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Functions of OSBP/ORP Family Proteins and Their Relation to Dyslipidemia

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1. Introduction

The pathway of intracellular cholesterol synthesis, uptake and efflux is much affected by both the positive and the negative feedbacks from direct interaction between cholesterol and its oxygenated derivatives (oxysterols) as well as the regulatory factors such as the sterol-regulatory-element-binding protein (SREBP)– cleavage-activating protein–Insig complex (Radhakrishnan, Ikeda et al. 2007), 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase (Sever, Song et al. 2003) and liver X receptors (LXRs) (Chen, Chen et al. 2007). Since these regulatory factors are located in the compartments with comparatively low cholesterol density, they can react promptly on acute changes in local cholesterol or oxysterol density. While much is known about the interaction between these regulatory factors and cholesterol, only little has been studied about the mechanism to deliver the cholesterol or oxysterol to its appropriate compartments.

Therefore, there arises a possibility that oxysterol-binding protein/oxysterol-binding protein-related protein (OSBP/ORP) family may regulate such processes by binding oxyterol and/or cholesterol and by functioning as a cholesterol sensor or cholesterol transporter. According to the study about the family members, it is now becoming clear that they affect the regulation such as the cholesterol or triglyceride level.

For comprehensive information on OSBP/ORP family, please refer to several good reviews already published (Fairn and McMaster 2008; Ngo, Colbourne et al. 2010; Raychaudhuri and Prinz 2010; Vihervaara, Jansen et al. 2011). This review focuses more on the family's association with dyslipidemia from a perspective of the individual features of the structure, the expression, the cellular localization, the molecular functions, and the epidemiologial study-based information of each member.

2. Overview of functions of OSBP/ORP family proteins and their relation to dyslipidemia

It has become widely known that each member of OSBP/ORP family respectively affects diverse processes considered to have an association with dyslipidemia, such as intracellular trafficking of cholesterol or neutral lipid. The first presented is a brief overview of the members as a whole before the individual explanation of each member.

OSBP negatively regulates ATP-binding cassette transporter A1 (ABCA1) protein stability (Bowden and Ridgway 2008). OSBP induces upregulation of SREBP-1c and enhances hepatic lipogenesis (Yan, Lehto et al. 2007).
ORP1L forms a RILP-Rab7-ORP1L complex (Johansson, Rocha et al. 2007) and is involved in both protein and lipid transport functions of the late endocytic compartments (Vihervaara, Uronen et al. 2011).
ORP1S and ORP2 enhance plasma membrane (PM)-to-lipid droplet (LD) sterol transport (Jansen, Ohsaki et al. 2011). ORP2 presents on LD and has a functional role in the regulation of neutral lipid metabolism, possibly as a factor that integrates the cellular metabolism of triglycerides (TG) with that of cholesterol (Hynynen, Suchanek et al. 2009).
ORP3 may play an important role in efficient directed membrane trafficking (Lehto, Mayranpaa et al. 2008). But the direct evidence that ORP3 functions to regulate dyslipidemia is yet to be reported.
ORP4 in an interaction with intermediate filaments inhibits an intracellular cholesterol-transport pathway mediated by vimentin (Wang, JeBailey et al. 2002).
ORP5 may cooperate with Niemann-Pick C1 (NPC1) to mediate the exit of cholesterol from endosomes/lysosomes (Du, Kumar et al. 2011).
ORP6 is identified as one of the candidate genes that are possibly involved in the regulation of high-density lipoprotein (HDL) cholesterol levels (North, Martin et al. 2003).
SNPs near ORP7 gene show a genome-wide significant association with low-density lipoprotein (LDL) cholesterol (Teslovich, Musunuru et al. 2010).
ORP8 negatively regulates ABCA1 expression and macrophage cholesterol efflux (Yan, Mayranpaa et al. 2008). ORP8 has the capacity to modulate lipid homeostasis and SREBP activity, probably through an indirect mechanism required Nup62 (Zhou, Li et al. 2011). The OSBPL8-ZDHHC17 region (chr12) is detected for HDL cholesterol identified by one new SNP with genome-wide significance (Ma, Yang et al. 2010).
ORP9 and ORP11 are dimerized and may act as an intracellular lipid sensor or transporter (Zhou, Li et al. 2010).
ORP10 suppresses hepatic lipogenesis and very-low-density lipoprotein production (Perttila, Merikanto et al. 2009). ORP10 is genetically associated with both TG (Perttila, Merikanto et al. 2009) and LDL cholesterol level (Koriyama, Nakagami et al. 2010).
SNPs in the ORP11 gene is associated with LDL cholesterol levels, hyperglycemia /diabetes as well as with metabolic syndrome per se (Bouchard, Faucher et al. 2009).

2.1 Phylogenetic distribution and molecular structure of OSBP/ORP family

As a result of differential promoter usage and splicing, there are 16 major OSBP/ORP family members. The human ORP family is divided into six subfamilies based on the gene structure and amino acid sequence homology (Fig. 1). Some of the proteins, for example ORP1 and ORP4, have both short (S) and long (L) variants.
A feature in common for all ORPs is a conserved C-terminal OSBP-related domain (ORD), which contains the highly conserved "OSBP-fingerprint (OF)" sequence EQVSHHPP (Fig. 1). Most of the human ORPs belong to the long subtype have a pleckstrin homology domain (PH domain), which bind phosphoinositides (PIPs). This interaction controls the subcellular localization of the proteins. 12 out of the 16 major mammalian OSBP/ORP family members contain a FFAT motif, which is a short sequence that binds VAMP associated proteins (VAPs), integral membrane proteins of the ER. Instead of an ER targeting FFAT motif, ORP5 and ORP8 contain a putative C-terminal transmembrane segment, which anchors these

proteins in the ER. The human ORP1L have at their N-terminus ankyrin repeats, which interacts with the active GTP-bound form of Rab7 on late endosomes, and thus mediates targeting of the protein to late endosomes.

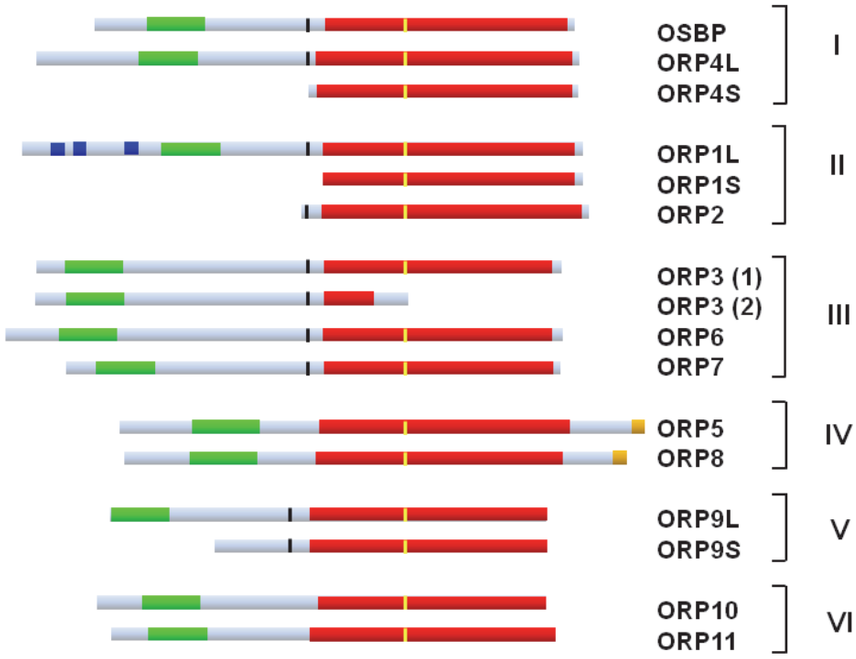

Fig. 1. Domain organization of the humam OSBP/ORP family.

Human OSBP/ORP family members are arranged into subfamilies I-VI. The color codes are: red, OSBP-related domain (ORD); yellow, OSBP-fingerprint (OF) motif; green, pleckstrin homology (PH) domain; Blue, ankirin repeats; black, VAP targeting motif (FFAT motif); Orange, transmembrane domain. L and S in the protein names indicate long and short variants, respectively.

2.2 OSBP

Structure, Tissue distribution and Intracellular localization: OSBP belongs to the subfamily I of OSBP/ORP homologues. OSBP has an ORD, a PH domain and an FFAT motif. OSBP shares the highest degree of similarity with ORP4 and dimerizes with ORP4. In the transfected cells, some of the OSBP was distributed diffusely in the cytoplasm, and some was bound to small vesicles near the nucleus. Upon addition of 25-hydroxycholesterol, most of the OSBP became concentrated in the Golgi apparatus (Ridgway, Dawson et al. 1992).

Molecular functions related to dyslipidemia: OSBP is the founding member of the OSBP/ORP family. Human OSBP was cloned in 1990 (Levanon, Hsieh et al. 1990) and was studied intensively (Ridgway, Dawson et al. 1992; Lagace, Byers et al. 1997; Ridgway, Badiani et al. 1998; Ridgway, Lagace et al. 1998; Storey, Byers et al. 1998; Lagace, Byers et al. 1999; Mohammadi, Perry et al. 2001; Levine and Munro 2002).

Yan et al. reported that adenovirus-mediated hepatic overexpression of OSBP induced a marked increase of VLDL TG. Also, the liver tissue TG were elevated in the AdOSBP-injected mice, and their TG secretion rate was increased by 70%. The messenger RNAs for enzymes of fatty acid synthesis and their transcriptional regulator, SREBP-1c, as well as the

Insig-1 mRNA, were upregulated two-fold in the OSBP expressing livers. Silencing of OSBP in hepatocytes suppressed the induction of SREBP1-c by insulin and resulted in a reduction of TG synthesis. These results demonstrate that OSBP regulates hepatic TG metabolism and suggest the involvement of OSBP in the insulin signaling pathways that control hepatic lipogenesis (Yan, Lehto et al. 2007).

Bowden et al. revealed that suppression of OSBP in Chinese hamster ovary cells by RNA interference resulted in increased ABCA1 protein expression and cholesterol efflux activity following induction with oxysterols or the synthetic LXR agonist TO901317. OSBP knockdown in J774 macrophages also increased ABCA1 expression in the presence and absence of LXR agonists. Their results demonstrate that OSBP opposes the activity of LXR by negatively regulating ABCA1 activity in the cytoplasm by sterol-binding domain-dependent protein destabilization (Bowden and Ridgway 2008).

Cephalostatin 1, OSW-1, ritterazine B and schweinfurthin A are natural products that potently, and in some cases selectively, inhibit the growth of cultured human cancer cell lines. Recently, Burgett et al. have discovered that these molecules target OSBP and its closest paralog, ORP4L, and have named these natural products ORPphilins (Burgett, Poulsen et al. 2011). By uncovering the cellular targets of the ORPphilins, they have revealed that OSBP and ORP4L are involved in cancer cell survival.

They also show that ORPphilins perturb the cellular localization of OSBP and affect sphingomyelin biosynthesis. The ORPphilins are powerful probes of OSBP and ORP4L that will be useful in uncovering their cellular functions and their roles in human diseases.

Epidemiological study: Epidemiological study of OSBP is not reported yet.

2.3 OSBPL1B (ORP1L)

Structure, Tissue distribution and Intracellular localization: ORP1L belongs to the subfamily II of OSBP/ORP homologues. ORP1L has an ORD, an FFAT motif, a PH domain and three ankyrin repeats.

While macrophages, brain, and lung are the areas where ORP1L is expressed most predominantly, it is also found in colon, kidney, and liver (Johansson, Bocher et al. 2003). ORP1L localizes to late endosomes.

Molecular functions related to dyslipidemia: Johansson et al. reported that ORP1L binds to Rab7, modifies its functional cycle, and can interfere with LE/lysosome organization and endocytic membrane trafficking (Johansson, Lehto et al. 2005).

They show that the GTPase Rab7, when bound to GTP, simultaneously binds to ORP1L and RILP to form a RILP-Rab7-ORP1L complex, which is required for the perinuclear localization of late endosomes/lysosomes (Johansson, Rocha et al. 2007). The later study of Rocha et al., went deeper in examining these processes more in detail. They found that the cholesterol levels in late endosomes are sensed by ORP1L and are lower in peripheral vesicles. Under low cholesterol conditions, ORP1L conformation induces the formation of endoplasmic reticulum (ER)- late endosome membrane contact sites. At these sites, the ER protein VAP (VAMP [vesicle-associated membrane protein]-associated ER protein) can interact in trans with the Rab7-RILP complex to remove p150 (Glued) and associated motors. late endosomes then move to the microtubule plus end. Under high cholesterol conditions, as in Niemann-Pick type C disease, this process is prevented, and late endosomes accumulate at the microtubule minus end as the result of dynein motor activity. These data explain how the ER and cholesterol control the association of late endosomes with motor proteins and their positioning in cells (Rocha, Kuijl et al. 2009).

Recently, Vihervaara et al. have shown that ORP1L silencing in macrophage foam cells inhibits the efflux of lipoprotein-derived endocytosed cholesterol to apolipoprotein A-I, providing evidence for the involvement of ORP1L in both protein and lipid transport functions of the late endocytic compartments (Vihervaara, Uronen et al. 2011).
The multivesicular body(MVB) sorting pathway is known to be involved in many processes, including growth factor receptor down-regulation, exosome secretion, antigen presentation, the budding of enveloped viruses, and cytokinesis. Recently, Kobuna et al. have shown that knockdown of ORP1L induces the formation of enlarged MVBs in HeLa cells. They suggest that the proper cholesterol level of late endosomes/lysosomes generated by ORPs is required for normal MVB formation and MVB–mediated membrane protein degradation (Kobuna, Inoue et al. 2010).
Epidemiological study: Epidemiological study of ORP1L is not reported yet.

2.4 OSBPL1A (ORP1S) and OSBPL2 (ORP2)

Structure, Tissue distribution and Intracellular localization: ORP1S and ORP2 belong to the subfamily II of OSBP/ORP homologues. ORP1S and ORP2 have an ORD and an FFAT motif but lack PH domain.
ORP1S is expressed predominantly in skeletal muscle and heart (Johansson, Bocher et al. 2003). ORP2 is expressed ubiquitously in mammalian tissues. Highest mRNA levels of ORP2 are present in specific parts of the central nervous system (cerebellum, pituitary gland, pons, and putamen) as well as in leukocytes, placenta, and pancreas (Laitinen, Lehto et al. 2002).
ORP1S has been reported to be largely cytosolic (Johansson, Bocher et al. 2003) and ORP2 localizes, in addition to a cytosolic fraction, on the surface of lipid droplets (LDs) and also the plasma membrane (PM) (Hynynen, Suchanek et al. 2009).
Molecular functions related to dyslipidemia: In the earlier study of Hynynen et al., overexpression of ORP2 induces enhancement of [14C]cholesterol efflux to all extracellular acceptors, which results in a reduction of cellular free cholesterol. They also show that ORP2 binds PtdIns(3,4,5)P(3) and enhances endocytosis.
In their recent study, Hynynen et al. discover that ORP2 localizes not only cytosolic fraction but also on cytoplasmic LDs and reveal its function in neutral lipid metabolism. They show that the ORP2 LD association depends on sterol binding: Treatment with 5 mM 22(R)OHC inhibits the LD association, while a mutant defective in sterol binding is constitutively LD bound. Silencing of ORP2 using RNA interference slows down cellular TG hydrolysis. Furthermore, ORP2 silencing increases the amount of [14C]cholesteryl esters but only under conditions in which lipogenesis and LD formation are enhanced by treatment with oleic acid (Hynynen, Suchanek et al. 2009). These results identify ORP2 as a sterol receptor present on LD and provide an evidence for its role in the regulation of neutral lipid metabolism, possibly as a factor that integrates the cellular metabolism of TG with that of cholesterol.
By overexpressing all mammalian ORPs, Jansen et al. found that especially ORP1S and ORP2 enhanced PM-to-LD sterol transport. This reflected the stimulation of transport from the PM to the ER, rather than from the ER to LDs. Double knockdown of ORP1S and ORP2 inhibited sterol transport from the PM to the ER and LDs, suggesting a physiological role for these ORPs in the process (Jansen, Ohsaki et al. 2011). These findings suggest that ORP1S and ORP2 are essential in controlling cellular neutral lipid and cholesterol and has a strong association with the pathophysiology of dyslipidemia.
Epidemiological study: Epidemiological studies of ORP1S or ORP2 are not reported yet.

2.5 OSBPL3 (ORP3)

Structure, Tissue distribution and Intracellular localization: ORP3 belongs to the subfamily III of OSBP/ORP homologues. ORP3 has an ORD, a PH domain and an FFAT motif. A total of eight isoforms of ORP3 were demonstrated with alternative splicing (Collier, Gregorio-King et al. 2003). In human tissues there was specific isoform distribution, with most tissues expressing varied levels of isoforms with the complete ORD; while only whole brain, kidney, spleen, thymus, and thyroid expressed high levels of the isoforms associated with the truncated ORD. The expression in cerebellum, heart, and liver of most isoforms was negligible. Lehto et al described that ORP3 was expressed at high levels in kidney tubule epithelia and in the human embryonic kidney cell line HEK293 (Lehto, Mayranpaa et al. 2008).

They also described that the endogenous ORP3 protein in HEK293 cells localized at the ER and the PM, especially thin filopodial cell-surface projections.

Molecular functions related to dyslipidemia: The direct evidence that ORP3 functions to regulate Dyslipidemia is yet to be reported.

ORP3 interacts with R-Ras, a small GTPase regulating cell adhesion, spreading and migration (Lehto, Mayranpaa et al. 2008). Gene silencing of ORP3 and overexpression of ORP3 in HEK293 cells or primary macrophages demonstrate the function of ORP3 as part of the machinery that controls the actin cytoskeleton, cell polarity and cell adhesion. These functional evidences, together with the abundant expression of ORP3 in polarized cell types, suggest that ORP3 may play an important role in efficient directed membrane trafficking.

Epidemiological study: Epidemiological study of ORP3 is not reported yet.

2.6 OSBPL4 (ORP4, OSBP2, HLM)

Structure, Tissue distribution and Intracellular localization: ORP4 belongs to the subfamily I of OSBP/ORP homologues. ORP4 has an ORD, a PH domain and an FFAT motif. ORP4 shares the highest degree of similarity with OSBP and dimerizes with OSBP.

Two ORP4 cDNAs were identified: a full-length ORP4 containing a PH domain and an ORD (designated ORP4-L), and a splice variant in which the PH domain and part of the ORD were deleted (designated ORP4-S). ORP4 mRNA and protein expression overlapped partially with OSBP and were restricted to brain, heart, muscle and kidney(Wang, JeBailey et al. 2002).

Immunofluorescence localization in stably transfected Chinese hamster ovary cells showed that ORP4-S co-localized with vimentin and caused the intermediate filament network to bundle or aggregate. ORP4-L displayed a diffuse staining pattern that did not overlap with vimentin except when the microtubule network was disrupted with nocodazole.

Molecular functions related to dyslipidemia: Cells overexpressing ORP4S had a 40% reduction in the esterification of low-density-lipoprotein-derived cholesterol, demonstrating that ORP4 in an interaction with intermediate filaments inhibits an intracellular cholesterol-transport pathway mediated by vimentin (Wang, JeBailey et al. 2002).

ORP4L bound [3H]25-hydroxycholesterol with high affinity and specificity. However, sterol-binding or a mutation that ablated sterol-binding did not influence the interaction of GST-ORP4 with vimentin (Wyles, Perry et al. 2007). Thus the precise mechanism about what ORP4L senses to regulate intracellular cholesterol-transport pathway still remains unidentified.

Epidemiological study: Epidemiological study of ORP4 is not reported yet.

2.7 OSBPL5 (ORP5)

Structure, Tissue distribution and Intracellular localization: ORP5 belongs to the subfamily IV of OSBP/ORP homologues. ORP5 has an ORD, a PH domain and a transmembrane domain. ORP5 localizes to the ER.

Molecular functions related to dyslipidemia: Knocking down ORP5 causes cholesterol accumulation in late endosomes and lysosomes, which is reminiscent of the cholesterol trafficking defect in Niemann Pick C (NPC) fibroblasts (Du, Kumar et al. 2011). Cholesterol appears to accumulate in the limiting membranes of endosomal compartments in ORP5-depleted cells, whereas depletion of NPC1 or both ORP5 and NPC1 results in luminal accumulation of cholesterol. Moreover, trans-Golgi resident proteins mislocalize to endosomal compartments upon ORP5 depletion, which depends on a functional NPC1.

Niemann-Pick type C (NPC) disease is most often caused by mutations in the NPC1 gene, whose protein product is believed to facilitate the egress of cholesterol and other lipids from late endosomes and lysosomes to other cellular compartments (Boadu and Francis 2006).

The results of the research by Du et al. establish the first link between NPC1 and a cytoplasmic sterol carrier, and suggest that ORP5 may cooperate with NPC1 to mediate the exit of cholesterol from endosomes/lysosomes.

Epidemiological study: Epidemiological study of ORP5 is not reported yet.

2.8 OSBPL6 (ORP6)

Structure, Tissue distribution and Intracellular localization: ORP6 belongs to the subfamily III of OSBP/ORP homologues. ORP6 has an ORD, a PH domain and an FFAT motif. ORP6 shows the highest expression in brain and skeletal muscle (Lehto, Tienari et al. 2004). Endogenous ORP6 associated predominantly with the nuclear envelope. When expressed from the cDNA in cultured cells, ORP6 was distributed between the cytosol and ER membranes, with a minor portion found at the PM.

Molecular functions related to dyslipidemia: The direct evidence that ORP6 functions to regulate Dyslipidemia is yet to be reported.

Epidemiological study: Using the Framingham Heart Study data set, a quantitative trait locus in the chromosome 2q was found to be significantly involved in variations of HDL cholesterol levels. ORP6 is identified as one of the candidate genes that are possibly involved in the regulation of HDL cholesterol levels in this region (North, Martin et al. 2003).

2.9 OSBPL7 (ORP7)

Structure, Tissue distribution and Intracellular localization: ORP7 belongs to the subfamily III of OSBP/ORP homologues. ORP7 has an ORD, a PH domain and a an FFAT motif. ORP7 shows the highest expression in the gastrointestinal tract (Lehto, Tienari et al. 2004). When expressed from the cDNA in cultured cells, ORP7 was distributed between the cytosol and ER membranes, with a minor portion found at the PM. The N-terminal portion of the proteins, containing a PH domain, has markedly strong PM targeting specificity, while the C-terminal half remains largely cytosolic. The dual targeting of the proteins indicates a putative role in communication between the ER and the PM.

Molecular functions related to dyslipidemia: Recently, Zhong et al. identified by yeast two-hybrid screening an interaction partner of ORP7, GATE-16, which (i) regulates the function and stability of Golgi SNARE of 28kDa (GS28), and (ii) plays a role in autophagosome biogenesis (Zhong, Zhou et al. 2011).

GATE-16 is a ubiquitin-like low molecular weight peripheral membrane protein which was initially reported to localize at the Golgi complex and to regulate docking/fusing reactions in intra-Golgi traffic and Golgi assembly from mitotic fragments via interactions with NSF and the Golgi v-SNARE GS28 (Sagiv, Legesse-Miller et al. 2000). GS28 was identified as a SNARE protein, the majority of which is associated with the cis-Golgi, and is implicated in both ER-Golgi and intra-Golgi transport (Subramaniam, Peter et al. 1996). In the presence of NSF, SNAP and ATP, GATE-16 interacts with GS28, apparently maintaining GS28 in a transport competent form and protecting it from proteolysis.

Zhong et al. revealed that ORP7 knockdown in 293A cells resulted in a 40% increase of GS28 protein while ORP7 overexpression had the opposite effect. Similar to ORP7 overexpression, treatment of cells with 25-hydroxycholesterol (25-OH) resulted in GS28 destabilization, which was potentiated by excess ORP7 and inhibited by ORP7 silencing. Their results suggest that ORP7 negatively regulates GS28 protein stability via sequestration of GATE-16, and may mediate the effect of 25-OH on GS28 and Golgi function.

Epidemiological study: It is reported that SNPs near ORP7 gene show genome-wide significant association with LDL cholesterol (Teslovich, Musunuru et al. 2010).

2.10 OSBPL8 (ORP8)

Structure, Tissue distribution and Intracellular localization: ORP8 belongs to the subfamily IV of OSBP/ORP homologues. ORP8 has an ORD, a PH domain and a transmembrane domain. ORP8 is expressed at the highest levels in macrophages, liver, spleen, kidney, and brain (Yan, Mayranpaa et al. 2008). ORP8 is localized in the ER via its C-terminal transmembrane domain.

Molecular functions related to dyslipidemia: It is reported that silencing of ORP8 by RNA interference in THP-1 macrophages increased the expression of ABCA1 and concomitantly cholesterol efflux to lipid-free apolipoprotein A-I. Experiments employing an ABCA1 promoter-luciferase reporter confirmed that ORP8 silencing enhances ABCA1 transcription. These data identify ORP8 as a negative regulator of ABCA1 expression and macrophage cholesterol efflux. But the precise mechanism to regulate the expression of ABCA1 has not been revealed.

Recently, Zhou et al. investigated the action of ORP8 in hepatic cells in vivo and in vitro. They found that adenoviral overexpression of ORP8 in mouse liver induced a decrease of cholesterol, phospholipids, and triglycerides in serum (-34%, -26%, -37%, respectively) and liver tissue (-40%, -12%, -24%), coinciding with reduction of nuclear (n)SREBP-1 and -2 and mRNA levels of their target genes. Consistently, excess ORP8 reduced nSREBPs in HuH7 cells, and ORP8 overexpression or silencing by RNA interference moderately suppressed or induced the expression of SREBP-1 and SREBP-2 target genes, respectively. In accordance, cholesterol biosynthesis was reduced by ORP8 overexpression and enhanced by ORP8 silencing in [(3)H]acetate pulse-labeling experiments.

They also performed yeast two-hybrid, bimolecular fluorescence complementation (BiFC), and co-immunoprecipitation analyses, and revealed the nuclear pore component Nup62 as an interaction partner of ORP8. They showed that the impact of overexpressed ORP8 on nSREBPs and their target mRNAs was inhibited in cells depleted of Nup62.

These results reveal that ORP8 has the capacity to modulate lipid homeostasis and SREBP activity, probably through an indirect mechanism required Nup62.

Epidemiological study: Ma et al. performed a genome-wide association analysis of total cholesterol and HDL cholesterol levels using the Framingham heart study data. In that study, single-locus effects and pairwise epistasis effects of 432,096 SNP markers were tested for their significance on log-transformed total cholesterol and HDL cholesterol levels.
As a result, the OSBPL8-ZDHHC17 region (chr12) was detected for HDL cholesterol identified by one new SNP with genome-wide significance (Ma, Yang et al. 2010).

2.11 OSBPL9 (ORP9)

Structure, Tissue distribution and Intracellular localization: ORP9 belongs to the subfamily V of OSBP/ORP homologues. ORP9 has an ORD, a PH domain and an FFAT motif. VAP binding FFAT motif and PH domains target ORP9 to the ER and a Golgi-COPII compartment, respectively (Wyles and Ridgway 2004).
Molecular functions related to dyslipidemia: Ngo et al. demonstrate that ORP9L partitioning between the trans-Golgi/trans-Golgi network (TGN), and the ER is mediated by a phosphatidylinositol 4-phosphate (PI-4P)-specific PH domain and VAP, respectively (Ngo and Ridgway 2009). In vitro, ORP9L mediates PI-4P-dependent cholesterol transport between liposomes, suggesting that its primary function in vivo is sterol transfer between the Golgi and ER. Depletion of ORP9L by RNAi caused Golgi fragmentation, inhibition of vesicular somatitus virus glycoprotein transport from the ER and accumulation of cholesterol in endosomes/lysosomes. These findings indicate that ORP9 maintains the integrity of the early secretory pathway by mediating transport of sterols between the ER and trans-Golgi/TGN.
It is also reported that ORP9, in interaction with ORP11, may act as an intracellular lipid sensor or transporter (Zhou, Li et al. 2010). (see also ORP11.)
Epidemiological study: Epidemiological study of ORP9 is not reported yet.

2.12 OSBPL10 (ORP10)

Structure, Tissue distribution and Intracellular localization: ORP10 belongs to the subfamily VI of OSBP/ORP homologues. ORP10 has an ORD and a PH domain but does not have an FFAT motif or a transmembrane domain.
ORP10 was shown to associate dynamically with microtubules, being consistent with its involvement in intracellular transport or organelle positioning (Perttila, Merikanto et al. 2009).
Immunofluorescence localization in transiently transfected bovine aorta endothelial cells showed that EGFP-ORP10 co-localized with alpha-tubulin (Fig. 2 c, g) and not with actin (Fig. 2 a, e) or vimentin (Fig. 2 b, f). The microtubules co-localize with EGFP-ORP10 show the aberrant bundled structures. These structures were disrupted by treatment with nocodazol (Fig. 2 d, h).
Molecular functions related to dyslipidemia: Silencing of ORP10 increased the incorporation of [(3)H]acetate into cholesterol and both [(3)H]acetate and [(3)H]oleate into triglycerides and enhanced the accumulation of secreted apolipoprotein B100 in growth medium, suggesting that ORP10 suppresses hepatic lipogenesis and very-low-density lipoprotein production.
Epidemiological study: We examined the association between polymorphisms in the ORP10 gene and risk factors for the metabolic syndrome in the Tanno and Sobetsu Study in Japan (Koriyama, Nakagami et al. 2010).

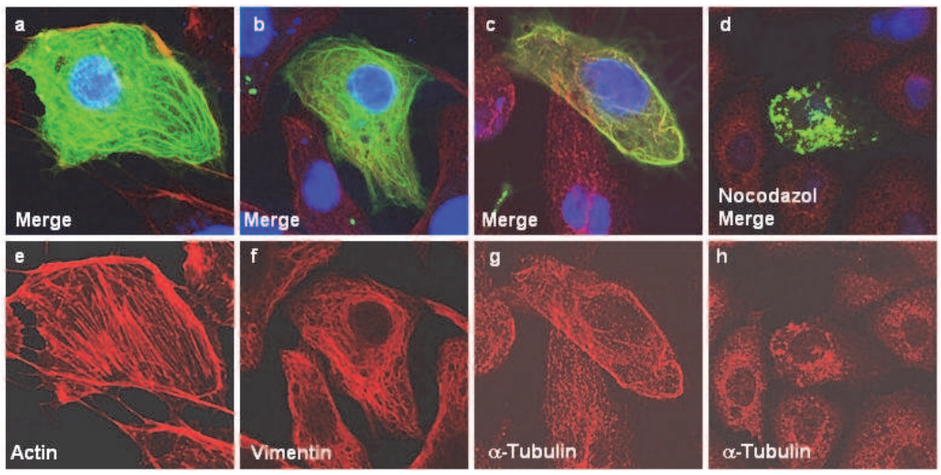

Fig. 2. Intracellular localization of ORP10.

As a result, we found that the LDL cholesterol of individuals with the rs2290532 (D254N) polymorphism was significantly greater in subjects with the CC+CT genotype than in subjects with the TT genotype (124.3+/-1.3 vs. 111.6+/-4.1 mg per 100 ml, P=0.009) (Fig. 3). Comparison of the genotype frequency in both groups indicated that the genotype associated with low risk (TT) reduced the risk of hyper-LDL cholesterolemia significantly (P=0.003), with an odds ratio of 0.35 (95% confidence interval=0.17-0.76). These findings suggest that the rs2290532 (D254N) polymorphism in OSBPL10 may predispose individuals with this SNP to hyper-LDL cholesterolemia.

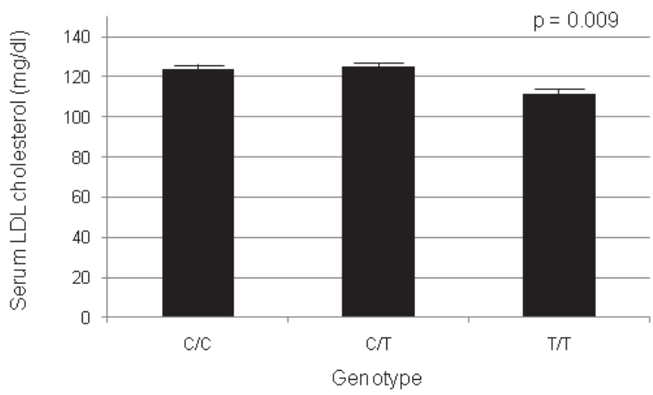

Fig. 3. Relation of rs2290532 of ORP10 with serum LDL cholesterol.

Perttila et al. also reported that the analysis of variants in ORP10 gene revealed suggestive linkage of ORP10 single-nucleotide polymorphisms (SNPs) with extreme end high TG (>90th percentile) trait. They carried out an association analysis in a metabolic syndrome subcohort (Genmets) of Health2000 examination survey (N = 2,138), revealing an association of multiple ORP10 SNPs with high serum TG levels (>95th percentile).
The result proves that ORP10 is genetically associated with both TG and LDL cholesterol levels. Though it is estimated that microtubule dependent intracellular transport of vesicles

plays an important role in that process, the mechanism to control TG and LDL cholesterol levels is yet to be explained. A further analysis is highly expected.

2.13 OSBPL11 (ORP11)

Structure, Tissue distribution and Intracellular localization: ORP11 belongs to the subfamily VI of OSBP/ORP homologues. ORP11 has an ORD and a PH domain but does not have an FFAT motif or a transmembrane domain. ORP11 is present at the highest levels in human ovary, testis, kidney, liver, stomach, brain, and adipose tissue. Immunohistochemistry demonstrates abundant ORP11 in the epithelial cells of kidney tubules, testicular tubules, caecum, and skin. ORP11 dimerizes with ORP9 and localizes at the Golgi-late endosome interface (Zhou, Li et al. 2010).

Molecular functions related to dyslipidemia: Cells overexpressing ORP11 displayed lamellar lipid bodies associated with vacuolar structures or the Golgi complex, indicating a disturbance of lipid trafficking. Similar multilamellar membranes arise in endo-lysosomal compartments in phospholipidosis occurring, for instance, upon incubation of macrophage with oxidized low-density lipoprotein, or associated with inheritable lysosomal storage disorders, situations in which normal lipid transport is disturbed. These findings indicate that ORP11, in interaction with ORP9, may act as an intracellular lipid sensor or transporter.

Epidemiological study: it is reported that ORP11 is significantly overexpressed in the visceral adipose tissue of obese men with metabolic syndrome (Bouchard, Faucher et al. 2009). Furthermore, they found SNPs in the ORP11 gene to be associated with several cardiovascular risk factors in obese individuals. IVS12+95 T>C, a newly discovered SNP of the study, was associated with LDL cholesterol levels ($OR = 1.63$; $P < 0.001$), hyperglycemia/diabetes ($OR = 1.48$; $P < 0.004$) as well as with metabolic syndrome per se ($OR = 1.56$; $P < 0.01$). These results suggest that ORP11 is involved in cholesterol and glucose metabolism in obese individuals.

3. Conclusion

Since OSBP/ORP family involves functional redundancy as well as overlap tissue expression and intracellular localization, the function of each family member has been mostly left unrevealed. Various studies including the genome-wide association study, however, have succeeded to prove the direct association between the individual members and dyslipidemia. Analyses on the individual members have also made it clear that the members affect the regulation of cholesterol and triglyceride level in interaction with diverse molecules.

Nevertheless, the precise molecular mechanism of the process still remains unascertained. The recent findings such as the identification of the small molecule which associates with OSBP are expected to act as a convenient tool to clarify the more detailed functions of OSBP/ORP family in future.

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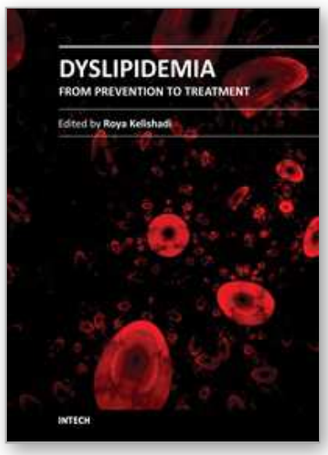

Dyslipidemia - From Prevention to Treatment
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Dyslipidemia has a complex pathophysiology consisting of various genetic, lifestyle, and environmental factors. It has many adverse health impacts, notably in the development of chronic non-communicable diseases. Significant ethnic differences exist due to the prevalence and types of lipid disorders. While elevated serum total- and LDL-cholesterol are the main concern in Western populations, in other countries hypertriglyceridemia and low HDL-cholesterol are more prevalent. The latter types of lipid disorders are considered as components of the metabolic syndrome. The escalating trend of obesity, as well as changes in lifestyle and environmental factors will make dyslipidemia a global medical and public health threat, not only for adults but for the pediatric age group as well. Several experimental and clinical studies are still being conducted regarding the underlying mechanisms and treatment of dyslipidemia. The current book is providing a general overview of dyslipidemia from diverse aspects of pathophysiology, ethnic differences, prevention, health hazards, and treatment.

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