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Review

The role of oxysterol-binding protein and its related proteins in cancer

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ABSTRACT

Oxysterol-binding protein (OSBP) and its related proteins (ORPs) constitute a large, evolutionarily conserved family of lipid-binding proteins that are associated with a wide range of cellular activities. The core function of OSBP/ORPs appears to be moving lipids between cellular membranes in a non-vesicular manner. Recent studies have unveiled a novel, counter-transport mechanism of cellular lipid transfer mediated by OSBP/ORPs at the membrane contact sites that involves phosphatidylinositol 4-phosphate. Importantly, the OSBP/ORPs family has also been implicated in cell signalling pathways and cancer development. Here, we summarize recent progress in understanding the role of OSBP/ORPs in cancer development, and discuss how the lipid transfer function of OSBP/ORPs may underpin their role in tumorigenesis.

Contents

1. Introduction

Within a cell, different species of membrane lipids are highly organised and unevenly distributed, representing a defining feature of different cellular organelles [1,2]. Disruption of proper membrane lipid distribution or metabolism can have serious consequences, and has been implicated in various diseases, including cancer, metabolic disorders, and neurodegenerative diseases [3–5]. The uneven distribution of membrane lipids largely relies on the mechanisms that govern intracellular lipid trafficking. At membrane contact sites (MCSs), non-vesicular transport of lipids by lipid transfer proteins has emerged as a major theme of lipid exchange between organelle membranes [6,7]. For example, a well-known lipid transfer protein, oxysterol-binding protein (OSBP), localizes to the endoplasmic reticulum (ER) and Golgi contact sites, where it exchanges sterols with phosphatidylinositol 4-phosphate (PI(4)P) [8].

OSBP and OSBP-related proteins (ORPs) constitute a large family of lipid transfer proteins. In mammalian cells, the OSBP/ORPs protein family are encoded by twelve genes that give rise to fifteen proteins due to alternate splicing and transcription [9] (Fig. 1). OSBP/ORPs share a characteristic feature of a conserved carboxyl-terminal OSBP related domain (ORD) or ligand-binding domain. The N-termini of these proteins often possess a FFAT motif (diphenylalanine in an acidic tract) and a pleckstrin homology (PH) domain. The FFAT motif and the PH domain are responsible for targeting

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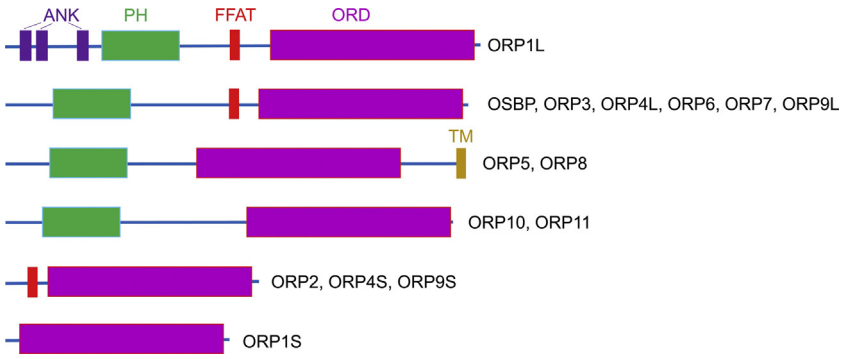

Fig 1. Schematic view of mammalian OSBP/ORPs superfamily based on domain organization. Some of the ORP splice variants are shown, including the long and short version of ORP1, ORP4 and ORP9. The protein family is characterized by the C-terminal OSBP-related ligand binding domain (ORD). Majority of the protein members possess the N-terminal pleckstrin homology (PH) domain, with some also having the motif "two phenylalanines in an acidic tract" (FFAT). ORP1L also has ankryin repeats (ANK) at its N-terminus. ORP5 and ORP8 have a unique C-terminal trans-membrane (TM) domain. L: long isoform; S: short isoform.

OSBP/ORPs to endoplasmic reticulum (ER) membranes and non-ER organelle membranes, respectively [10–12]. These two membrane-targeting determinants enable OSBP and some ORPs to function at ER-associated membrane contact sites, where they contribute to the intracellular exchange of lipids [13].

Apart from sensing and moving lipids, OSBP and various ORPs also play a role in the regulation of cell signalling pathways. Importantly, there is growing body of evidence that certain members of the OSBP/ORPs family are linked to cancer. Whether the role of OSBP/ORPs in cell signalling and cancer development is dependent upon their lipid sensing and transfer functions is currently unclear. Here, we highlight recent progress in understanding the lipid transfer, cell signalling and cancer-related functions of OSBP/ORPs, aiming to provide insights into the connections between cancer and intracellular lipid transport and metabolism.

2. OSBP/ORPs transport lipids at MCSs

OSBP was first identified as a high affinity cytosolic receptor for oxysterols, such as 25-hydroxycholesterol [14]. Homologues to OSBP have subsequently been isolated in virtually all eukaryotes including 12 members in mammals (Fig. 1), 14 in zebrafish *Danio rerio*, 4 in *Caenorhabditis elegans*, 4 in *Drosophila melanogaster*, and 7 members in the budding yeast *Saccharomyces cerevisiae* [15]. Members of the OSBP/ORP family vary in length: the short ORPs comprise primarily the ORD, whereas the long ones also possess other domains including the PH domain. OSBP and some of its homologues can target different cell membranes. For example, OSBP associates with the Golgi via its PH domain and the ER via binding to ER vesicle-associated membrane protein-associated proteins (VAPs) through its FFAT motif, which is also present in the well-known ceramide transporter, CERT [11]. In the case of mammalian ORP5 and ORP8, they lack the FFAT motif but carry a C-terminal transmembrane domain (TM) that anchors them to the ER [16,17]. The dual membrane targeting ability of most OSBP/ORPs suggests that they may promote the formation of membrane contact sites (MCSs), where they sense the lipid compositions and move lipids between the ER and other organelle membranes.

Indeed, OSBP has been shown to mediate sterol/PI(4)P exchange between the ER and Golgi in mammalian cells [8]. OSBP can be translocated to the contact sites between the ER and the Golgi apparatus, where it is attached to the ER membrane by binding VAPs using its FFAT motif and to the Golgi membrane by binding Golgi PI(4)P via its PH domain. OSBP, VAPs and the PI(4)P phosphatase Sac1 cooperate at MCSs between the ER and the Golgi to promote the specific exchange of lipids [8]. OSBP extracts and binds cholesterol from the ER using its ORD and efficiently transports cholesterol from the ER to the Golgi. The OSBP-ORD exchanges cholesterol with PI(4)P synthesised at the Golgi and transports PI(4)P back to the ER, where it is hydrolysed by a PI(4)P phosphatase, Sac1. Hydrolysis of PI(4)P by Sac1 in the ER allows OSBP to function in a cyclic manner, i.e. the forward transfer of sterol by OSBP is coupled to the backward transport of PI(4)P. Thus, the OSBP cycle is made possible via the collaboration of Sac1, a PI-4-kinase, and VAPs between the ER and Golgi. The segregation of these proteins allows PI(4)P hydrolysis at the ER to supply the energy source for OSBP to transfer sterol against a concentration gradient [8].

Among all OSBP/ORPs, ORP5 and ORP8 are unique because they are the only ORP members with a transmembrane domain (Fig. 1). Both proteins are known to localize to the ER through the transmembrane domain and share ~80% sequence identity [16,17]. ORP5, but not ORP8, has been shown to associate with late endosomes and play a role in low density lipoprotein-derived cholesterol transport to the ER [16]. ORP5 is also capable of transferring sterols between liposomes *in vitro* [16]. ORP5 and ORP8 have been recently shown to mediate lipid exchange at ER-plasma membrane contact sites [18]. The localization of ORP5 and ORP8 to ER-plasma membrane contact sites requires the PH domain, which was shown to bind PI(4)P [18]. The ORD of ORP5 and ORP8 was reported to bind PI(4)P and phosphatidylserine (PS), one at a time, and exchange these two lipids between the ER and the plasma membrane: ORP5 and ORP8 were shown to deliver PI(4)P to the ER for degradation by the PI(4)P phosphatase Sac1, and PS from the ER to the plasma membrane against a concentration gradient [18].

Taken together, the emerging paradigm suggests that PI(4)P is a critical lipid for the transport of many other lipid cargos, such as PS by ORP5/8 [18] and Osh6p [19], and cholesterol by OSBP [8] and Osh4p [20]. While this model appears attractive, the evidence that the counter transfer of lipids by OSBP and related proteins occurs in intact cells needs to be firmly established. In addition, it is not clear if other phosphoinositides, such as PI(4,5)P_2 enriched in the plasma membrane, are involved in the targeting and especially the transport function of OSBP/ORPs.

3. OSBP and ORP4 are the targets of anti-cancer drugs

Disrupted membrane lipid distribution or metabolism can have serious consequences for cellular homeostasis and health. For example, alterations in lipid metabolism have been frequently reported in tumor progression [21], and impaired PI(4,5)P_2 homeostasis in the plasma membrane has been implicated in various cancers and metabolic disorders [3]. The critical role that OSBP/ORPs play in intracellular lipid trafficking suggests that these proteins may be highly relevant to human diseases, especially can-

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