

# World Journal of *Clinical Cases*

*World J Clin Cases* 2020 January 6; 8(1): 1-244



**REVIEW**

- 1 Role of oxysterol-binding protein-related proteins in malignant human tumours  
*Liu H, Huang S*

**ORIGINAL ARTICLE****Case Control Study**

- 11 Oncogenic role of Tc17 cells in cervical cancer development  
*Zhang ZS, Gu Y, Liu BG, Tang H, Hua Y, Wang J*

**Retrospective Study**

- 20 Acute distal common bile duct angle is risk factor for post-endoscopic retrograde cholangiopancreatography pancreatitis in beginner endoscopist  
*Han SY, Kim DU, Lee MW, Park YJ, Baek DH, Kim GH, Song GA*
- 29 Three-dimensional computed tomography mapping of posterior malleolar fractures  
*Su QH, Liu J, Zhang Y, Tan J, Yan MJ, Zhu K, Zhang J, Li C*
- 38 Application of a modified surgical position in anterior approach for total cervical artificial disc replacement  
*Hou WX, Zhang HX, Wang X, Yang HL, Luan XR*
- 46 Potential role of the compound Eucommia bone tonic granules in patients with osteoarthritis and osteonecrosis: A retrospective study  
*Hu CX, Hu KY, Wang JF*
- 54 Prognostic factors for overall survival in prostate cancer patients with different site-specific visceral metastases: A study of 1358 patients  
*Cui PF, Cong XF, Gao F, Yin JX, Niu ZR, Zhao SC, Liu ZL*
- 68 Application of multiple Roux-en-Y hepaticojejunostomy reconstruction by formation of bile hilar duct lake in the operation of hilar cholangiocarcinoma  
*Yang XJ, Dong XH, Chen SY, Wu B, He Y, Dong BL, Ma BQ, Gao P*

**Observational Study**

- 76 Relationship between  $\beta$ -amyloid protein 1-42, thyroid hormone levels and the risk of cognitive impairment after ischemic stroke  
*Mao L, Chen XH, Zhuang JH, Li P, Xu YX, Zhao YC, Ma YJ, He B, Yin Y*

**Prospective Study**

- 88 Can the wet suction technique change the efficacy of endoscopic ultrasound-guided fine-needle aspiration for diagnosing autoimmune pancreatitis type 1? A prospective single-arm study  
*Sugimoto M, Takagi T, Suzuki R, Konno N, Asama H, Sato Y, Irie H, Watanabe K, Nakamura J, Kikuchi H, Takasumi M, Hashimoto M, Kato T, Hikichi T, Notohara K, Ohira H*

**CASE REPORT**

- 97 Pembrolizumab - emerging treatment of pulmonary sarcomatoid carcinoma: A case report  
*Cimpeanu E, Ahmed J, Zafar W, DeMarinis A, Bardarov SS, Salman S, Bloomfield D*
- 103 Sclerosing angiomatoid nodular transformation of the spleen, a rare cause for splenectomy: Two case reports  
*Chikhladze S, Lederer AK, Fichtner-Feigl S, Wittel UA, Werner M, Aumann K*
- 110 Postpartum pubic symphysis diastasis-conservative and surgical treatment methods, incidence of complications: Two case reports and a review of the literature  
*Norvilaite K, Kezeviciute M, Ramasauskaite D, Arlauskiene A, Bartkeviciene D, Uvarovas V*
- 120 Use of omental patch and endoscopic closure technique as an alternative to surgery after endoscopic full thickness resection of gastric intestinal stromal tumors: A series of cases  
*Sachdev AH, Iqbal S, Ribeiro IB, de Moura DTH*
- 126 Primary maxillary chondrosarcoma: A case report  
*Cuevas-González JC, Reyes-Escalera JO, González JL, Sánchez-Romero C, Espinosa-Cristóbal LF, Reyes-López SY, Tovar Carrillo KL, Donohue Cornejo A*
- 133 Hyalinizing clear cell carcinoma-a rare entity in the oral cavity: A case report  
*Donohue-Cornejo A, Paes de Almeida O, Sánchez-Romero C, Espinosa-Cristóbal LF, Reyes-López SY, Cuevas-González JC*
- 140 Jejunal cavernous lymphangioma manifested as gastrointestinal bleeding with hypogammaglobulinemia in adult: A case report and literature review  
*Tan B, Zhang SY, Wang YN, Li Y, Shi XH, Qian JM*
- 149 Large pelvic mass arising from the cervical stump: A case report  
*Zhang K, Jiang JH, Hu JL, Liu YL, Zhang XH, Wang YM, Xue FX*
- 157 Mechanical intestinal obstruction due to isolated diffuse venous malformations in the gastrointestinal tract: A case report and review of literature  
*Li HB, Lv JF, Lu N, Lv ZS*
- 168 Two-level percutaneous endoscopic lumbar discectomy for highly migrated upper lumbar disc herniation: A case report  
*Wu XB, Li ZH, Yang YF, Gu X*

- 175 Successful treatment of congenital palate perforation: A case report  
*Zhang JF, Zhang WB*
- 179 Calcitonin-negative neuroendocrine tumor of the thyroid with metastasis to liver-rare presentation of an unusual tumor: A case report and review of literature  
*Cai HJ, Wang H, Cao N, Huang B, Kong FL, Lu LR, Huang YY, Wang W*
- 188 Giant exophytic cystic adenomyosis with a levonorgestrel containing intrauterine device out of the uterine cavity after uterine myomectomy: A case report  
*Zhou Y, Chen ZY, Zhang XM*
- 194 Unusual presentation of bladder neuroblastoma in a child: A case report  
*Cai JB, Wang JH, He M, Wang FL, Xiong JN, Mao JQ, Li MJ, Zhu K, Liang JW*
- 200 Value of dynamic plasma cell-free DNA monitoring in septic shock syndrome: A case report  
*Liu JP, Zhang SC, Pan SY*
- 208 Sarcomatoid intrahepatic cholangiocarcinoma mimicking liver abscess: A case report  
*Wang Y, Ming JL, Ren XY, Qiu L, Zhou LJ, Yang SD, Fang XM*
- 217 Clinical characteristics on manifestation and gene mutation of a transient neonatal cyanosis: A case report  
*Yuan J, Zhu XP*
- 222 Six families with balanced chromosome translocation associated with reproductive risks in Hainan Province: Case reports and review of the literature  
*Chen YC, Huang XN, Kong CY, Hu JD*
- 234 Primary intestinal extranodal natural killer/T-cell lymphoma, nasal type: A case report  
*Dong BL, Dong XH, Zhao HQ, Gao P, Yang XJ*

**LETTER TO THE EDITOR**

- 242 Cluster headache as a manifestation of a stroke-like episode in a carrier of the *MT-ND3* variant m.10158T>C  
*Finsterer J*

**ABOUT COVER**

Editorial Board Member of *World Journal of Clinical Cases*, Maddalena Zippi, MD, PhD, Doctor, Unit of Gastroenterology and Digestive Endoscopy, Sandro Pertini Hospital, Rome 00157, Italy

**AIMS AND SCOPE**

The primary aim of *World Journal of Clinical Cases (WJCC, World J Clin Cases)* is to provide scholars and readers from various fields of clinical medicine with a platform to publish high-quality clinical research articles and communicate their research findings online.

*WJCC* mainly publishes articles reporting research results and findings obtained in the field of clinical medicine and covering a wide range of topics, including case control studies, retrospective cohort studies, retrospective studies, clinical trials studies, observational studies, prospective studies, randomized controlled trials, randomized clinical trials, systematic reviews, meta-analysis, and case reports.

**INDEXING/ABSTRACTING**

The *WJCC* is now indexed in PubMed, PubMed Central, Science Citation Index Expanded (also known as SciSearch®), and Journal Citation Reports/Science Edition. The 2019 Edition of Journal Citation Reports cites the 2018 impact factor for *WJCC* as 1.153 (5-year impact factor: N/A), ranking *WJCC* as 99 among 160 journals in Medicine, General and Internal (quartile in category Q3).

**RESPONSIBLE EDITORS FOR THIS ISSUE**

Responsible Electronic Editor: *Yan-Xia Xing*

Proofing Production Department Director: *Yun-Xiaojuan Wu*

**NAME OF JOURNAL**

*World Journal of Clinical Cases*

**ISSN**

ISSN 2307-8960 (online)

**LAUNCH DATE**

April 16, 2013

**FREQUENCY**

Semimonthly

**EDITORS-IN-CHIEF**

Dennis A Bloomfield, Bao-Gan Peng, Sandro Vento

**EDITORIAL BOARD MEMBERS**

<https://www.wjnet.com/2307-8960/editorialboard.htm>

**EDITORIAL OFFICE**

Jin-Lei Wang, Director

**PUBLICATION DATE**

January 6, 2020

**COPYRIGHT**

© 2020 Baishideng Publishing Group Inc

**INSTRUCTIONS TO AUTHORS**

<https://www.wjnet.com/bpg/gerinfo/204>

**GUIDELINES FOR ETHICS DOCUMENTS**

<https://www.wjnet.com/bpg/GerInfo/287>

**GUIDELINES FOR NON-NATIVE SPEAKERS OF ENGLISH**

<https://www.wjnet.com/bpg/gerinfo/240>

**PUBLICATION MISCONDUCT**

<https://www.wjnet.com/bpg/gerinfo/208>

**ARTICLE PROCESSING CHARGE**

<https://www.wjnet.com/bpg/gerinfo/242>

**STEPS FOR SUBMITTING MANUSCRIPTS**

<https://www.wjnet.com/bpg/GerInfo/239>

**ONLINE SUBMISSION**

<https://www.f6publishing.com>

## Role of oxysterol-binding protein-related proteins in malignant human tumours

Hao Liu, Shuai Huang

**ORCID number:** Hao Liu (0000-0002-7598-7511); Shuai Huang (0000-0002-5724-2321).

**Author contributions:** Liu H and Huang S contributed to the design and writing of the review; all the authors read and approved the final manuscript.

**Conflict-of-interest statement:** There is no conflict of interest.

**Open-Access:** This article is an open-access article that was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially and license their derivative works on different terms provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

**Manuscript source:** Unsolicited Manuscript

**Received:** October 7, 2019

**Peer-review started:** October 7, 2019

**First decision:** November 9, 2019

**Revised:** December 5, 2019

**Accepted:** December 13, 2019

**Article in press:** December 13, 2019

**Published online:** January 6, 2020

**P-Reviewer:** Morales-González JA, Slomiany BL

**S-Editor:** Wang YQ

**L-Editor:** Wang TQ

**Hao Liu, Shuai Huang,** Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital of Zhengzhou University, Zhengzhou 450052, Henan Province, China

**Corresponding author:** Shuai Huang, PhD, Doctor, Department of Hepatobiliary and Pancreatic Surgery, The First Affiliated Hospital of Zhengzhou University, 1 Jianshe East Road, Erqi District, Zhengzhou 450052, Henan Province, China. [fcchuangs@zzu.edu.cn](mailto:fcchuangs@zzu.edu.cn)

### Abstract

The oxysterol-binding protein-related protein (ORP) family is a group of proteins that mediate oxysterol metabolism and bioactivity in cells. ORPs constitute a large family of lipid transfer proteins. Much of the current evidence indicates that certain members of the family of oxysterol-binding proteins (OSBPs) can lead to cancer. Many studies have revealed the putative roles of OSBPs in various cancer types. However, the exact effects and mechanisms of action of members of the OSBP/ORP family in cancer initiation and progression are currently unclear. This review focuses on ORP family members that can accelerate human tumour cell proliferation, migration, and invasion. The mechanisms and functions of various ORPs are introduced in detail. We also attempt to identify the roles of these proteins in malignant tumours with the ultimate aim of determining the exact role of the OSBP/ORP family in human tumour cells.

**Key words:** Oxysterol-binding protein family; Oxysterol-binding protein-related protein; Malignant tumour; Role; Human tumour; Tumour proliferation, migration, and invasion

©The Author(s) 2020. Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** This review focuses on the oxysterol binding protein-related protein (ORP) family, which has the capacity to accelerate human tumour cell proliferation, migration, and invasion. The mechanisms and functions of various ORP proteins are introduced in detail. We also question the roles exerted by these proteins in malignant tumours. We hope that one day, we can finally determine the exact role of the oxysterol-binding protein/ORP protein family in human tumour cells. We believe that one day, the ORP family will definitely serve as a potential and clinically significant therapeutic target in cancer patients.

**Citation:** Liu H, Huang S. Role of oxysterol-binding protein-related proteins in malignant human tumours. *World J Clin Cases* 2020; 8(1): 1-10

**URL:** <https://www.wjnet.com/2307-8960/full/v8/i1/1.htm>

E-Editor: Xing YX

DOI: <https://dx.doi.org/10.12998/wjcc.v8.i1.1>

## INTRODUCTION

Oxysterols are oxygenated derivatives of cholesterol molecules that are formed in our human body or ingested *via* the diet and oxygenated forms of plant sterols, which are phytosterols. Moreover, cholesterol precursors could also be named oxysterols<sup>[1]</sup>. Under different circumstances, oxysterols exert opposite effects depending on the oxysterol concentration. For example, oxysterols are natural components found at low concentrations in the human body and can intervene in many physiological capabilities<sup>[2,3]</sup> by not only taking part in cholesterol metabolism regulation but also being involved in respective signalling pathways, membrane fluidity, and the activity of many membrane proteins<sup>[1]</sup>. Additionally, oxysterols are involved in certain human clinical pathologies and even influence the carcinogenesis and progression of malignant tumours, such as breast, prostate, colon, and bile duct cancers<sup>[1]</sup>. However, the role of oxysterols in carcinogenesis and cancer progression needs to be further elucidated. Oxysterols exert a very sophisticated effect on miscellaneous cell lines. Various studies have noted that oxysterols can adjust inflammatory and signalling pathways or exert pro-cancerous and pro-proliferative activities through oxysterol-binding proteins (OSBPs)<sup>[1]</sup>.

The OSBP family is a group of proteins that mediate oxysterol metabolism and bioactivity in cells. In human malignant tumour cells, 12 genes can encode members of the OSBP-related protein (ORP) family and produce 15 proteins through alternative splicing and transcription<sup>[1]</sup>. The ORP family consists of at least 12 members characterized by a conserved domain that might bind oxysterols, cholesterol, or phospholipids and strongly affects lipid metabolism, cellular signal transduction, or vesicle transport in response to binding to the corresponding ligand<sup>[1,4]</sup>. OSBPs and ORPs form a very large number of lipid transfer proteins. The ORP family participates in the regulation of metabolism and the trafficking of cholesterol and lipid molecules, particularly in the endoplasmic reticulum (ER) and Golgi apparatus<sup>[4]</sup>. These proteins also affect other cellular processes, such as vesicular trafficking, by acting as scaffolds in cell signalling pathways and being involved in cell cytoskeleton formation and cell adhesion<sup>[4]</sup>. It is believed that OSBPs are associated with cell proliferation, cell migration, and carcinogenesis. In human cancer cells, ORPs are differentially expressed at the mRNA or protein level, which suggests that they play a role in tumorigenesis and progression<sup>[1,4]</sup>. Many studies have revealed the putative role of OSBPs in various cancer types<sup>[1]</sup>. ORPs have the capacity to accelerate human tumour cell proliferation, migration, and invasion. Oncogenic signalling can reprogram metabolic pathways, and this mechanism has been proposed as a hallmark of cancer cells and could offer attractive targets for anticancer strategies. Many studies have revealed the putative role of OSBPs in various human cancer types<sup>[5-7]</sup>. The present review focuses on the biological role of ORP family members, particularly in malignant human tumours (Table 1).

Substantial lines of evidence indicate that certain members of the OSBP/ORP family can result in cancer development. However, the exact mechanism that OSBP/ORP family members play in cancer cell initiation and progression and their effects in these processes are currently unclear. Complete elucidation of the exact roles that OSBP and ORP family members play in human tumour cells will allow the conquering of malignant tumours and significant improvements in the overall prognosis of cancer patients. This is a grand plan; thus, the ORP family has a very high potential research value and awaits further exploration. The ORP family will definitely provide potential and important clinical therapeutic targets in cancer patients.

## ORPS AS SCAFFOLDS FOR SIGNALLING PROTEIN COMPLEXES

Eighteen years ago, it was revealed that ORPs participate in the management of cell signalling and development<sup>[8]</sup>. The *Caenorhabditis elegans* ORPs determine the functions of bone morphogenetic protein receptor-associated molecule-interacting protein in transforming growth factor- $\beta$  signalling and body length regulation. A study conducted in 2005 showed that human ORPs work as scaffolds for two protein

**Table 1** Specific types and functions of different oxysterol binding protein-related proteins and their associations with malignant human tumours

Ref.	Type of ORP (protein)	Length (kDa)	Function	Ref.
Lehto <i>et al</i> <sup>[23]</sup> , 2008	ORP3	110	Regulates cell adhesion and migration	[23,24]
Burgett <i>et al</i> <sup>[29]</sup> , 2011	ORP4	85	Increases tumour cell invasion and metastasis	[25-31]
Koga <i>et al</i> <sup>[37]</sup> , 2008	ORP5	40	Increases tumour cell invasion and metastasis	[37,39,41,42]
Lehto <i>et al</i> <sup>[54]</sup> , 2004	ORP6	115	Regulates cell adhesion and migration	[9,52-55]
Goldfinger <i>et al</i> <sup>[22]</sup> , 2007	ORP7	106	Regulates cell adhesion and migration	[22]
Zhong <i>et al</i> <sup>[57]</sup> , 2015	ORP8	45	Regulates apoptosis	[57,58]
Ngo <i>et al</i> <sup>[17]</sup> , 1998	ORP9	100	Maintains the functional integrity of the early secretory pathway	[17]
Koriyama <i>et al</i> <sup>[48]</sup> , 2010	ORP10	130	Associated with high LDL cholesterol and high serum TAG levels	[20,48,49]
Bouchard <i>et al</i> <sup>[47]</sup> , 2007	ORP11	85	High risks of cardiovascular disease	[47]

phosphatases, PP2A and HePTP, and thus regulate the activity of ERK in a sterol-specific manner<sup>[9]</sup>. Moreover, cholesterol-bound ORPs bind with active phosphatases and induce the migration of cholesterol and the dissociation of oxysterol 25-hydroxycholesterol (25-OHC) from the complex, and these effects are concomitant with the targeting of ORPs to the Golgi complex. In contrast, Romeo *et al*<sup>[10]</sup> found that the upregulation of 7-ketocholesterol (7KC) *via* ORPs regulates profilin-1, which is an actin-binding protein associated with endothelial dysfunction and atherosclerosis. This signalling transparently involves the reciprocity of the ORP-7KC complex with tyrosine kinase JAK-2, which phosphorylates Tyr394 on ORPs to induce STAT3 activation and profilin expression. Interestingly, a previous study<sup>[11]</sup> revealed that ORP9, whose phosphorylation targets contain phosphorylated protein kinase 2, is dependent on mammalian target of protein kinase C-b or rapamycin. ORP9 interacts with these kinases and negatively regulates the phosphorylation of PDK-2 in Akt/protein kinase B, which is a major regulator of cell survival, cell cycle progression, and glucose metabolism. A key implication of these findings is that ORPs can also function as scaffold-like lipid sensors in tumour cell signalling. Whether these signalling capabilities of ORPs are based on their localization at membrane contact sites is unclear, and we used OSBPs and ERK as examples and found that the above-described regulatory function of OSBPs appears to represent a behaviour mode that is independent of membrane contact sites (MCS). The location of OSBPs in the Golgi apparatus is closely related to several phenotypic effects of OSBP manipulation. When located in the Golgi complex, ORPs activate the ceramide transporter CERT in a sterol-dependent manner, and this effect enhances the non-vesicular flux of ceramide to trans-Golgi and promotes sphingomyelin synthesis. ORPs therefore act in cooperation with CERT and the PC transfer protein Nir2 to regulate the lipid composition of Golgi membranes<sup>[13]</sup>. Protein kinase D-mediated phosphorylation can negatively regulate the ORPs in the Golgi apparatus<sup>[14]</sup>. Based on a previous study<sup>[15]</sup>, it is known that ORP overexpression in a human neuroglioma cell line and human HEK293 cells inhibits the processing of amyloid precursor protein to b-amyloid, whereas the knockdown of OSBPs exerts the opposite effect. ORPs induce the sequestration of APP-Notch2 heterodimers in the Golgi complex, and this effect is reversed by the addition of the high-affinity OSBP ligand 25-OHC, which is consistent with the distribution of ORPs<sup>[16]</sup>.

## ROLE OF MAMMALIAN ORPS IN INTRACELLULAR MEMBRANE TRAFFICKING

Substantial lines of evidence indicate that ORPs can manage human intracellular membrane trafficking. In human cells, the overexpression of ORP9S could tamper ER-Golgi protein transport, and deletion of the long variant ORP9L, which is a protein localized in the ER and trans-Golgi membrane, results in fragmentation of the Golgi apparatus, inhibition of the transfer of proteins from the ER to the Golgi apparatus, and the accumulation of cholesterol in the endoplasm<sup>[17]</sup>. These results suggest that ORP9 can maintain the functional integrity of the early secretory pathway by controlling the lipid composition and organization at the ER and trans-Golgi<sup>[18]</sup>. The significant findings revealed that an excess of the PH domain can potentially interfere with the small GTPase ARF, resulting in Golgi PI4P sequestration<sup>[19]</sup>. ORP10 can control the secretion of hepatocyte apoB100-containing lipoproteins, which

localize to not only microtubules but also Golgi membranes<sup>[20]</sup>. ORP9 management is considered to reflect an imbalance in the sterol distribution in membranes associated with the early secretory mechanism<sup>[17]</sup>. However, ORP10 can function as a specific carrier in microtubule-dependent dynamics. ORP7 interacts with GATE-16, which is a small ubiquitin-like protein that functions as a chaperone for the attachment of soluble NSF with the protein receptor GS28 in the Golgi complex<sup>[21]</sup>. ORP7 hurts the ability of GATE-16 to escort GS28, which can enhance GS28 proteasomal degradation. ORP7 has a function in mediating the sterol regulation of Golgi membrane trafficking *via* this function.

---

## ORP3 IS A PHOSPHOPROTEIN THAT REGULATES CELL ADHESION

---

ORP7, a small GTPase that regulates cell adhesion and migration<sup>[22]</sup>, interacts physically with R-Ras, and ORP7 and ORP3 play a role in Ras signalling. Previous studies<sup>[23]</sup> have revealed that ORP3 can control cell adhesion and spreading on a fibronectin substratum, organization of the actin cytoskeleton,  $\beta$ 1-integrin activity, and macrophage phagocytic function, and these cellular processes are also regulated by R-Ras. Based on the latest results, we know that the interaction between ORP3 and its ER membrane anchors depends on the phosphorylation of ORP3, and the targeting of ORP3 to the plasma membrane is changed by the PH domain, which leads to the localization of some proteins at the putative ER-plasma membrane contact site. This finding reveals a functional interplay between ORP3 and protein kinase signalling cascades and suggests that this protein could mediate communication between the ER and the plasma membrane in response to specific signals; for instance, ORP3 could have a function similar to that of yeast Osh3p<sup>[24]</sup>. ORP3 is expressed abundantly in leukocytes and in several types of epithelia, and elevated expression of this protein has been detected in certain forms of leukaemia and solid tumours, which suggests that this protein might regulate cell signalling and adhesion in a manner that facilitates malignant growth (Figure 1).

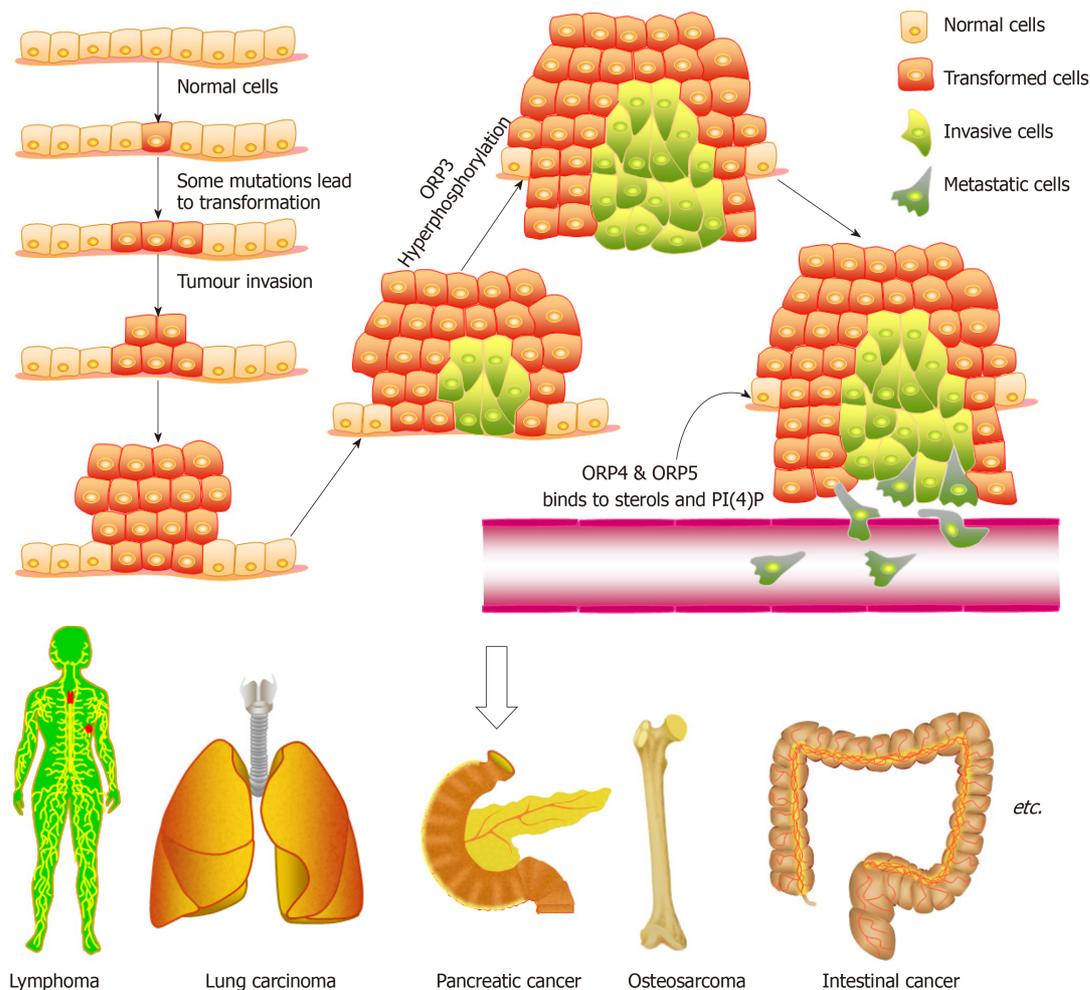
---

## ORP4 IS A PREREQUISITE FOR TUMOUR CELL GROWTH

---

ORP4 is expressed as three important variants: ORP4L, ORP4M, and ORP4S<sup>[25]</sup>. ORP4 is constitutively expressed in the human brain, heart, and testis but is absent in other human and mouse tissues<sup>[26,27]</sup>. ORP4-knockout mice exhibit teratozoospermia due to the death of developing spermatozoa, which indicates that ORP4 is essential for the liveness of specific cell populations<sup>[26]</sup>. Early studies discovered ORP4L in leukocytes from patients with chronic myeloid leukaemia but not in those from healthy donors<sup>[27]</sup>. Recent studies have shown that ORP4L is involved in human malignant tumour cell proliferation and survival<sup>[28]</sup> and is a target of the natural anti-proliferative steroidal saponin OSW-1<sup>[29]</sup>, and these findings reveal the participation of ORP4L in the control of oncogenic cell growth.

ORP4 has a human cell growth regulatory activity<sup>[28]</sup>. Similar to other ORPs, ORP4 binds to sterols and PI(4)P. ORP4 requires sterol-binding activity and PI(4)P-binding activity to boost human malignant cell survival and proliferation<sup>[26]</sup>. In human nontransformed intestinal epithelial cells-18, ORP4 silencing can rapidly activate the apoptotic cell death pathway, including nuclear PARP proteolysis, fragmentation of DNA, caspase-3 and JNK phosphorylation, and nucleosome release<sup>[28]</sup>. ORP4 is highly expressed in IEC-18 cells transformed with mammalian oncogenic H-Ras. ORP4 is not involved in silencing-mediated apoptotic responses, partly because oncogenic H-Ras conversion activates tumour proliferative pathways and suppresses tumour apoptotic pathways. In contrast, the overexpression of ORP4 in IEC-RAS clones can promote tumour transformation, but ORP4 cannot be silenced by gene knockdown and leads to apoptosis. The silencing of ORP4 in HEK293 and HeLa cells can inhibit cell proliferation to result in growth arrest but not cell death<sup>[28]</sup>. A recent study showed that ORP4L boosts cervical carcinoma cell (including HeLa, C33A, and CaSki) proliferation<sup>[30]</sup>. ORP4L contains human tumour cell growth by engaging intracellular  $\text{Ca}^{2+}$  signalling. ORP4 expression has continuously been implicated in breast tumours, lung tumours, and leukaemia<sup>[27,31-33]</sup>. A previous study<sup>[33]</sup> revealed that T-cell acute lymphoblastic leukaemia (T-ALL) cells are characterized by increased levels of oxidative phosphorylation and a higher ATP content. The cell number is proportional to the content of cellular ATP<sup>[31]</sup>. ORP4L is primarily expressed in most T-ALL cells but not in normal T-cells. ORP4L acts as an adaptor responsible for the assembly of CD3e, Gαq/11, and PLCβ3 into a complex that activates PLCβ3<sup>[31]</sup>. Moreover, ORP4L



**Figure 1** Oxysterol binding-related protein family members promote tumour transformation, invasion, migration, and metastasis at the cellular, tissue, and organ levels.

overexpression has the opposite outcomes: The silencing of ORP4L can inhibit PLC3 activation, reduce the production of IP<sub>3</sub>, and suppress the release of Ca<sup>2+</sup> from the ER. In addition, ORP4L promotes the transfer of Ca<sup>2+</sup> to the mitochondrion, and pyruvate dehydrogenase is dephosphorylated by Ca<sup>2+</sup>-dependent phosphatase<sup>[30]</sup>. ORP4L silencing can cause cell death, which might be due to defects in the transmission of Ca<sup>2+</sup> from the ER to the mitochondrion, leading to activation of the cell energy sensor AMP kinase and the induction of autophagy<sup>[31]</sup>. The important role of ORP4L in Ca<sup>2+</sup> signalling and T-ALL cell survival appears to be separate from intracellular cholesterol transport. The silencing of ORP4L has no effect on cholesterol distribution in the ER, plasma membrane, and mitochondrion<sup>[31]</sup>. Therefore, whether other lipids are bound to and carried by ORP4 to promote prosurvival activity in human T-lymphocyte cells remains unclear.

## ORP5 IS ENGAGED IN HUMAN TUMOUR CELL INVASION AND TUMOUR PROGRESSION

ORP5 is a tail-anchored ER membrane protein that functions as a lipid transporter amidst intracellular membranes<sup>[34]</sup>. ER-anchored ORP5 serves as a phosphatidylserine transporter due to its ORD<sup>[35]</sup>. Through a countertransport process occurring at membrane link sites, ORP5 transfers PS from the ER to the cell plasma membrane and PI(4)P to the ER<sup>[19]</sup>. Previous studies have investigated the role of ORP5 in conveying PS from the ER to the mitochondrion and in sustaining appropriate mitochondrial action<sup>[36]</sup>.

ORP5 expression has been connected to increases in human tumour cell invasion or metastasis. ORP5 is generally expressed in human pancreatic tumour cells. The invasion rate of both murine and human pancreatic tumour cells is increased by ORP5

overexpression and decreased by ORP5 consumption<sup>[37]</sup>. Moreover, through analyses of clinical samples, we revealed that in our cohort of patients with pancreatic tumours, ORP5 overexpression was connected with a poor prognosis<sup>[37]</sup>. Previous studies have revealed that ORP5 is overexpressed in human lung tumour tissues, particularly in human lung tissues of metastatic individuals<sup>[38]</sup>. The specific correlation of high ORP5 expression with human tumour cell invasion or tumour progression is currently unexplained. The ORD of ORP5 carries a charge that gives it the ability to extract, bind, and transport lipid substances between the ER and other cell membranes<sup>[34,39,40]</sup>. The mutation of some residues in the ORD of ORP5 that can bind to PS<sup>[35]</sup> or PI(4)P<sup>[39,41]</sup> obviously reduces the capacity of ORP5 to accelerate human malignant tumour cell invasion, proliferation, and migration. These results reveal that ORP5 regulates the distribution of PS and other lipids and thus plays an important role in tumour cell survival. For example, PS is essential for Akt signalling activation<sup>[40]</sup>. The ORP5-mediated transport of PS might actually activate the Akt signalling pathway, causing reinforced tumour cell movement. Consistent with this possibility, we found that in human HepG2 cells, ORP5 depletes insulin-induced Akt activation or the mTORC1 signalling pathway. Moreover, PS is also responsible for the tissue distribution of cholesterol in the cytoplasmic leaflets of the plasma membrane<sup>[42]</sup>. However, the ORP5-mediated function of PS might be related to intracellular cholesterol transport<sup>[34]</sup>. Because proper intracellular cholesterol transport plays an important role in mTOR transduction<sup>[43]</sup>, the ORP5-mediated transport of PS might promote mTORC1 activation and cell proliferation in some tumour cells.

---

## ORP10 IS A MEMBER OF THE OSBP FAMILY, AND GENETIC VARIATIONS IN OSBPL10 ARE ASSOCIATED WITH DYSLIPIDAEMIAS AND PERIPHERAL ARTERY DISEASE

---

Increasing lines of evidence suggest that OSBPs and ORPs are involved in dyslipidaemias. OSBPs were isolated as high-affinity cytoplasmic receptors for several oxysterols<sup>[44,45]</sup>. In mammals, including humans, the OSBP-like (OSBPL) gene family consists of 12 members, and these members display different expression patterns, subcellular localizations, and substrate specificities.

ORPs are divided into six subfamilies, and subfamily VI includes the closely related RP10 and ORP11. Single-nucleotide polymorphisms (SNPs) in genes encoding subfamily VI proteins (OSBPL10 and 11) have been associated with dyslipidaemic diseases. ORP11 expression is upregulated in the visceral adipose tissue of obese men at a high risk for cardiovascular disease<sup>[46]</sup>. Further studies associated a number of SNPs in the OSBPL11 gene with risk factors for cardiovascular disease, including hypertension and hyperglycaemia<sup>[47]</sup>. Some studies have shown that polymorphisms in the OSBPL10 gene are associated with high serum TAG levels in Finnish patients with dyslipidaemia. In addition, polymorphisms in the OSBPL10 gene are reportedly associated with high LDL cholesterol levels<sup>[48]</sup> and peripheral arterial disease<sup>[49]</sup> in Japanese subjects.

---

## OTHER ORPS AND TUMOURS

---

In our latest study, ORP4, ORP5, and many other members of the ORP family were also linked to tumours. For instance, all types of malignancies, including colorectal adenocarcinoma, lymphoma, testicular tumour, and osteosarcoma, are strongly associated with elevated ORP3 expression levels<sup>[9,50-54]</sup>. The highest expression of ORP6 is found in the brain and skeletal muscle. In F9 cells, endogenous ORP6 is predominantly associated with the nuclear envelope. The expression data demonstrate that ORP3, ORP6, and ORP7 are not merely redundant gene products but show marked quantitative differences in tissue expression, which suggests that their functions have tissue-specific aspects. Moreover, cholangiocarcinoma patients exhibit high levels of several ORPs, which indicates that oxysterols are involved in cancer progression through OSBPs or that OSBPs might serve as molecular markers for cholangiocarcinoma<sup>[55]</sup>. ORP3 reportedly activates the small GTPase R-Ras<sup>[23]</sup>. Overphosphorylated ORP3 interacts with the ER membrane protein VAPA to stimulate R-Ras signalling<sup>[56]</sup>. The mutual effect of ORP3-VAPA improves Akt signalling and the activity of 1-integrin<sup>[56]</sup>. ORP3 can alter human tumour cells and cell signalling pathway adhesion functions to promote tumour cell proliferation, migration, and invasion<sup>[23,56]</sup>. More importantly, similar to ORP5, ORP8 is primarily expressed in many tumour cells. However, ORP8 is expressed at a very low level in

human haematoma cells, whereas the microRNA miR-143, which downregulates ORP8 expression, is reportedly upregulated in these cells<sup>[57,58]</sup>. The apoptosis of human haematoma cells requires the expression of ORP8. Although ORP8 can affect Fas translocation, the precise mechanism through which ORP8 regulates apoptosis remains to be discovered<sup>[57]</sup>.

Many studies have demonstrated a substantial relationship of apoptosis with oxysterols, the suppression of proliferation, and cell cycle arrest. A previous study<sup>[59]</sup> explained this phenomenon using bile duct cancer formation as an example. The lesion caused by oxysterols, which mediate oxidative DNA, needs to be repaired. The mutations associated with absent or incorrect DNA repair cause either carcinogenesis or cell death<sup>[60]</sup>. In contrast, oxysterol receptors, such as LXRs, might regulate anti-proliferative function. However, different oxysterols play different roles in many cell types. For instance, the Ames test showed a CT mutagenic effect. The CT treatment of Chinese mouse ovarian epithelial cells increases the formation of reactive oxygen species and chromosome aberrations<sup>[61]</sup>. In contrast, the CT precursor cholestane-5 $\alpha$ ,6 $\alpha$ -epoxy-3 $\beta$ -ol exerts anti-proliferative effects, resulting in cell cycle arrest in the human malignant leukaemia cell lines HL-60 and Molt-4<sup>[62]</sup>. Moreover, the cytotoxicity of oxysterols differs in various cell lines, *e.g.*, the IC<sub>50</sub> values of 25-HC and 7 $\beta$ -HC are variable in many human leukaemia cell lineages<sup>[63]</sup>. Oxysterols induce all types of effects when used alone or in admixtures. For instance, the application of a mixture of 7 $\beta$ -HC and 25-HC yields lower pro-apoptotic outcomes than the usage of 7 $\beta$ -HC alone<sup>[64]</sup>. Other studies have reported varying effects of oxysterols administered alone or in admixtures<sup>[65]</sup>. In addition, representative combinations of oxysterol compounds in diets should be further investigated (Figure 2).

---

## CONCLUSION

---

We can conclude that ORP3 has the ability to regulate cell adhesion and migration. ORP4 can increase tumour cell invasion and metastasis, and ORP5 has the ability to increase tumour cell invasion and metastasis. In addition, ORP6 can regulate cell adhesion and migration, ORP7 has the ability to regulate cell adhesion and migration, and ORP8 can regulate apoptosis. ORP9 has the ability to maintain the functional integrity of the early secretory pathway, and ORP10 might cause high LDL cholesterol and high serum TAG levels. Moreover, ORP11 might be associated with high risks of cardiovascular disease.

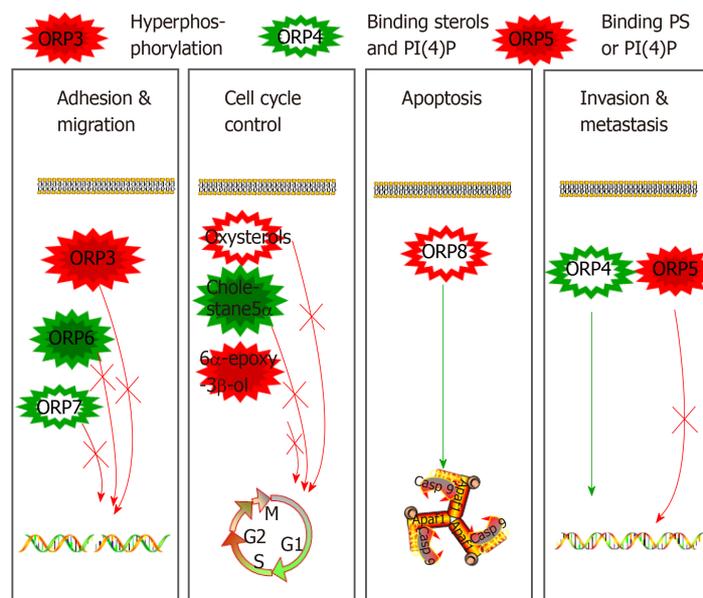
Further studies on oxysterols are required to confirm their important functions in tumour prevention, prognosis, or treatment and in carcinogenesis. Therefore, the extraction of various samples from the human circulation and target tissues at different pathological states for genomic, proteomic, and metabolomic analyses is required for the clinical application of oxysterol in diagnosis and treatment. It is believed that the application of the ORP family in the treatment of malignant tumours will be spectacular, and we believe that all human malignant tumours and related challenges will be conquered in the future.

In the past few years, accumulating lines of evidence from studies conducted by different research groups in the field of malignant tumours have revealed that ORP family members are linked to tumours and have the capacity to accelerate human tumour cell proliferation, migration, and invasion. It is believed that future research will provide more detailed information on the mechanism through which ORPs regulate the growth of tumour cells and will help us establish ORPs as new targets for the treatment of various cancers.

In conclusion, the ORP family plays an essential role in malignant tumour diseases. Many mechanistic questions remain, and much research work needs to be performed. Specifically, the establishment of new bioanalytical technologies and novel experimental animal models could help researchers uncover the secrets of the ORP family.

The ORP family members can accelerate human tumour cell proliferation, migration, and invasion. In this review, the mechanisms and functions of various ORPs are introduced in detail. We also attempt to identify the roles these proteins play in malignant tumours with the ultimate aim of determining the exact role of the OSBP/ORP family in human tumour cells.

The following are the remaining questions regarding the relationship between sterol signalling and sensory genes: Can we find their genetic variation or sporadic mutations in target tissues, and do these mutations exhibit individual differences based on oxysterol levels? Are there invasive or non-invasive markers that can be used to predict pathological risk? Are there any signs showing that a potential preventive measure, namely, the use of oxysterols, could be used to reduce disease



**Figure 2** Mechanism through which oxysterol binding-related protein family members promote tumour migration, invasion, and metastasis via hyperphosphorylation or binding to the sterols PS and PI(4)P.

risk? Finally, can certain genes or proteins in the oxysterol pathway be used as targets in personalized treatment?

## REFERENCES

- 1 Kloudova A, Guengerich FP, Soucek P. The Role of Oxysterols in Human Cancer. *Trends Endocrinol Metab* 2017; **28**: 485-496 [PMID: 28410994 DOI: 10.1016/j.tem.2017.03.002]
- 2 Mutemberezi V, Guillemot-Legris O, Muccioli GG. Oxysterols: From cholesterol metabolites to key mediators. *Prog Lipid Res* 2016; **64**: 152-169 [PMID: 27687912 DOI: 10.1016/j.plipres.2016.09.002]
- 3 Griffiths WJ, Crick PJ, Wang Y. Methods for oxysterol analysis: past, present and future. *Biochem Pharmacol* 2013; **86**: 3-14 [PMID: 23395696 DOI: 10.1016/j.bcp.2013.01.027]
- 4 Weber-Boyyat M, Zhong W, Yan D, Olkkonen VM. Oxysterol-binding proteins: functions in cell regulation beyond lipid metabolism. *Biochem Pharmacol* 2013; **86**: 89-95 [PMID: 23428468 DOI: 10.1016/j.bcp.2013.02.016]
- 5 Bowden K, Ridgway ND. OSBP negatively regulates ABCA1 protein stability. *J Biol Chem* 2008; **283**: 18210-18217 [PMID: 18450749 DOI: 10.1074/jbc.M800918200]
- 6 Zhou T, Li S, Zhong W, Vihervaara T, Béaslas O, Perttilä J, Luo W, Jiang Y, Lehto M, Olkkonen VM, Yan D. OSBP-related protein 8 (ORP8) regulates plasma and liver tissue lipid levels and interacts with the nucleoporin Nup62. *PLoS One* 2011; **6**: e21078 [PMID: 21698267 DOI: 10.1371/journal.pone.0021078]
- 7 Escajadillo T, Wang H, Li L, Li D, Sewer MB. Oxysterol-related-binding-protein related Protein-2 (ORP2) regulates cortisol biosynthesis and cholesterol homeostasis. *Mol Cell Endocrinol* 2016; **427**: 73-85 [PMID: 26992564 DOI: 10.1016/j.mce.2016.03.006]
- 8 Sugawara K, Morita K, Ueno N, Shibuya H. BIP, a BRAM-interacting protein involved in TGF-beta signalling, regulates body length in *Caenorhabditis elegans*. *Genes Cells* 2001; **6**: 599-606 [PMID: 11473578 DOI: 10.1046/j.1365-2443.2001.00444.x]
- 9 Wang PY, Weng J, Anderson RG. OSBP is a cholesterol-regulated scaffolding protein in control of ERK 1/2 activation. *Science* 2005; **307**: 1472-1476 [PMID: 15746430 DOI: 10.1126/science.1107710]
- 10 Romeo GR, Kazlauskas A. Oxysterol and diabetes activate STAT3 and control endothelial expression of profilin-1 via OSBP1. *J Biol Chem* 2008; **283**: 9595-9605 [PMID: 18230613 DOI: 10.1074/jbc.M710092200]
- 11 Lessmann E, Ngo M, Leitges M, Minguet S, Ridgway ND, Huber M. Oxysterol-binding protein-related protein (ORP) 9 is a PDK-2 substrate and regulates Akt phosphorylation. *Cell Signal* 2007; **19**: 384-392 [PMID: 16962287 DOI: 10.1016/j.cellsig.2006.07.009]
- 12 Perry RJ, Ridgway ND. Oxysterol-binding protein and vesicle-associated membrane protein-associated protein are required for sterol-dependent activation of the ceramide transport protein. *Mol Biol Cell* 2006; **17**: 2604-2616 [PMID: 16571669 DOI: 10.1091/mbc.e06-01-0060]
- 13 Peretti D, Dahan N, Shimoni E, Hirschberg K, Lev S. Coordinated lipid transfer between the endoplasmic reticulum and the Golgi complex requires the VAP proteins and is essential for Golgi-mediated transport. *Mol Biol Cell* 2008; **19**: 3871-3884 [PMID: 18614794 DOI: 10.1091/mbc.E08-05-0498]
- 14 Nhek S, Ngo M, Yang X, Ng MM, Field SJ, Asara JM, Ridgway ND, Toker A. Regulation of oxysterol-binding protein Golgi localization through protein kinase D-mediated phosphorylation. *Mol Biol Cell* 2010; **21**: 2327-2337 [PMID: 20444975 DOI: 10.1091/mbc.E10-02-0090]
- 15 Zerbinatti CV, Cordy JM, Chen CD, Guillily M, Suon S, Ray WJ, Seabrook GR, Abraham CR, Wolozin B. Oxysterol-binding protein-1 (OSBP1) modulates processing and trafficking of the amyloid precursor protein. *Mol Neurodegener* 2008; **3**: 5 [PMID: 18348724 DOI: 10.1186/1750-1326-3-5]
- 16 Ridgway ND, Dawson PA, Ho YK, Brown MS, Goldstein JL. Translocation of oxysterol binding protein to Golgi apparatus triggered by ligand binding. *J Cell Biol* 1992; **116**: 307-319 [PMID: 1730758 DOI: 10.1083/jcb.116.3.307]

- 10.1083/jcb.116.2.307]
- 17 **Ngo M**, Ridgway ND. Oxysterol binding protein-related Protein 9 (ORP9) is a cholesterol transfer protein that regulates Golgi structure and function. *Mol Biol Cell* 2009; **20**: 1388-1399 [PMID: [19129476](#) DOI: [10.1091/mbc.E08-09-0905](#)]
  - 18 **Levine TP**, Munro S. The pleckstrin homology domain of oxysterol-binding protein recognises a determinant specific to Golgi membranes. *Curr Biol* 1998; **8**: 729-739 [PMID: [9651677](#) DOI: [10.1016/s0960-9822\(98\)70296-9](#)]
  - 19 **Levine TP**, Munro S. Targeting of Golgi-specific pleckstrin homology domains involves both PtdIns 4-kinase-dependent and -independent components. *Curr Biol* 2002; **12**: 695-704 [PMID: [12007412](#) DOI: [10.1016/s0960-9822\(02\)00779-0](#)]
  - 20 **Nissilä E**, Ohsaki Y, Weber-Boyyvat M, Perttilä J, Ikonen E, Olkkonen VM. ORP10, a cholesterol binding protein associated with microtubules, regulates apolipoprotein B-100 secretion. *Biochim Biophys Acta* 2012; **1821**: 1472-1484 [PMID: [22906437](#) DOI: [10.1016/j.bbali.2012.08.004](#)]
  - 21 **Zhong W**, Zhou Y, Li S, Zhou T, Ma H, Wei K, Li H, Olkkonen VM, Yan D. OSBP-related protein 7 interacts with GATE-16 and negatively regulates GS28 protein stability. *Exp Cell Res* 2011; **317**: 2353-2363 [PMID: [21669198](#) DOI: [10.1016/j.yexcr.2011.05.028](#)]
  - 22 **Goldfinger LE**, Ptak C, Jeffery ED, Shabanowitz J, Han J, Haling JR, Sherman NE, Fox JW, Hunt DF, Ginsberg MH. An experimentally derived database of candidate Ras-interacting proteins. *J Proteome Res* 2007; **6**: 1806-1811 [PMID: [17439166](#) DOI: [10.1021/pr060630l](#)]
  - 23 **Lehto M**, Mäyränpää MI, Pellinen T, Ihalmo P, Lehtonen S, Kovanen PT, Groop PH, Ivaska J, Olkkonen VM. The R-Ras interaction partner ORP3 regulates cell adhesion. *J Cell Sci* 2008; **121**: 695-705 [PMID: [18270267](#) DOI: [10.1242/jcs.016964](#)]
  - 24 **Stefan CJ**, Manford AG, Baird D, Yamada-Hanff J, Mao Y, Emr SD. Osh proteins regulate phosphoinositide metabolism at ER-plasma membrane contact sites. *Cell* 2011; **144**: 389-401 [PMID: [21295699](#) DOI: [10.1016/j.cell.2010.12.034](#)]
  - 25 **Wang C**, JeBailey L, Ridgway ND. Oxysterol-binding-protein (OSBP)-related protein 4 binds 25-hydroxycholesterol and interacts with vimentin intermediate filaments. *Biochem J* 2002; **361**: 461-472 [PMID: [11802775](#) DOI: [10.1042/0264-6021:3610461](#)]
  - 26 **Udagawa O**, Ito C, Ogonuki N, Sato H, Lee S, Tripvanuntakul P, Ichi I, Uchida Y, Nishimura T, Murakami M, Ogura A, Inoue T, Toshimori K, Arai H. Oligo-astheno-teratozoospermia in mice lacking ORP4, a sterol-binding protein in the OSBP-related protein family. *Genes Cells* 2014; **19**: 13-27 [PMID: [24245814](#) DOI: [10.1111/gtc.12105](#)]
  - 27 **Fournier MV**, Guimarães da Costa F, Paschoal ME, Ronco LV, Carvalho MG, Pardee AB. Identification of a gene encoding a human oxysterol-binding protein-homologue: a potential general molecular marker for blood dissemination of solid tumors. *Cancer Res* 1999; **59**: 3748-3753 [PMID: [10446991](#)]
  - 28 **Charman M**, Colbourne TR, Pietrangelo A, Kreplak L, Ridgway ND. Oxysterol-binding protein (OSBP)-related protein 4 (ORP4) is essential for cell proliferation and survival. *J Biol Chem* 2014; **289**: 15705-15717 [PMID: [24742681](#) DOI: [10.1074/jbc.M114.571216](#)]
  - 29 **Burgett AW**, Poulsen TB, Wangkanont K, Anderson DR, Kikuchi C, Shimada K, Okubo S, Fortner KC, Mimaki Y, Kuroda M, Murphy JP, Schwab DJ, Petrella EC, Cornella-Taracido I, Schirle M, Tallarico JA, Shair MD. Natural products reveal cancer cell dependence on oxysterol-binding proteins. *Nat Chem Biol* 2011; **7**: 639-647 [PMID: [21822274](#) DOI: [10.1038/nchembio.625](#)]
  - 30 **Li JW**, Xiao YL, Lai CF, Lou N, Ma HL, Zhu BY, Zhong WB, Yan DG. Oxysterol-binding protein-related protein 4L promotes cell proliferation by sustaining intracellular Ca<sup>2+</sup> homeostasis in cervical carcinoma cell lines. *Oncotarget* 2016; **7**: 65849-65861 [PMID: [27588468](#) DOI: [10.18632/oncotarget.11671](#)]
  - 31 **Silva NH**, Pimenta G, Pulcheri WA, Fournier MV, Spector N, da Costa Carvalho MG. Detection of messenger RNA in leukocytes or plasma of patients with chronic myeloid leukemia. *Oncol Rep* 2001; **8**: 693-696 [PMID: [11295104](#) DOI: [10.3892/or.8.3.693](#)]
  - 32 **Henriques Silva N**, Vasconcellos Fournier M, Pimenta G, Pulcheri WA, Spector N, da Costa Carvalho Mda G. HLM/OSBP2 is expressed in chronic myeloid leukemia. *Int J Mol Med* 2003; **12**: 663-666 [PMID: [12964051](#)]
  - 33 **Zhong W**, Yi Q, Xu B, Li S, Wang T, Liu F, Zhu B, Hoffmann PR, Ji G, Lei P, Li G, Li J, Li J, Olkkonen VM, Yan D. ORP4L is essential for T-cell acute lymphoblastic leukemia cell survival. *Nat Commun* 2016; **7**: 12702 [PMID: [27581363](#) DOI: [10.1038/ncomms12702](#)]
  - 34 **Du X**, Kumar J, Ferguson C, Schulz TA, Ong YS, Hong W, Prinz WA, Parton RG, Brown AJ, Yang H. A role for oxysterol-binding protein-related protein 5 in endosomal cholesterol trafficking. *J Cell Biol* 2011; **192**: 121-135 [PMID: [21220512](#) DOI: [10.1083/jcb.201004142](#)]
  - 35 **Maeda K**, Anand K, Chiapparino A, Kumar A, Poletto M, Kaksonen M, Gavin AC. Interactome map uncovers phosphatidylserine transport by oxysterol-binding proteins. *Nature* 2013; **501**: 257-261 [PMID: [23934110](#) DOI: [10.1038/nature12430](#)]
  - 36 **Galmes R**, Houcine A, van Vliet AR, Agostinis P, Jackson CL, Giordano F. ORP5/ORP8 localize to endoplasmic reticulum-mitochondria contacts and are involved in mitochondrial function. *EMBO Rep* 2016; **17**: 800-810 [PMID: [27113756](#) DOI: [10.15252/embr.201541108](#)]
  - 37 **Koga Y**, Ishikawa S, Nakamura T, Masuda T, Nagai Y, Takamori H, Hirota M, Kanemitsu K, Baba Y, Baba H. Oxysterol binding protein-related protein-5 is related to invasion and poor prognosis in pancreatic cancer. *Cancer Sci* 2008; **99**: 2387-2394 [PMID: [19032366](#) DOI: [10.1111/j.1349-7006.2008.00987.x](#)]
  - 38 **Nagano K**, Imai S, Zhao X, Yamashita T, Yoshioka Y, Abe Y, Mukai Y, Kamada H, Nakagawa S, Tsutsumi Y, Tsunoda S. Identification and evaluation of metastasis-related proteins, oxysterol binding protein-like 5 and calumenin, in lung tumors. *Int J Oncol* 2015; **47**: 195-203 [PMID: [25963840](#) DOI: [10.3892/ijo.2015.3000](#)]
  - 39 **Chung J**, Torta F, Masai K, Lucast L, Czaplá H, Tanner LB, Narayanaswamy P, Wenk MR, Nakatsu F, De Camilli P. INTRACELLULAR TRANSPORT. PI4P/phosphatidylserine countertransport at ORP5- and ORP8-mediated ER-plasma membrane contacts. *Science* 2015; **349**: 428-432 [PMID: [26206935](#) DOI: [10.1126/science.aab1370](#)]
  - 40 **Huang BX**, Akbar M, Kevala K, Kim HY. Phosphatidylserine is a critical modulator for Akt activation. *J Cell Biol* 2011; **192**: 979-992 [PMID: [21402788](#) DOI: [10.1083/jcb.201005100](#)]
  - 41 **de Saint-Jean M**, Delfosse V, Douguet D, Chicanne G, Payrastré B, Bourguet B, Antonny B, Drin G. Osh4p exchanges sterols for phosphatidylinositol 4-phosphate between lipid bilayers. *J Cell Biol* 2011; **195**: 965-978 [PMID: [22162133](#) DOI: [10.1083/jcb.201104062](#)]
  - 42 **Maekawa M**, Fairn GD. Complementary probes reveal that phosphatidylserine is required for the proper

- transbilayer distribution of cholesterol. *J Cell Sci* 2015; **128**: 1422-1433 [PMID: 25663704 DOI: 10.1242/jcs.164715]
- 43 **Xu J**, Dang Y, Ren YR, Liu JO. Cholesterol trafficking is required for mTOR activation in endothelial cells. *Proc Natl Acad Sci USA* 2010; **107**: 4764-4769 [PMID: 20176935 DOI: 10.1073/pnas.0910872107]
- 44 **Dawson PA**, Van der Westhuyzen DR, Goldstein JL, Brown MS. Purification of oxysterol binding protein from hamster liver cytosol. *J Biol Chem* 1989; **264**: 9046-9052 [PMID: 2722817]
- 45 **Dawson PA**, Ridgway ND, Slaughter CA, Brown MS, Goldstein JL. cDNA cloning and expression of oxysterol-binding protein, an oligomer with a potential leucine zipper. *J Biol Chem* 1989; **264**: 16798-16803 [PMID: 2777807]
- 46 **Bouchard L**, Tchernof A, Deshaies Y, Marceau S, Lescelleur O, Biron S, Vohl MC. ZFP36: a promising candidate gene for obesity-related metabolic complications identified by converging genomics. *Obes Surg* 2007; **17**: 372-382 [PMID: 17546847 DOI: 10.1007/s11695-007-9067-5]
- 47 **Bouchard L**, Faucher G, Tchernof A, Deshaies Y, Marceau S, Lescelleur O, Biron S, Bouchard C, Pérusse L, Vohl MC. Association of OSBPL11 gene polymorphisms with cardiovascular disease risk factors in obesity. *Obesity (Silver Spring)* 2009; **17**: 1466-1472 [PMID: 19325544 DOI: 10.1038/oby.2009.71]
- 48 **Koriyama H**, Nakagami H, Katsuya T, Akasaka H, Saitoh S, Shimamoto K, Ogihara T, Kaneda Y, Morishita R, Rakugi H. Variation in OSBPL10 is associated with dyslipidemia. *Hypertens Res* 2010; **33**: 511-514 [PMID: 20224571 DOI: 10.1038/hr.2010.28]
- 49 **Koriyama H**, Nakagami H, Katsuya T, Sugimoto K, Yamashita H, Takami Y, Maeda S, Kubo M, Takahashi A, Nakamura Y, Ogihara T, Rakugi H, Kaneda Y, Morishita R. Identification of evidence suggestive of an association with peripheral arterial disease at the OSBPL10 locus by genome-wide investigation in the Japanese population. *J Atheroscler Thromb* 2010; **17**: 1054-1062 [PMID: 20610895 DOI: 10.5551/jat.4291]
- 50 **Tsafirir D**, Bacolod M, Selvanayagam Z, Tsafirir I, Shia J, Zeng Z, Liu H, Krier C, Stengel RF, Barany F, Gerald WL, Paty PB, Domany E, Notterman DA. Relationship of gene expression and chromosomal abnormalities in colorectal cancer. *Cancer Res* 2006; **66**: 2129-2137 [PMID: 16489013 DOI: 10.1158/0008-5472.CAN-05-2569]
- 51 **Graves TG**, Harr MW, Crawford EL, Willey JC. Stable low-level expression of p21WAF1/CIP1 in A549 human bronchogenic carcinoma cell line-derived clones down-regulates E2F1 mRNA and restores cell proliferation control. *Mol Cancer* 2006; **5**: 1 [PMID: 16403226 DOI: 10.1186/1476-4598-5-1]
- 52 **Juric D**, Sale S, Hromas RA, Yu R, Wang Y, Duran GE, Tibshirani R, Einhorn LH, Sicik BI. Gene expression profiling differentiates germ cell tumors from other cancers and defines subtype-specific signatures. *Proc Natl Acad Sci USA* 2005; **102**: 17763-17768 [PMID: 16306258 DOI: 10.1073/pnas.0509082102]
- 53 **Gashaw I**, Grümmer R, Klein-Hitpass L, Dushaj O, Bergmann M, Brehm R, Grobholz R, Kliesch S, Neuvians TP, Schmid KW, von Ostau C, Winterhager E. Gene signatures of testicular seminoma with emphasis on expression of ets variant gene 4. *Cell Mol Life Sci* 2005; **62**: 2359-2368 [PMID: 16158187 DOI: 10.1007/s00018-005-5250-9]
- 54 **Lehto M**, Tienari J, Lehtonen S, Lehtonen E, Olkkonen VM. Subfamily III of mammalian oxysterol-binding protein (OSBP) homologues: the expression and intracellular localization of ORP3, ORP6, and ORP7. *Cell Tissue Res* 2004; **315**: 39-57 [PMID: 14593528 DOI: 10.1007/s00441-003-0817-y]
- 55 **Loilome W**, Wechagama P, Namwat N, Jusakul A, Sripa B, Miwa M, Kuver R, Yongvanit P. Expression of oxysterol binding protein isoforms in opisthorchiasis-associated cholangiocarcinoma: a potential molecular marker for tumor metastasis. *Parasitol Int* 2012; **61**: 136-139 [PMID: 21763455 DOI: 10.1016/j.parint.2011.07.003]
- 56 **Weber-Boyyat M**, Kentala H, Lilja J, Vihervaara T, Hanninen R, Zhou Y, Peränen J, Nyman TA, Ivaska J, Olkkonen VM. OSBP-related protein 3 (ORP3) coupling with VAMP-associated protein A regulates R-Ras activity. *Exp Cell Res* 2015; **331**: 278-291 [PMID: 25447204 DOI: 10.1016/j.yexcr.2014.10.019]
- 57 **Zhong W**, Qin S, Zhu B, Pu M, Liu F, Wang L, Ye G, Yi Q, Yan D. Oxysterol-binding protein-related protein 8 (ORP8) increases sensitivity of hepatocellular carcinoma cells to Fes-mediated apoptosis. *J Biol Chem* 2015; **290**: 8876-8887 [PMID: 25596532 DOI: 10.1074/jbc.M114.610188]
- 58 **Jordan SD**, Krüger M, Willmes DM, Redemann N, Wunderlich FT, Brönneke HS, Merkwirth C, Kashkar H, Olkkonen VM, Böttger T, Braun T, Seibler J, Brüning JC. Obesity-induced overexpression of miRNA-143 inhibits insulin-stimulated AKT activation and impairs glucose metabolism. *Nat Cell Biol* 2011; **13**: 434-446 [PMID: 21441927 DOI: 10.1038/ncb2211]
- 59 **Jusakul A**, Loilome W, Namwat N, Haigh WG, Kuver R, Dechakhamphu S, Sukontawarin P, Pinlaor S, Lee SP, Yongvanit P. Liver fluke-induced hepatic oxysterols stimulate DNA damage and apoptosis in cultured human cholangiocytes. *Mutat Res* 2012; **731**: 48-57 [PMID: 22044627 DOI: 10.1016/j.mrfmmm.2011.10.009]
- 60 **Jusakul A**, Loilome W, Namwat N, Techasen A, Kuver R, Ioannou GN, Savard C, Haigh WG, Yongvanit P. Anti-apoptotic phenotypes of cholestan-3 $\beta$ ,5 $\alpha$ ,6 $\beta$ -triol-resistant human cholangiocytes: characteristics contributing to the genesis of cholangiocarcinoma. *J Steroid Biochem Mol Biol* 2013; **138**: 368-375 [PMID: 23959098 DOI: 10.1016/j.jsbmb.2013.08.004]
- 61 **Cheng YW**, Kang JJ, Shih YL, Lo YL, Wang CF. Cholesterol-3- $\beta$ , 5- $\alpha$ , 6- $\beta$ -triol induced genotoxicity through reactive oxygen species formation. *Food Chem Toxicol* 2005; **43**: 617-622 [PMID: 15721210 DOI: 10.1016/j.fct.2005.01.007]
- 62 **Ishimaru C**, Yonezawa Y, Kuriyama I, Nishida M, Yoshida H, Mizushima Y. Inhibitory effects of cholesterol derivatives on DNA polymerase and topoisomerase activities, and human cancer cell growth. *Lipids* 2008; **43**: 373-382 [PMID: 18214566 DOI: 10.1007/s11745-007-3149-y]
- 63 **Lim HK**, Kang HK, Yoo ES, Kim BJ, Kim YW, Cho M, Lee JH, Lee YS, Chung MH, Hyun JW. Oxysterols induce apoptosis and accumulation of cell cycle at G(2)/M phase in the human monocytic THP-1 cell line. *Life Sci* 2003; **72**: 1389-1399 [PMID: 12527036 DOI: 10.1016/s0024-3205(02)02377-9]
- 64 **Aupeix K**, Weltin D, Mejia JE, Christ M, Marchal J, Freyssinet JM, Bischoff P. Oxysterol-induced apoptosis in human monocytic cell lines. *Immunobiology* 1995; **194**: 415-428 [PMID: 8749234 DOI: 10.1016/S0171-2985(11)80108-7]
- 65 **Biasi F**, Leonarduzzi G, Vizio B, Zanetti D, Sevanian A, Sottero B, Verde V, Zingaro B, Chiarpotto E, Poli G. Oxysterol mixtures prevent proapoptotic effects of 7-ketocholesterol in macrophages: implications for proatherogenic gene modulation. *FASEB J* 2004; **18**: 693-695 [PMID: 14977888 DOI: 10.1096/fj.03-0401fje]



Published By Baishideng Publishing Group Inc  
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA  
Telephone: +1-925-2238242  
E-mail: [bpgoffice@wjgnet.com](mailto:bpgoffice@wjgnet.com)  
Help Desk: <https://www.f6publishing.com/helpdesk>  
<https://www.wjgnet.com>

