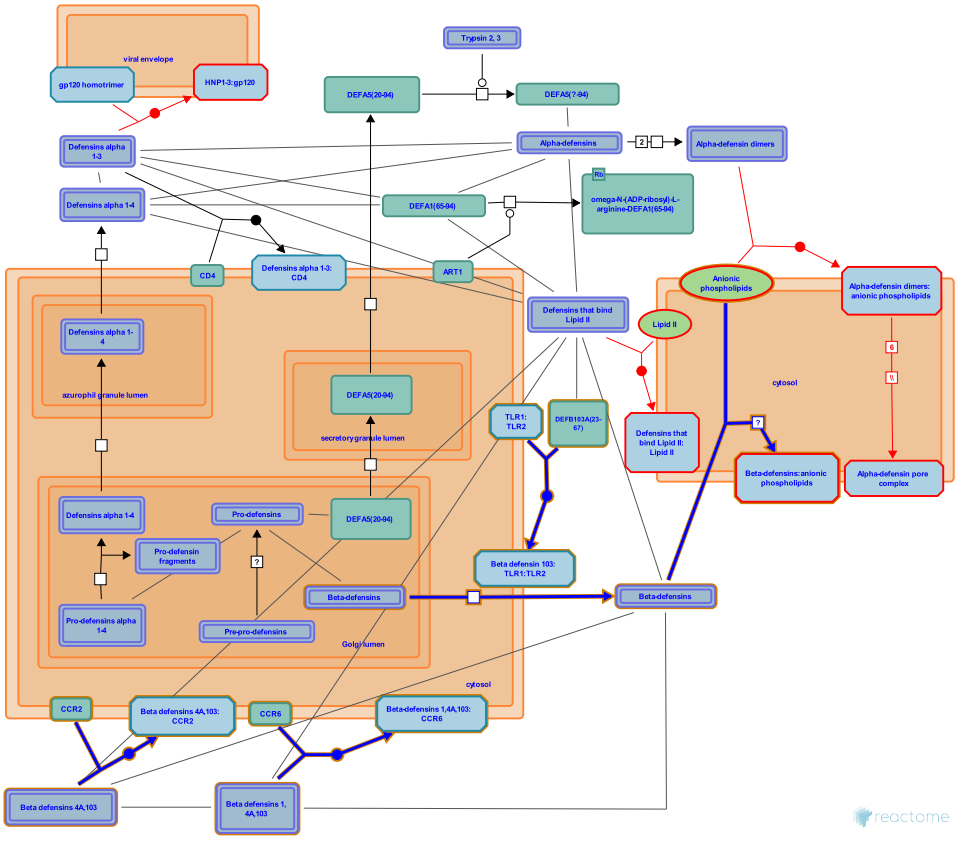
Beta defensins



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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. ↗

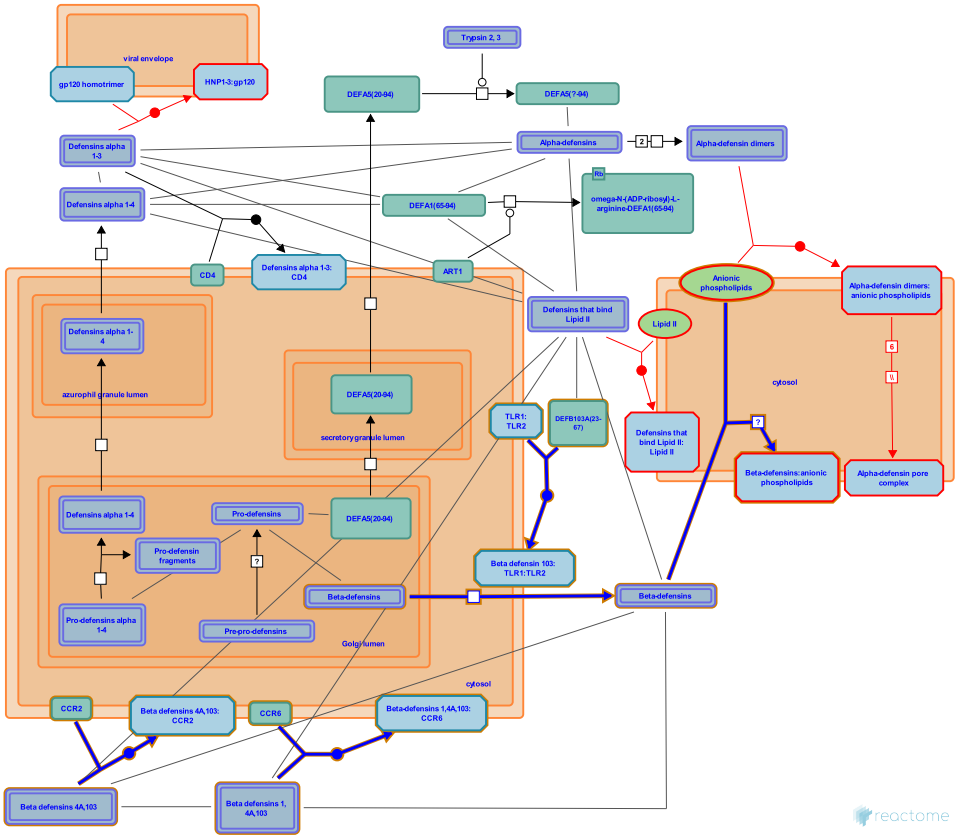
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Beta defensins ↗

Stable identifier: R-HSA-1461957



Humans have 38 beta-defensin genes plus 9-10 pseudogenes (details available on the HGNC website at http://www.genenames.org/genefamilies/DEFB). Many beta-defensins are encoded by recently duplicated genes giving rise to identical transcripts. Nomenclature is confusing and currently in transition. Uniprot recommended names are used throughout this pathway.
Many beta-defensins show expression that correlates with infection (Sahl et al. 2005, Pazgier et al. 2006). All so far characterized beta-defensins, i.e. beta-defensin 1 (hBD1), 4A (hBD2), 103 (hBD3), 104 (hBD4), 106 (hBD6), 118 (hBD18) and 128 (hBD28) have antimicrobial properties (Pazgier et al. 2006). For beta-defensins 4A, 103 and 118 (hBD2, 3, and 18) this has been shown to correlate with membrane permeabilization effects (Antcheva et al. 2004, Sahl et al. 2005, Yenugu et al. 2004). Electrostatic interaction and disruption of microbial membranes is widely believed to the primary mechanism of action for beta-defensins. Two models explain how membrane disruption takes place, the 'pore model' which postulates that beta-defensins form transmembrane pores in a similar manner to alpha-defensins, and the 'carpet model', which suggests that beta-defensins act as detergents. Beta-defensins contain 6 conserved cysteine residues that in beta-defensins 1, 4A and 103 (hBD1-3) are experimentally confirmed to be cross-linked 1-5, 2-4, 3-6. The canonical sequence for beta-defensins is x2-10Cx5-6(G/A)xCX3-4Cx9-13Cx4-7CCxn. Structurally they are similar to alpha-defensins but with much shorter pre-regions. Though dimerization of some beta-defensins has been reported this is not the case for all and it is unclear whether it is required for function. The majority of functional studies have focused on beta-defensin 103 (hBD3), which has the most significant antimicrobial activity at physiological salt concentrations (Harder et al. 2001). Beta-defensin 103 is highly cationic with a net charge of +11 e0. It exhibits broad-spectrum antimicrobial activity against gram-positive bacteria and some gram-negative bacteria (Harder et al. 2001), though some species are highly resistant (Sahly et al. 2003). Sensitivity correlates with lipid composition of the membrane, with more negatively-charged lipids correlating with larger beta-defensin 103-induced changes in membrane capacitance (Bohling et al. 2006). Though membrane disruption is widely believed to be the primary mechanism of action of beta-defensins they have other antimicrobial properties, such as inhibition of cell wall biosynthesis (Sass et al. 2010), and chemoattractant effects (Yang et al. 1999, Niyonsaba et al. 2002, 2004). The chemotactic activity of beta-defensins 1, 4A and 103 (hBD1-3) for memory T cells and immature DCs is mediated through binding to the chemokine receptor CCR6 and probably another unidentified Gi-coupled receptor (Yang et al. 1999, 2000).

Like defensins, the human cathelicidin LL37 peptide is rich in positively-charged residues (Lehrer & Ganz 2002).
Expression of certain beta-defensins can be induced in response to various signals, such as bacteria, pathogen-associated molecular patterns (PAMPs), or proinflammatory cytokines (Ganz 2003, Yang et al. 2004). Like the alpha-defensins, copy number variation has been reported for DEFB4, DEFB103 and DEFB104 with individuals

having 2-12 copies per diploid genome. In contrast DEFB1 does not show such variation but exhibits a number of SNPs (Hollox et al. 2003, Linzmier & Ganz 2005).

Literature references

Lubkowski, J., Hoover, DM., Yang, D., Pazgier, M., Lu, W. (2006). Human beta-defensins. *Cell Mol Life Sci, 63*, 1294-313. ↗

Editions

2011-04-28	Authored	Jupe, S.
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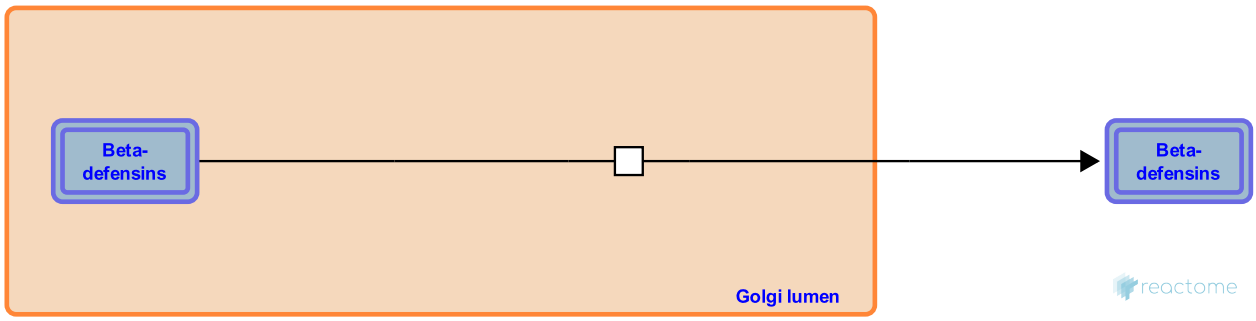
Beta-defensins are secreted ↗

Location: Beta defensins

Stable identifier: R-HSA-1471322

Type: transition

Compartments: Golgi lumen, extracellular region



Beta defensin precursors are more simple in structure than those of alpha defensins, having a signal sequence, a short or absent propiece and the mature defensin sequence at the C-terminus. The signal sequence is cleaved off by a signal peptidase in the endoplasmic reticulum (Ganz 2003). Mature beta defensins 1, 2, 3, and 4 are secreted primarily by epithelial cells but are also produced by some immune cells such as monocytes, macrophages and dendritic cells (Duits et al. 2000, Ryan et al. 2003).

Followed by: Beta-defensins bind microbial membranes causing disruption

Literature references

Garcia-Lopez, G., Flores-Espinosa, P., Zaga-Clavellina, V. (2010). Tissue-specific human beta-defensins (HBD)1, HBD2, and HBD3 secretion from human extra-placental membranes stimulated with Escherichia coli. *Reprod Biol Endocrinol, 8*, 146. ↗

McCray PB, Jr., Ganz, T., Park, CH., Valore, EV., Quayle, AJ., Wiles, KR. (1998). Human beta-defensin-1: an antimicrobial peptide of urogenital tissues. *J Clin Invest, 101*, 1633-42. ↗

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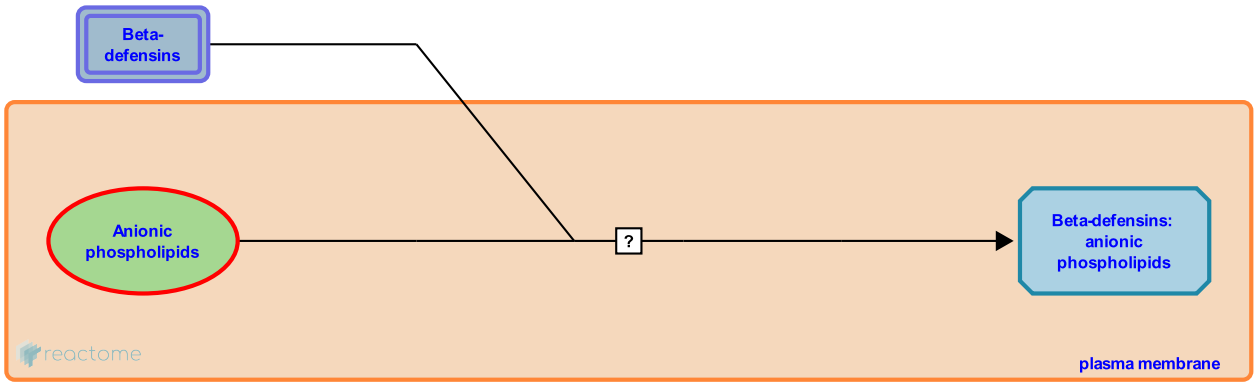
Beta-defensins bind microbial membranes causing disruption ↗

Location: Beta defensins

Stable identifier: R-HSA-1467269

Type: uncertain

Compartments: plasma membrane, extracellular region



Binding and disruption of microbial membranes is widely believed to be the primary mechanism of action for beta-defensins. There is no direct evidence of this, but a growing number of studies support this model (Pazgier et al. 2006). Beta-defensins have antimicrobial properties that correlate with membrane permeabilization effects (Antcheva et al. 2004, Sahl et al. 2005, Yenugu et al. 2004). The sensitivity of microbes to beta-defensins correlates with the lipid composition of the membrane; more negatively-charged lipids correlate with larger beta-defensin 103-induced changes in membrane capacitance (Bohling et al. 2006). Beta-defensin-103 was observed to give rise to ionic currents in Xenopus membranes (Garcia et al. 2001) and cell wall perforation was observed in S. aureus when treated with HBD-3 (Harder et al. 2001). Two models explain how membrane disruption takes place. The 'pore model' postulates that beta-defenisns form transmembrane pores in a similar manner to alpha-defensins, while the 'carpet model' suggests that beta-defensins act as detergents, causing a less organised disruption. Beta-defensins have a structure that is topologically distinct from that of alpha-defensins, suggesting a different mode of dimerization and an electrostatic charge-based mechanism of membrane permeabilization rather than a mechanism based on formation of bilayer-spanning pores (Hoover et al. 2000).

Preceded by: Beta-defensins are secreted

Literature references

Jaumann, F., Adermann, K., Vogelmeier, C., Bals, R., Schulz, S., Klüver, E. et al. (2001). Identification of a novel, multifunctional beta-defensin (human beta-defensin 3) with specific antimicrobial activity. Its interaction with plasma membranes of Xenopus oocytes and the induction of macrophage chemoattraction. *Cell Tissue Res, 306*, 257-64. ↗

Bartels, J., Christophers, E., Harder, J., Schroder, JM. (2001). Isolation and characterization of human beta -defensin-3, a novel human inducible peptide antibiotic. *J Biol Chem, 276*, 5707-13. ↗

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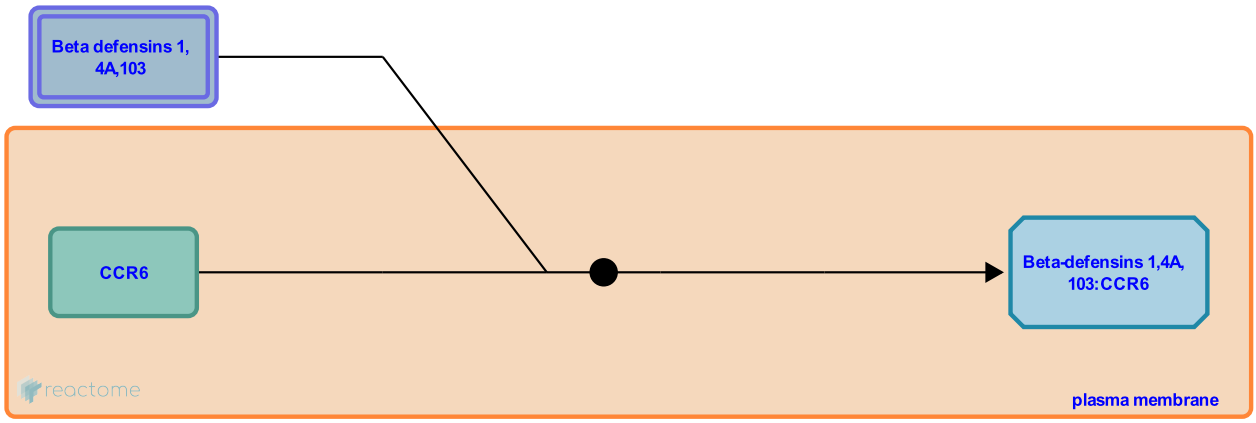
Beta-defensins 1, 4A and 103 bind CCR6 ↗

Location: Beta defensins

Stable identifier: R-HSA-1471338

Type: binding

Compartments: plasma membrane, extracellular region



The chemotactic activity of beta-defensins 1, 4A and 103 (hBD1-3) for immune and inflammatory cells such as memory T cells and immature dendritic cells is mediated through binding to the chemokine receptor CCR6.

Literature references

Nagaoka, I., Niyonsaba, F., Ogawa, H., Iwabuchi, K., Matsuda, H. (2002). Epithelial cell-derived human beta-defensin-2 acts as a chemotaxin for mast cells through a pertussis toxin-sensitive and phospholipase C-dependent pathway. *Int Immunol, 14*, 421-6. ↗

Howard, OM., Schröder, JM., Buffo, MJ., Chertov, O., Wang, JM., Oppenheim, JJ. et al. (1999). Beta-defensins: linking innate and adaptive immunity through dendritic and T cell CCR6. *Science, 286*, 525-8. ↗

Chertov, O., Oppenheim, JJ., Yang, D., Chen, Q. (2000). Human neutrophil defensins selectively chemoattract naive T and immature dendritic cells. *J Leukoc Biol, 68*, 9-14. ↗

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2011-04-28	Authored	Jupe, S.
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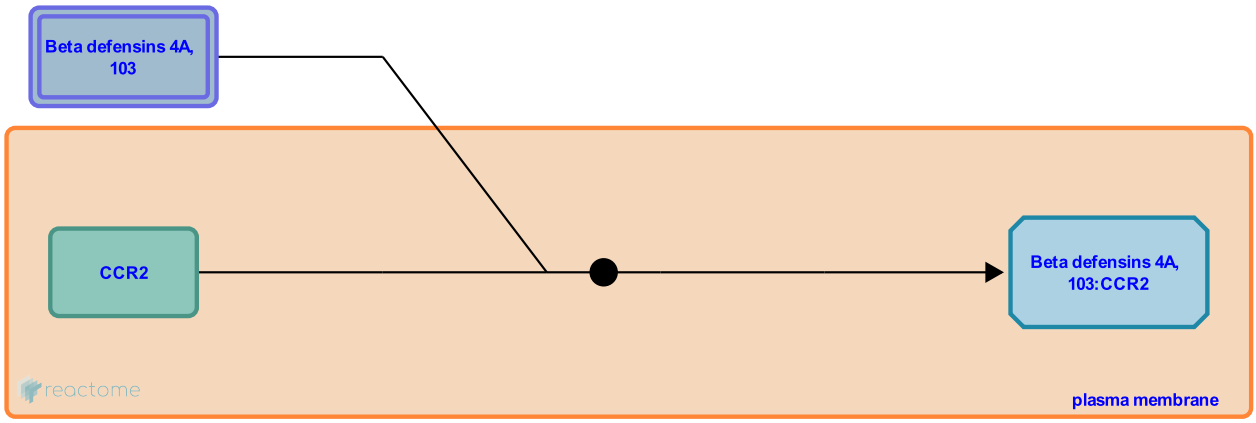
Beta-defensins 4A and 103 bind CCR2 ↗

Location: Beta defensins

Stable identifier: R-HSA-1973968

Type: binding

Compartments: plasma membrane, extracellular region



human beta-defensin (hBD)4A and 103 interact with CCR2, a chemokine receptor expressed on monocytes, macrophages, and neutrophils.

Literature references

Oppenheim, JJ., Yang, D., Röhrl, J., Hehlgans, T. (2010). Human beta-defensin 2 and 3 and their mouse orthologs induce chemotaxis through interaction with CCR2. *J Immunol, 184*, 6688-94. ↗

Editions

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2011-11-07	Edited	Jupe, S.

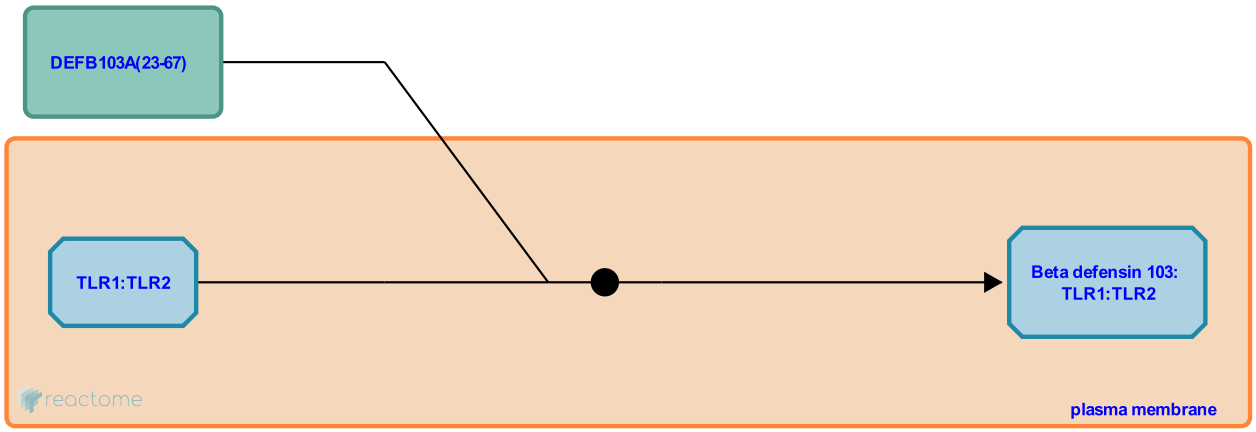
Beta defensin 103 activates TLR1:TLR2 ↗

Location: Beta defensins

Stable identifier: R-HSA-1974676

Type: binding

Compartments: plasma membrane, extracellular region



Beta defensin 103 (hBD-3) can induce expression of the costimulatory molecules CD80, CD86 and CD40 on monocytes and myeloid dendritic cells in a Toll-like receptor (TLR)-dependent manner. Activation by hBD-3 is mediated by an interaction that requires TLRs 1 and 2 (Funderburg et al. 2007, 2011).

Literature references

Lederman, MM., Harding, CV., Drage, MG., Feng, Z., Funderburg, N., Jadlowsky, J. et al. (2007). Human -defensin-3 activates professional antigen-presenting cells via Toll-like receptors 1 and 2. *Proc Natl Acad Sci U S A, 104*, 18631-5. ↗

Editions

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