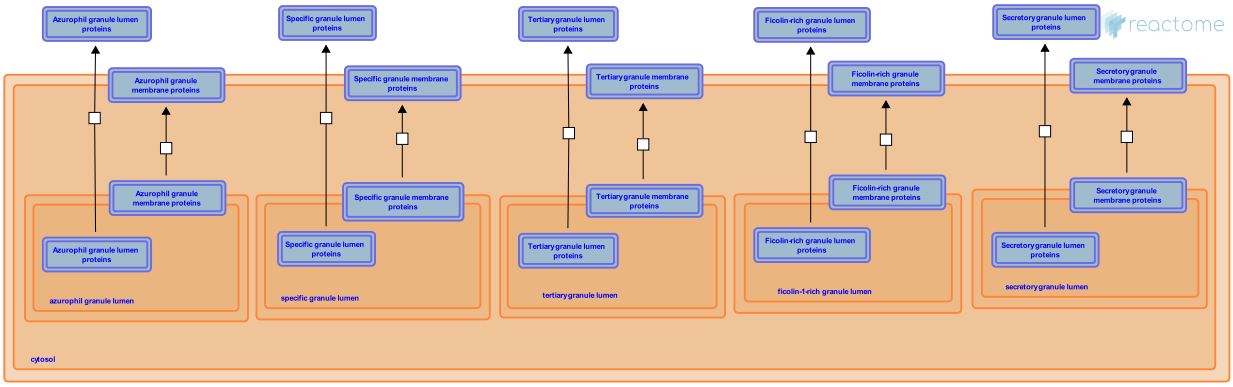
Neutrophil degranulation



Heegaard, N., Jupe, S.

European Bioinformatics Institute, New York University Langone Medical Center, Ontario Institute for Cancer Research, Oregon Health and Science University.

16/11/2024

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. ↗

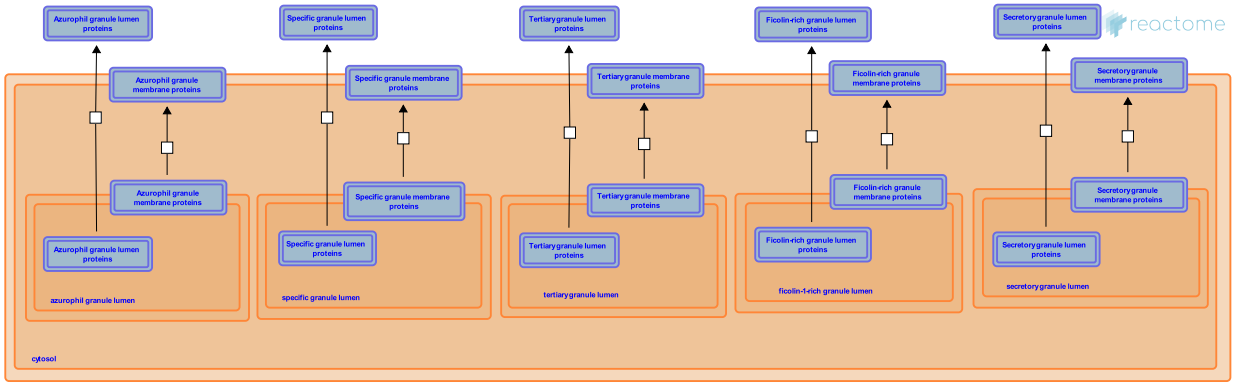
Sidiropoulos, K., Viteri, G., Sevilla, C., Jupe, S., Webber, M., Orlic-Milacic, M. et al. (2017). Reactome enhanced pathway visualization. *Bioinformatics, 33*, 3461-3467. ↗

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. ↗

Neutrophil degranulation ↗

Stable identifier: R-HSA-6798695



Neutrophils are the most abundant leukocytes (white blood cells), indispensable in defending the body against invading microorganisms. In response to infection, neutrophils leave the circulation and migrate towards the inflammatory focus. They contain several subsets of granules that are mobilized to fuse with the cell membrane or phagosomal membrane, resulting in the exocytosis or exposure of membrane proteins. Traditionally, neutrophil granule constituents are described as antimicrobial or proteolytic, but granules also introduce membrane proteins to the cell surface, changing how the neutrophil responds to its environment (Borregaard et al. 2007). Primed neutrophils actively secrete cytokines and other inflammatory mediators and can present antigens via MHC II, stimulating T-cells (Wright et al. 2010).

Granules form during neutrophil differentiation. Granule subtypes can be distinguished by their content but overlap in structure and composition. The differences are believed to be a consequence of changing protein expression and differential timing of granule formation during the terminal processes of neutrophil differentiation, rather than sorting (Le Cabec et al. 1996).

The classical granule subsets are Azurophil or primary granules (AG), secondary granules (SG) and gelatinase granules (GG). Neutrophils also contain exocytosable storage cell organelles, storage vesicles (SV), formed by endocytosis they contain many cell-surface markers and extracellular, plasma proteins (Borregaard et al. 1992). Ficolin-1-rich granules (FG) are like GGs highly exocytosable but gelatinase-poor (Rorvig et al. 2009).

Literature references

Heegaard, NH., Rørvig, S., Borregaard, N., Østergaard, O. (2013). Proteome profiling of human neutrophil granule subsets, secretory vesicles, and cell membrane: correlation with transcriptome profiling of neutrophil precursors. *J. Leukoc. Biol., 94*, 711-21. ↗

Sørensen, OE., Borregaard, N., Theilgaard-Mönch, K. (2007). Neutrophil granules: a library of innate immunity proteins. *Trends Immunol., 28*, 340-5. ↗

Nielsen, MH., Johnsen, AH., Bjerrum, OW., Borregaard, N., Kjeldsen, L., Rygaard, K. et al. (1992). Stimulus-dependent secretion of plasma proteins from human neutrophils. *J. Clin. Invest., 90*, 86-96. ↗

Bucknall, RC., Wright, HL., Edwards, SW., Moots, RJ. (2010). Neutrophil function in inflammation and inflammatory diseases. *Rheumatology (Oxford), 49*, 1618-31. ↗

Le Cabec, V., Borregaard, N., Calafat, J., Cowland, JB. (1996). Targeting of proteins to granule subsets is determined by timing and not by sorting: The specific granule protein NGAL is localized to azurophil granules when expressed in HL-60 cells. *Proc. Natl. Acad. Sci. U.S.A., 93*, 6454-7. ↗

Editions

2015-09-21	Authored	Jupe, S.
2016-06-13	Reviewed	Heegaard, N.
2016-06-13	Edited	Jupe, S.

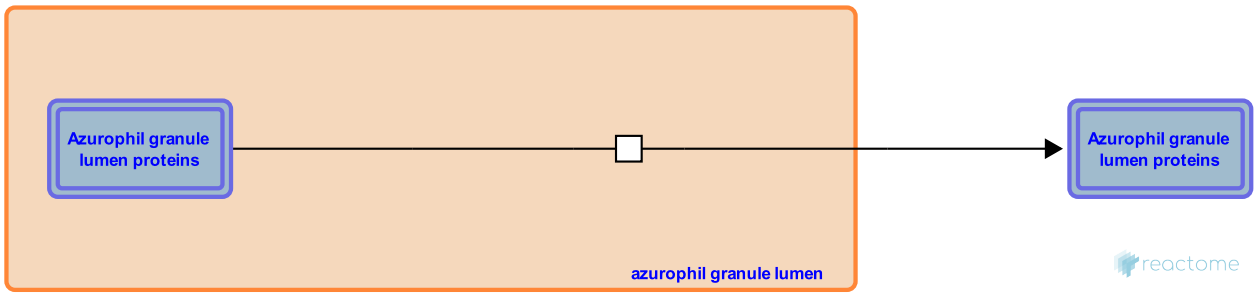
Exocytosis of azurophil granule lumen proteins ↗

Location: Neutrophil degranulation

Stable identifier: R-HSA-6798751

Type: transition

Compartments: azurophil granule lumen, extracellular region



Azurophil or primary granules were originally defined by their high content of myeloperoxidase (MPO) and their affinity for the basic dye azure A (Spicer & Hardin 1969). Azurophil granules are generally described as spherical. Like lysosomes, they contain CD63 in their membrane (Cham et al. 1994) but are regarded as specialized secretory granules rather than lysosomes (Cieutat et al. 1998). Azurophil granules undergo limited exocytosis in response to stimulation (Sengelov et al. 1993, Faurschou et al. 2002), their primary role is believed to be killing and degradation of engulfed microbes in the phagolysosome (Joiner et al. 1989). MPO reacts with H2O2 formed by NADPH oxidase, increasing its toxicity by formation of hypochlorous acid and other chlorination products, tyrosine radicals and reactive nitrogen intermediates which attack the surface of microbes (Klebanoff et al. 2013).

Literature references

Le Cabec, V., Borregaard, N., Calafat, J., Cowland, JB. (1996). Targeting of proteins to granule subsets is determined by timing and not by sorting: The specific granule protein NGAL is localized to azurophil granules when expressed in HL-60 cells. *Proc. Natl. Acad. Sci. U.S.A., 93*, 6454-7. ↗

Editions

2015-09-21	Authored	Jupe, S.
2016-06-13	Reviewed	Heegaard, N.
2016-06-13	Edited	Jupe, S.

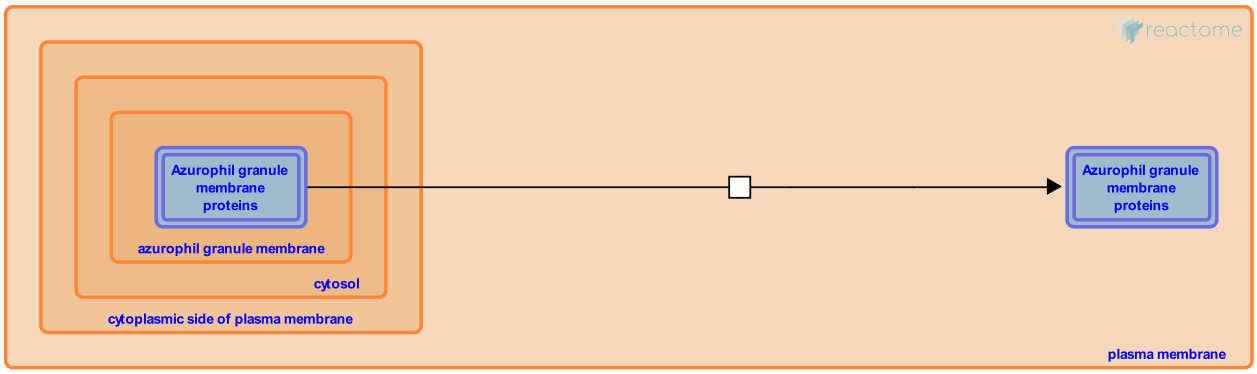
Exocytosis of azurophil granule membrane proteins ↗

Location: Neutrophil degranulation

Stable identifier: R-HSA-6798739

Type: transition

Compartments: plasma membrane, azurophil granule membrane



Azurophil or primary granules were originally defined by their high content of myeloperoxidase (MPO) and their affinity for the basic dye azure A (Spicer & Hardin 1969). Azurophil granules are generally described as spherical. Like lysosomes, they contain CD63 in their membrane (Cham et al. 1994) but are regarded as specialized secretory granules rather than lysosomes (Cieutat et al. 1998). Azurophil granules undergo limited exocytosis in response to stimulation (Sengelov et al. 1993, Faurschou et al. 2002), their primary role is believed to be killing and degradation of engulfed microbes in the phagolysosome (Joiner et al. 1989).

Literature references

Le Cabec, V., Borregaard, N., Calafat, J., Cowland, JB. (1996). Targeting of proteins to granule subsets is determined by timing and not by sorting: The specific granule protein NGAL is localized to azurophil granules when expressed in HL-60 cells. *Proc. Natl. Acad. Sci. U.S.A., 93*, 6454-7. ↗

Editions

2015-09-21	Authored	Jupe, S.
2016-06-13	Reviewed	Heegaard, N.
2016-06-13	Edited	Jupe, S.

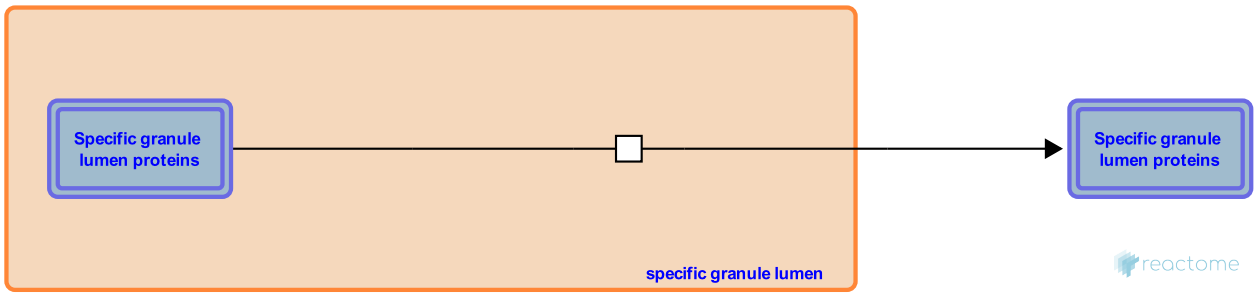
Exocytosis of specific granule lumen proteins ↗

Location: Neutrophil degranulation

Stable identifier: R-HSA-6798749

Type: transition

Compartments: specific granule lumen, extracellular region



Secondary (specific) granules are peroxidase-negative and rich in antimicrobial substances (Joiner et al. 1989, Rorvig et al. 2012). They are more irregular and elongated in form than azurophil granules (Bainton et al. 1971). This might reflect volume adjustment in azurophil granules, which are known to proteolytically process a significant fraction of the proteins that are targeted to them, while little or no processing and therefore no increase in osmotic activity due to proteolysis has been observed in secondary granules (Borregaard & Cowland 1997). Secondary and tertiary granules have overlapping contents but can be discriminated by their intrinsic buoyant densities when centrifuged on gradient media (Kjeldsen et al. 1994).

Literature references

Heegaard, NH., Rørvig, S., Borregaard, N., Østergaard, O. (2013). Proteome profiling of human neutrophil granule subsets, secretory vesicles, and cell membrane: correlation with transcriptome profiling of neutrophil precursors. *J. Leukoc. Biol., 94*, 711-21. ↗

Editions

2015-09-21	Authored	Jupe, S.
2016-06-13	Reviewed	Heegaard, N.
2016-06-13	Edited	Jupe, S.

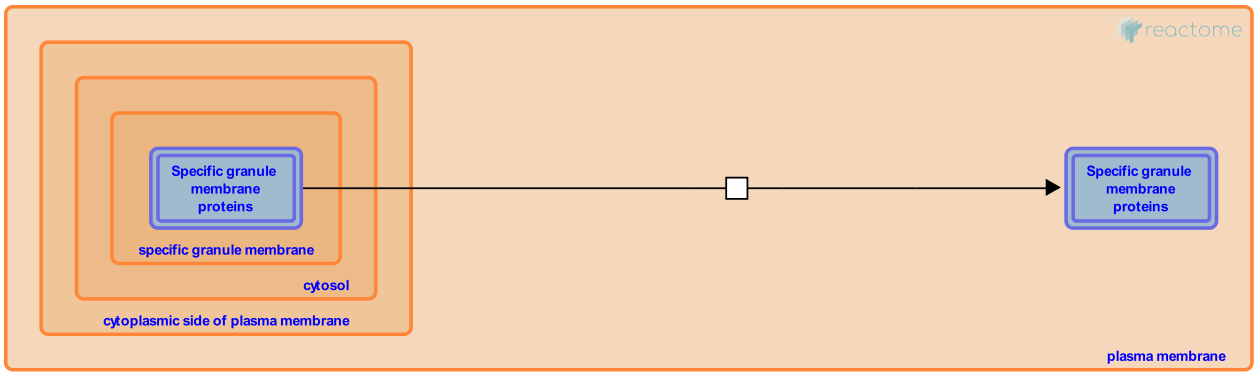
Exocytosis of specific granule membrane proteins ↗

Location: Neutrophil degranulation

Stable identifier: R-HSA-6799350

Type: transition

Compartments: plasma membrane, specific granule membrane



Secondary (specific) granules are peroxidase-negative and rich in antimicrobial substances (Joiner et al. 1989, Rorvig et al. 2012). They are more irregular and elongated in form than azurophil granules (Bainton et al. 1971). This may reflect volume adjustment in azurophil granules, which are known to proteolytically process a significant fraction of the proteins that are targeted to them, while little or no processing and therefore no increase in osmotic activity due to proteolysis has been observed in secondary granules (Borregaard & Cowland 1997). Secondary and tertiary granules have overlapping contents but can be discriminated by their intrinsic buoyant densities when centrifuged on gradient media (Kjeldsen et al. 1994).

Literature references

Heegaard, NH., Rørvig, S., Borregaard, N., Østergaard, O. (2013). Proteome profiling of human neutrophil granule subsets, secretory vesicles, and cell membrane: correlation with transcriptome profiling of neutrophil precursors. *J. Leukoc. Biol., 94*, 711-21. ↗

Editions

2015-09-21	Authored	Jupe, S.
2016-06-13	Reviewed	Heegaard, N.
2016-06-13	Edited	Jupe, S.

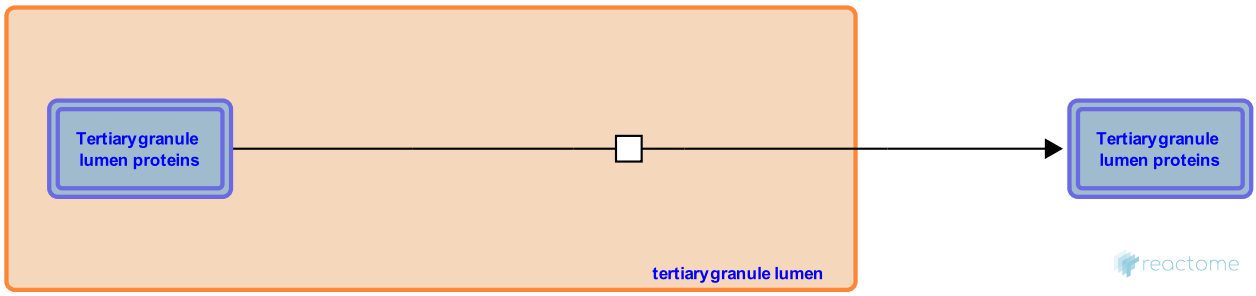
Exocytosis of tertiary granule lumen proteins ↗

Location: Neutrophil degranulation

Stable identifier: R-HSA-6798745

Type: transition

Compartments: tertiary granule lumen, extracellular region



Tertiary (gelatinase) granules are part of a continuum of peroxidase-negative granules formed in myelocytes, metamyelocytes, band cells and segmented neutrophils. They differ from secondary granules by having a low content of antimicrobial substances, and are more readily exocytosed (Sengelov et al. 1995). Tertiary granules are primarily a reservoir of extracellular matrix degrading enzymes and membrane receptors that are needed for neutrophil extravasation and diapedesis (Faurschou & Borregaard 2003).

Literature references

Heegaard, NH., Rørvig, S., Borregaard, N., Østergaard, O. (2013). Proteome profiling of human neutrophil granule subsets, secretory vesicles, and cell membrane: correlation with transcriptome profiling of neutrophil precursors. *J. Leukoc. Biol., 94*, 711-21. ↗

Editions

2015-09-21	Authored	Jupe, S.
2016-06-13	Reviewed	Heegaard, N.
2016-06-13	Edited	Jupe, S.

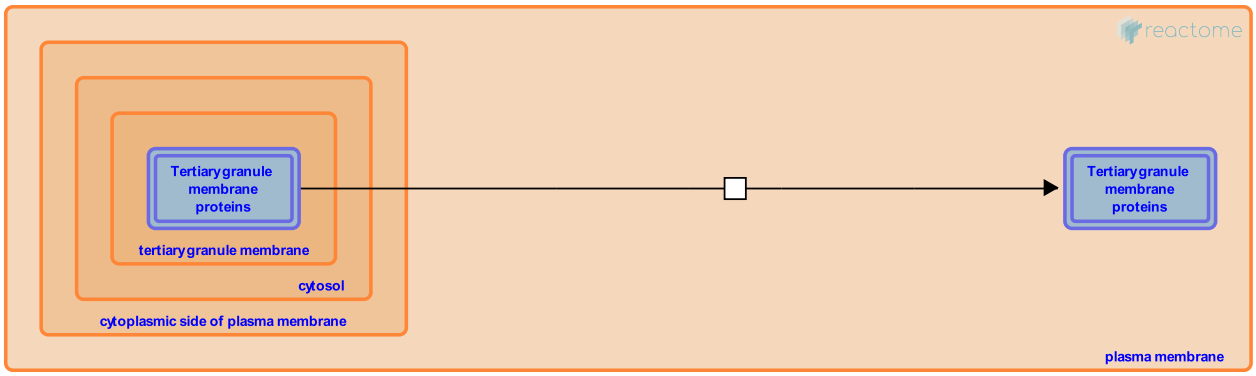
Exocytosis of tertiary granule membrane proteins ↗

Location: Neutrophil degranulation

Stable identifier: R-HSA-6798747

Type: transition

Compartments: plasma membrane, tertiary granule membrane



Tertiary (gelatinase) granules are part of a continuum of peroxidase-negative granules formed in myelocytes, metamyelocytes, band cells and segmented neutrophils. They differ from secondary granules by having a low content of antimicrobial substances, and are more readily exocytosed (Sengelov et al. 1995). Tertiary granules are primarily a reservoir of extracellular matrix degrading enzymes and membrane receptors that are required for neutrophil extravasation and diapedesis (Faurschou & Borregaard 2003).

Literature references

Heegaard, NH., Rørvig, S., Borregaard, N., Østergaard, O. (2013). Proteome profiling of human neutrophil granule subsets, secretory vesicles, and cell membrane: correlation with transcriptome profiling of neutrophil precursors. *J. Leukoc. Biol., 94*, 711-21. ↗

Editions

2015-09-21	Authored	Jupe, S.
2016-06-13	Reviewed	Heegaard, N.
2016-06-13	Edited	Jupe, S.

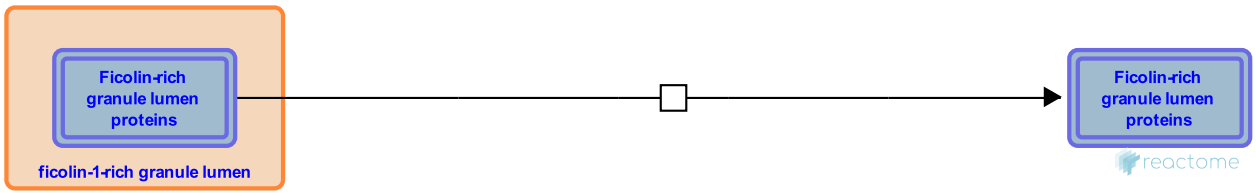
Exocytosis of ficolin-rich granule lumen proteins ↗

Location: Neutrophil degranulation

Stable identifier: R-HSA-6800434

Type: transition

Compartments: extracellular region, ficolin-1-rich granule lumen



Ficoli-1 rich granules are a relatively new fourth neutrophil granule population that is enriched in the microbial lectin ficolin-1. Ficolin-1 is present in tertiary granules, but ficolin-1 rich granules can be differentiated by having low levels of gelatinases and an elevated exocytosis propensity (Rorvig et al. 2009, 2013). The importance of these granules may be to provide rapid release of pattern recognition molecules to activate the lectin complement pathway (Rorvig et al. 2009).

Literature references

Heegaard, NH., Rørvig, S., Borregaard, N., Østergaard, O. (2013). Proteome profiling of human neutrophil granule subsets, secretory vesicles, and cell membrane: correlation with transcriptome profiling of neutrophil precursors. *J. Leukoc. Biol., 94*, 711-21. ↗

Editions

2015-09-21	Authored	Jupe, S.
2016-06-13	Reviewed	Heegaard, N.
2016-06-13	Edited	Jupe, S.

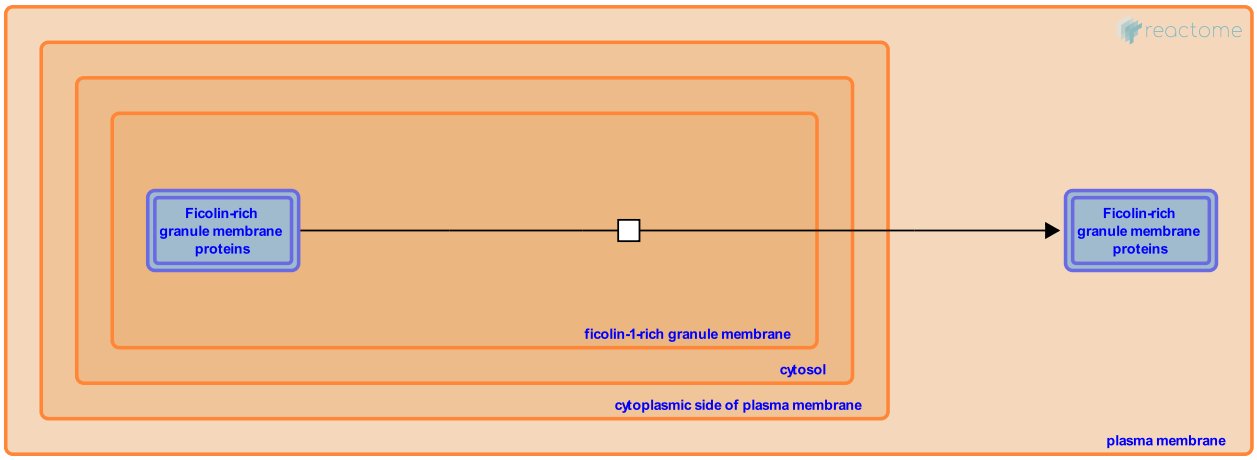
Exocytosis of ficolin-rich granule membrane proteins ↗

Location: Neutrophil degranulation

Stable identifier: R-HSA-6800426

Type: transition

Compartments: ficolin-1-rich granule membrane, plasma membrane



Ficoli-1 rich granules are a relatively new fourth neutrophil granule population that is enriched in the microbial lectin ficolin-1. Ficolin-1 is present in tertiary granules, but ficolin-1 rich granules can be differentiated by having low levels of gelatinases and an elevated exocytosis propensity (Rorvig et al. 2009, 2013). The importance of these granules may be to provide rapid release of pattern recognition molecules to activate the lectin complement pathway (Rorvig et al. 2009).

Literature references

Heegaard, NH., Rørvig, S., Borregaard, N., Østergaard, O. (2013). Proteome profiling of human neutrophil granule subsets, secretory vesicles, and cell membrane: correlation with transcriptome profiling of neutrophil precursors. *J. Leukoc. Biol., 94*, 711-21. ↗

Editions

2015-09-21	Authored	Jupe, S.
2016-06-13	Reviewed	Heegaard, N.
2016-06-13	Edited	Jupe, S.

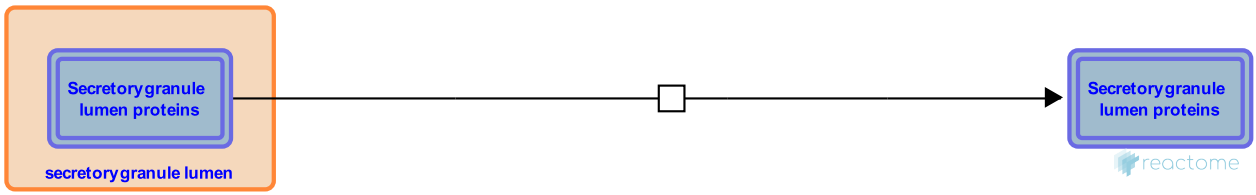
Exocytosis of secretory granule lumen proteins ↗

Location: Neutrophil degranulation

Stable identifier: R-HSA-6798748

Type: transition

Compartments: extracellular region, secretory granule lumen



Secretory vesicles provide a reservoir of secreted proteins and membrane-associated receptors that are required at the earliest stages of the neutrophil-mediated inflammatory response. They are mobilized in response to a wide variety of inflammatory stimuli (Sengelov et al. 1993a,b). Resultant cell surface changes allow the neutrophil to establish firm contact with activated vascular epithelium (Faurschou & Borregaard 2003).

Literature references

Heegaard, NH., Rørvig, S., Borregaard, N., Østergaard, O. (2013). Proteome profiling of human neutrophil granule subsets, secretory vesicles, and cell membrane: correlation with transcriptome profiling of neutrophil precursors. *J. Leukoc. Biol., 94*, 711-21. ↗

Editions

2015-09-21	Authored	Jupe, S.
2016-06-13	Reviewed	Heegaard, N.
2016-06-13	Edited	Jupe, S.

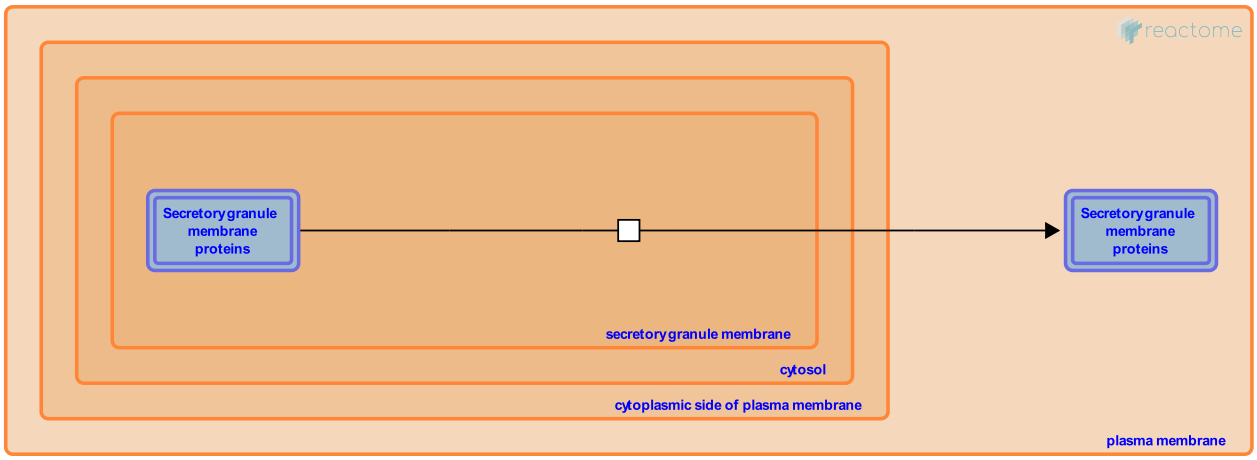
Exocytosis of secretory granule membrane proteins ↗

Location: Neutrophil degranulation

Stable identifier: R-HSA-6798743

Type: transition

Compartments: secretory granule membrane, plasma membrane



Secretory vesicles provide a reservoir of membrane-associated receptors that are required at the earliest stages of the neutrophil-mediated inflammatory response. They are mobilized in response to a wide variety of inflammatory stimuli (Sengelov et al. 1993a,b). Resultant cell surface changes allow the neutrophil to establish firm contact with activated vascular epithelium (Faurschou & Borregaard 2003).

Literature references

Heegaard, NH., Rørvig, S., Borregaard, N., Østergaard, O. (2013). Proteome profiling of human neutrophil granule subsets, secretory vesicles, and cell membrane: correlation with transcriptome profiling of neutrophil precursors. *J. Leukoc. Biol., 94*, 711-21. ↗

Editions

2015-09-21	Authored	Jupe, S.
2016-06-13	Reviewed	Heegaard, N.
2016-06-13	Edited	Jupe, S.

Table of Contents