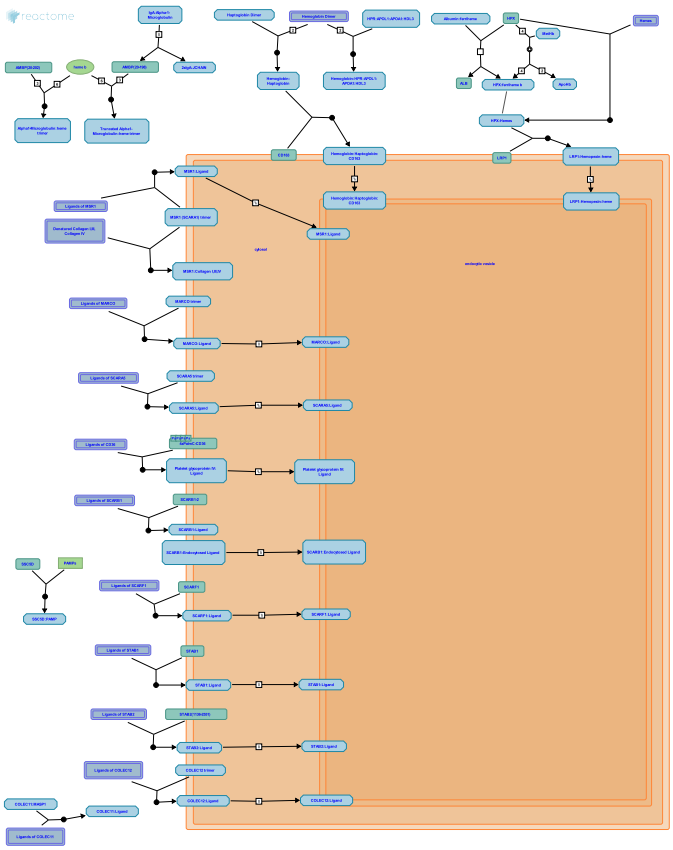
Binding and Uptake of Ligands by Scavenger Receptors



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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.

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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. ↗

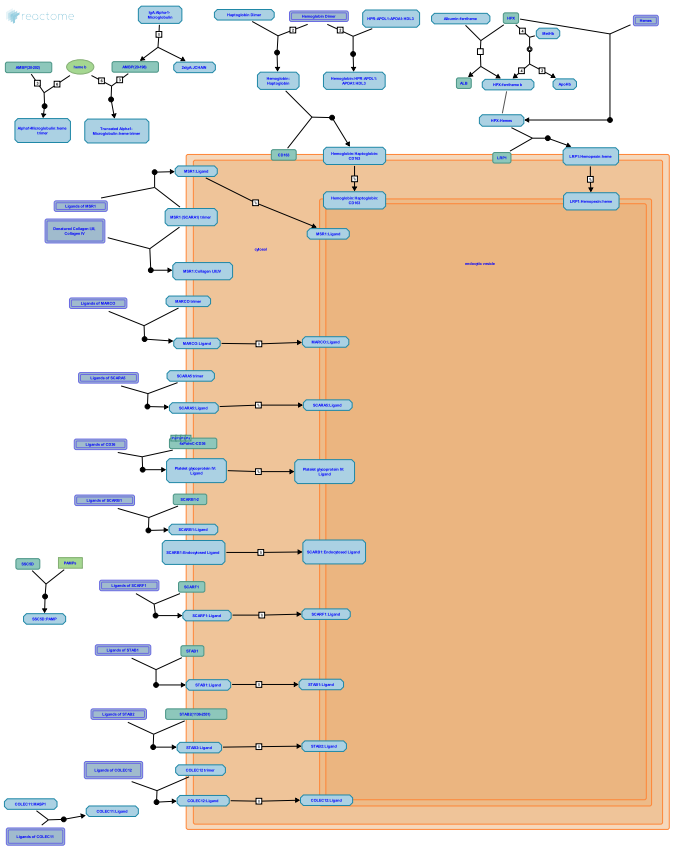
Reactome database release: 88

This document contains 6 pathways (see Table of Contents)

Binding and Uptake of Ligands by Scavenger Receptors ↗

Stable identifier: R-HSA-2173782

Compartments: extracellular region, plasma membrane, endocytic vesicle membrane



Scavenger receptors bind free extracellular ligands as the initial step in clearance of the ligands from the body (reviewed in Ascenzi et al. 2005, Areschoug and Gordon 2009, Nielsen et al. 2010). Some scavenger receptors, such as the CD163-haptoglobin system, are specific for only one ligand. Others, such as the SCARA receptors (SR-A receptors) are less specific, binding several ligands which share a common property, such as polyanionic charges.
Brown and Goldstein originated the idea of receptors dedicated to scavenging aberrant molecules such as modified low density lipoprotein particles (Goldstein et al. 1979) and such receptors have been shown to participate in pathological processes such as atherosclerosis. Based on homology, scavenger receptors have been categorized into classes A-H (reviewed in Murphy et al. 2005).

Literature references

Gordon, S., Areschoug, T. (2009). Scavenger receptors: role in innate immunity and microbial pathogenesis. *Cell. Microbiol., 11*, 1160-9. ↗

Moestrup, SK., Møller, HJ., Nielsen, MJ. (2010). Hemoglobin and heme scavenger receptors. *Antioxid. Redox Signal., 12*, 261-73. ↗

Brown, MS., Ho, YK., Goldstein, JL., Basu, SK. (1979). Binding site on macrophages that mediates uptake and degradation of acetylated low density lipoprotein, producing massive cholesterol deposition. *Proc. Natl. Acad. Sci. U.S.A. , 76*, 333-7. ↗

Ponnambalam, S., Homer-Vanniasinkam, S., Walker, JH., Murphy, JE., Tedbury, PR. (2005). Biochemistry and cell biology of mammalian scavenger receptors. *Atherosclerosis, 182*, 1-15. ↗

Bocedi, A., Ascenzi, P., Beringhelli, T., Altruda, F., Tolosano, E., Visca, P. et al. (2005). Hemoglobin and heme scavenging. *IUBMB Life, 57*, 749-59. ↗

Editions

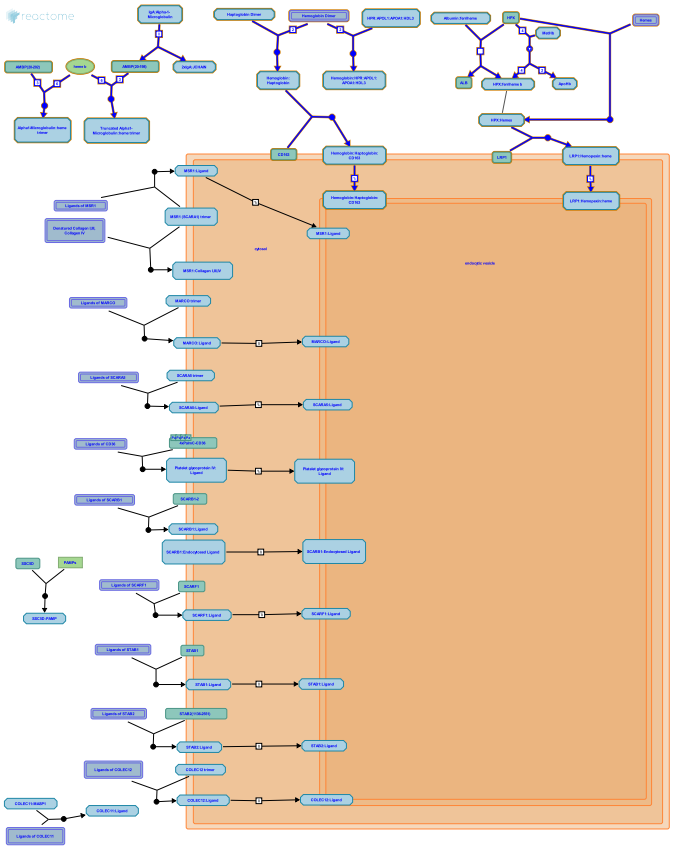
2012-03-25	Authored, Edited	May, B.
2013-02-13	Reviewed	Fiorito, V., Tolosano, E.
2013-02-18	Reviewed	Moestrup, SK.
2013-03-22	Authored, Reviewed	Neyen, C.

Scavenging of heme from plasma ↗

Location: Binding and Uptake of Ligands by Scavenger Receptors

Stable identifier: R-HSA-2168880

Compartments: plasma membrane, extracellular region, endocytic vesicle membrane



Free heme is damaging to tissues as it intercalates into biologic membranes, perturbing lipid bilayers and promoting the conversion of low-density lipoprotein to cytotoxic oxidized products. Moreover, it represents a source of redox-active iron that, participating in the Fenton reaction, generates oxygen radicals (reviewed in Gutteridge 1989). Free heme in plasma is mainly generated from hemoglobin released by circulating erythrocytes in pathologic conditions associated with intravascular hemolysis. Free hemoglobin in plasma is scavenged by the extracellular protein haptoglobin. Haptoglobin is produced by the liver and secreted into the plasma. Haptoglobin binds dimers of hemoglobin subunits rather than the intact tetramer (reviewed in Nielsen et al. 2010, Levy et al. 2010, Ascenzi et al. 2005, Madsen et al. 2001). The resulting haptoglobin:hemoglobin complex is then bound by CD163, expressed on plasma membranes of monocytes and macrophages, and endocytosed. When the buffering capacity of plasma haptoglobin is overwhelmed, heme is released from methemoglobin and it is bound by albumin and then transferred to hemopexin (reviewed in Chiabrando et al. 2011, Nielsen et al. 2010, Tolosano et al. 2010, Ascenzi et al. 2005, Tolosano and Altruda 2002). Hemopexin is produced mainly in the liver. Once secreted into the plasma, hemopexin binds heme and the hemopexin:heme complex is then preferentially delivered to liver hepatocytes, bound by LRP1 (CD91) and endocytosed.

Literature references

Moestrup, SK., Madsen, M., Graversen, JH. (2001). Haptoglobin and CD163: captor and receptor gating hemoglobin to macrophage lysosomes. *Redox Rep., 6*, 386-8. ↗

Veas, F. (2011). Haptoglobin and Hemopexin in heme detoxification and iron re cycling, Acute Phase Proteins. *InTech - Open Access Publisher*, 261-288.

Altruda, F., Tolosano, E. (2002). Hemopexin: structure, function, and regulation. *DNA Cell Biol., 21*, 297-306. ↗

Fagoonee, S., Fiorito, V., Tolosano, E., Vinchi, F., Morello, N. (2010). Heme scavenging and the other facets of hemopexin. *Antioxid. Redox Signal., 12*, 305-20. ↗

Moestrup, SK., Møller, HJ., Nielsen, MJ. (2010). Hemoglobin and heme scavenger receptors. *Antioxid. Redox Signal., 12*, 261-73. ↗

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2012-03-21	Authored, Edited	May, B.
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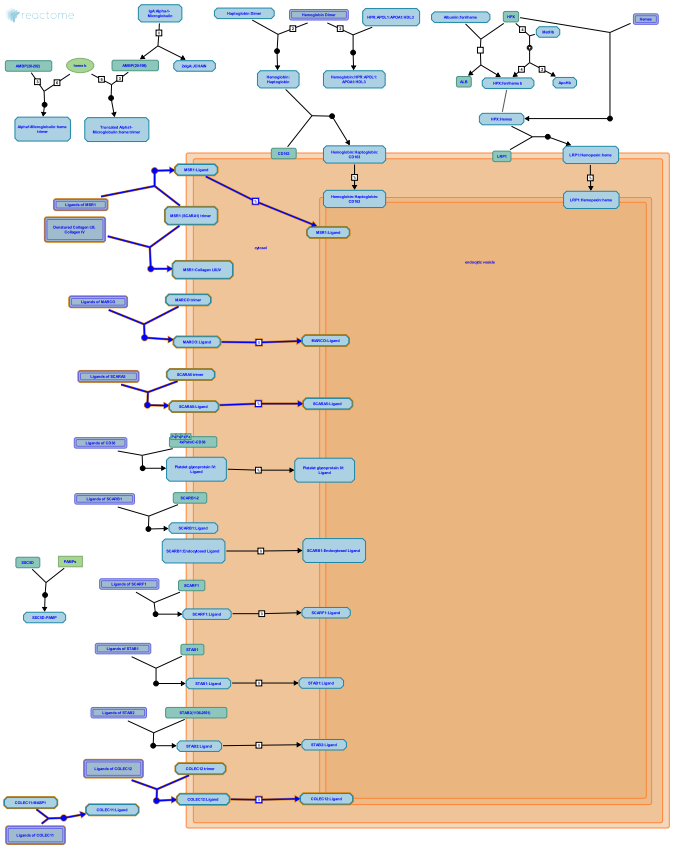
Scavenging by Class A Receptors ↗

Location: Binding and Uptake of Ligands by Scavenger Receptors

Stable identifier: R-HSA-3000480

Compartments: plasma membrane, extracellular region, endocytic vesicle membrane



Class A scavenger receptors contain an intracellular domain, a transmembrane region, a coiled-coil domain, a collagenous domain, and the SR cysteine-rich domain (reviewed in Areschoug and Gordon 2009, Bowdish and Gordon 2009). The coiled coil domains interact to form trimers. The collagenous domain (Rohrer et al. 1990, Acton et al. 1993) and/or the SR cysteine-rich domain (Brannstrom et al. 2002) bind ligands and determine the specificity of the receptor.

Literature references

Resnick, D., Ashkenas, J., Ekkel, Y., Acton, S., Freeman, M., Krieger, M. (1993). The collagenous domains of macrophage scavenger receptors and complement component C1q mediate their similar, but not identical, binding specificities for polyanionic ligands. *J. Biol. Chem., 268*, 3530-7. ↗

Gordon, S., Areschoug, T. (2009). Scavenger receptors: role in innate immunity and microbial pathogenesis. *Cell. Microbiol., 11*, 1160-9. ↗

Kodama, T., Freeman, M., Penman, M., Krieger, M., Rohrer, L. (1990). Coiled-coil fibrous domains mediate ligand binding by macrophage scavenger receptor type II. *Nature, 343*, 570-2. ↗

Pikkarainen, T., Brännström, A., Sankala, M., Tryggvason, K. (2002). Arginine residues in domain V have a central role for bacteria-binding activity of macrophage scavenger receptor MARCO. *Biochem. Biophys. Res. Commun., 290*, 1462-9. ↗

Gordon, S., Bowdish, DM. (2009). Conserved domains of the class A scavenger receptors: evolution and function. *Immunol. Rev., 227*, 19-31. ↗

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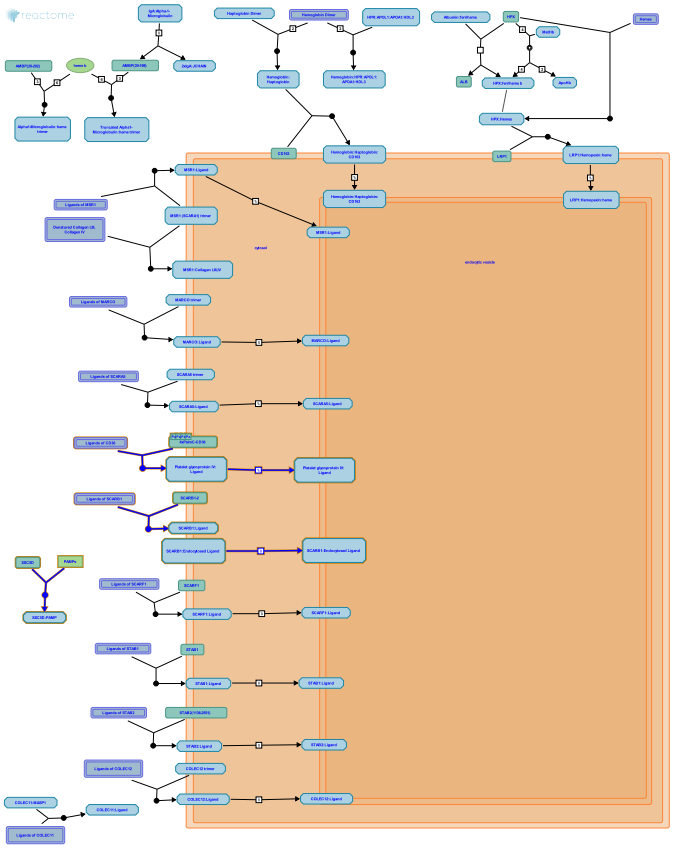
Scavenging by Class B Receptors ↗

Location: Binding and Uptake of Ligands by Scavenger Receptors

Stable identifier: R-HSA-3000471

Compartments: plasma membrane, extracellular region, endocytic vesicle membrane



Class B receptors have two transmembrane domains separated by an extracellular loop (reviewed in Adachi and Tsujimoto 2006, Areschoug and Gordon 2009).

Literature references

Adachi, H., Tsujimoto, M. (2006). Endothelial scavenger receptors. *Prog. Lipid Res., 45*, 379-404. ↗

Gordon, S., Areschoug, T. (2009). Scavenger receptors: role in innate immunity and microbial pathogenesis. *Cell. Microbiol., 11*, 1160-9. ↗

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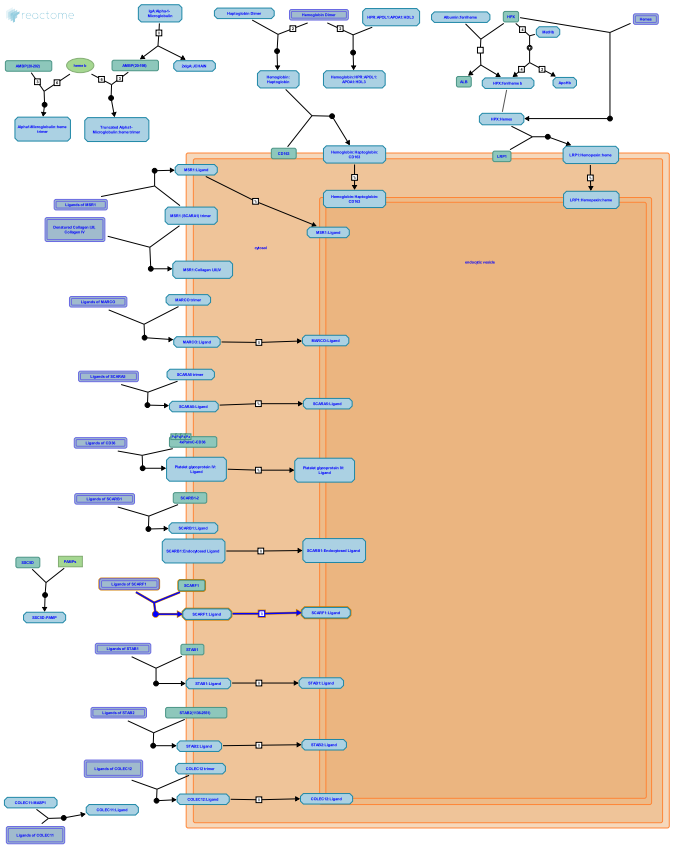
Scavenging by Class F Receptors ↗

Location: Binding and Uptake of Ligands by Scavenger Receptors

Stable identifier: R-HSA-3000484

Compartments: plasma membrane, extracellular region, endocytic vesicle membrane



SCARF1 (SREC-I) and SCARF2 (SREC-II) are transmembrane proteins that contain multiple extracellular EGF-like domains (Ishii et al. 2002, reviewed in Areschoug and Gordon 2009). SCARF2 may be involved in cell adhesion rather than ligand binding.

Literature references

Ishii, J., Tomita, S., Koizumi, H., Arai, H., Inoue, K., Adachi, H. et al. (2002). SREC-II, a new member of the scavenger receptor type F family, trans-interacts with SREC-I through its extracellular domain. *J. Biol. Chem., 277*, 39696-702 . ↗

Gordon, S., Areschoug, T. (2009). Scavenger receptors: role in innate immunity and microbial pathogenesis. *Cell. Microbiol., 11*, 1160-9. ↗

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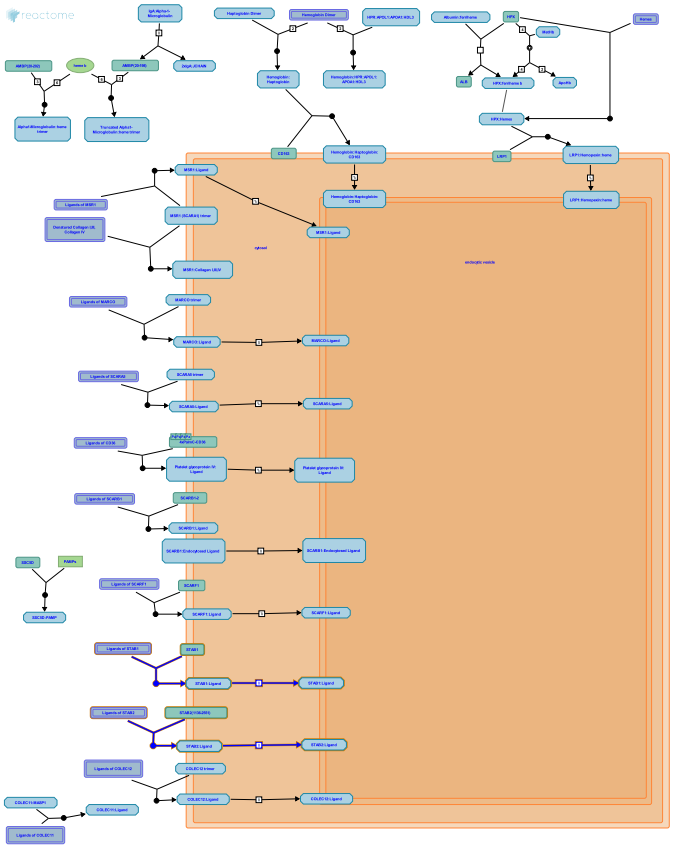
2013-03-22	Authored, Reviewed	Neyen, C.

Scavenging by Class H Receptors ↗

Location: Binding and Uptake of Ligands by Scavenger Receptors

Stable identifier: R-HSA-3000497

Compartments: plasma membrane, extracellular region, endocytic vesicle membrane



STAB1 (FEEL-1) and STAB2 (FEEL-2) are very large transmambrane proteins containing fasciclin domains, EGF-like domains, and hyaluronan-like domains (Politz et al. 2002, reviewed in Areschoug and Gordon 2009).

Literature references

Longati, P., Kannicht, C., Johansson, S., Guillot, P., Politz, O., Svineng, G. et al. (2002). Stabilin-1 and -2 constitute a novel family of fasciclin-like hyaluronan receptor homologues. *Biochem. J., 362*, 155-64. ↗

Gordon, S., Areschoug, T. (2009). Scavenger receptors: role in innate immunity and microbial pathogenesis. *Cell. Microbiol., 11*, 1160-9. ↗

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