Advances in the basic function of the small GTPase SAR1B and its regulatory role in the biological behavior of tumor cells (Review)

QINGCHUN YANG[1-3], GUODONG HUANG[1-3*], CHI LU[1-3*], ZHANG LEI[1-3*] and HONGDA LU[1-3]

[1]Department of Oncology, Central Hospital of Wuhan, Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430000, P.R. China; [2]Cancer Research Institute of Wuhan, Wuhan, Hubei 430000, P.R. China; [3]Key Laboratory for Molecular Diagnosis of Hubei, Wuhan Central Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology, Wuhan, Hubei 430000, P.R. China

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Abstract. The secretion associated Ras related GTPase 1B (SAR1B) is a member of the ADP-ribosylation factor (Arf) subfamily of small GTPases. It participates in various physiological activities, such as protein transport, lipid metabolism and stress response of cells by regulating the formation of coat protein complex II (COPII) vesicles. Moreover, SAR1B is an important link in the transduction of tumor cell signaling pathways [for example, mechanistic target of rapamycin kinase (mTOR), Wnt/β-catenin]. In the present article, the structure and basic function of SAR1B, as well as the research progress of SAR1B in tumor cell substance transport and metabolism, stress autophagy regulation and tumor signaling pathway, were reviewed. In addition, approaches to rationally utilizing the different functions of SAR1B in different physiological and pathological environments to achieve effective inhibition of tumor cell growth, proliferation and migration, were discussed. Furthermore, a theoretical basis for the use of SAR1B as a new target for tumor therapy was provided.

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Correspondence to: Dr Hongda Lu or Dr Zhang Lei, Key Laboratory for Molecular Diagnosis of Hubei, Wuhan Central Hospital Affiliated to Tongji Medical College, Huazhong University of Science and Technology, 16 Gusaoshu Road, Jianghan, Wuhan, Hubei 430000, P.R. China
E-mail: phlonda@163.com
E-mail: leizhang003@126.com

*Contributed equally

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1. Introduction

The secretion associated Ras related GTPase 1B (SAR1B) gene is a key regulator of coat protein complex II (COPII) coat protein complex formation and plays an important role in maintaining cellular homeostasis by mediating protein secretion, regulating lipid metabolism, and influencing autophagosome synthesis. It is established that SAR1B gene defects cause chylomicron retention disease, a lipid metabolism disorder (1). In recent years, research has demonstrated that the SAR1B gene is involved in the regulation of various biological behaviors of tumor cells, such as participating in the epithelial-mesenchymal transition (EMT) of tumor cells, regulating membrane synthesis and energy metabolism by affecting lipid metabolism, controlling the secretion of key proteins in the signaling pathway of tumor cells to influence signaling, and regulating the tumor development process by affecting the synthesis of autophagosomes under stress. It has been found that the SAR1B gene is abnormally expressed in numerous malignant tumors, such as colorectal cancer (CRC) and lung cancer (LC), and has the potential to be used as a prognostic marker. The functional basis of mediating the formation of COPII envelope protein complexes can be used as a target for novel drug research. However, the specific mechanism underlying the role of the SAR1B gene in tumor cell development, migration and invasion has not been systematically elucidated. Further research is warranted to investigate the clinical potential of the SAR1B gene and explore the possibility of using this gene as a therapeutic target for malignant tumors.

2. Structure, origin and physiological function of the SAR1B gene

Structure and origin of the SAR1B gene. The human SAR1B gene is located on chromosome 5q31.1 and encodes a GTPase

protein containing 198 amino acids, a core component of the COPII complex. It is evolutionarily highly conserved and widespread in eukaryotes. The SAR1B protein contains a GTP-binding structural domain (N-terminal) and an effector structural domain (C-terminal) that contains a unique Sar1-NH2 terminal activation recruitment (STAR) motif composed of nine amino acids. This evolutionarily conserved cluster of bulky hydrophobic amino acids facilitates membrane binding and contains specific sequence information necessary for COPII complex formation (2) (Fig. 1). SAR1B and its paralogous homologue SAR1A are jointly involved in the formation of the COPII complex. SAR1A and SAR1B share up to 89% amino acid sequence identity and have a similar secondary structure of the N-terminal amphiphilic α-helix (3). During COPII vesicle outgrowth, they can compensate for each other's functional defects.

SAR1B is a member of the ADP-ribosylation factor (Arf) subfamily of the small GTPase family. The small GTPase family, also known as the small guanosine triphosphatase (GTPase) superfamily, is a family of proteins that can act as signaling commanders, play a regulatory role in a variety of physiological functions of cells, and affect the development, invasion and migration of tumor cells through various pathways. The rat sarcoma virus (RAS) oncogene was discovered in 1980; this gene can stimulate the proliferation and differentiation of cells in human cancer cells and was classified as a small GTPase (4). Thereafter, the large family of small G proteins was discovered through continuous and in-depth exploration and research. According to their structure and function, these proteins have been subdivided into five subfamilies (that is, Ras, Rho, Rab, Arf/Sar and Ran) (5). The gene encoding the Ras superfamily of small GTPases is one of the most frequently mutated or dysregulated genes in human cancers.

Although these subfamilies have different physiological functions, they have a common mechanism of action, namely they can act as 'molecular switches'. Under the binding effect of the regulatory factors guanine nucleotide exchange factor (GEF) and GTPase activating protein (GAP), they can realize the cycle of activation and inactivation states through phosphorylation/dephosphorylation cycles, and transmit the upstream information to the downstream effectors through conformational changes (5). For example, members of the Ras family can regulate cell proliferation-related pathways through the activation of plasma membrane-localized GEFs, while members of the Arf family rely on endoplasmic reticulum (ER)-localized GEFs (for example, SEC12, an activator of SAR1) to initiate vesicular transport programs. The mechanism by which SAR1B of the Arf family initiates protein vesicular transport is discussed below.

Physiological mechanisms of SAR1B-mediated COPII complex formation. After synthesis, the protein undergoes preliminary processing and modification in the rough ER and is correctly folded and assembled to form a protein with a certain spatial structure. Subsequently, this protein is transported to the Golgi apparatus via vesicle transport at the exit site of the ER and then transferred to other organelles or secreted out of the cell from the Golgi apparatus. Whereas the process of transport from the ER to the Golgi requires that proteins be concentrated and packaged into vesicles, SAR1B can initiate vesicle assembly. The vesicles that package cargo proteins are known as the COPII shell protein complex and have the functions of selecting, binding, and concentrating the transported cargo proteins. The COPII shell protein complex consists of five core proteins (that is, SAR1B and the shell proteins SEC23, SEC24, SEC13 and SEC31). Among them, SAR1B is the most important component of the COPII shell protein complex (6). Initially, the selection of cargoes transported in the ER is performed by the SAR1B-SEC23-SEC24 complex. Subsequently, SAR1B is recruited to the ER exit site by SEC12, which is activated by SEC12 and binds to the ER membrane to initiate COPII shell assembly. SEC12 is a unique activator of SAR1B, an integral membrane glycoprotein localized to the ER that serves as a GEF, and a fragment of which was previously named as the transcription factor prolactin regulatory element binding protein. It has been shown that knockdown of SEC12 using small interfering RNA results in diminished SAR1B activation signaling at the ER exit (7). Activated SAR1B sequentially recruits the SEC23-SEC24 complex and the SEC13-SEC31 complex to complete the assembly of the inner and outer layers of the COPII coat, respectively (8). SEC23 and SEC31 acting as a GAP to dephosphorylate SAR1B. After cargo recruitment and concentration in the ER lumen mediated by SEC24, SAR1B recruits SEC13 and SEC31 to form the outer coating. Continuous formation of the outer coating leads to the deformation of the ER membrane, which is highly curved and subsequently shrinks and breaks off at the neck, ultimately forming the intact vesicle. Finally, the COPII shell protein complex carries cargo proteins for transport to the Golgi apparatus (Fig. 2). Although the process by which SAR1B initiates the assembly of COPII vesicles is well understood, the mechanism underlying its role in the process of membrane outgrowth and rupture remains poorly understood and needs to be explored (9).

This precise regulation guarantees the accurate transport of proteins in normal physiological activities and plays an important role in the transport of proteins and other nutrients in tumor cells. SAR1B is also able to play a dual role in basal metabolism and response to stress by receiving different signals from the cell and regulating the formation of COPII vesicles.

3. SAR1B regulates lipid metabolism in malignant tumor cells

SAR1B has a higher affinity for the shell protein SEC23 than SAR1A, leading to its unique ability of lipoprotein secretion (10). It was found that SAR1B is typically able to produce larger vesicles than SAR1A and highly associated with impaired lipid metabolism (3). Lipid metabolism is critical in cancer cell proliferation, survival and other biochemical processes. Lipid metabolism disorders have become a hallmark of malignant tumors. When nutrients (for example, lipids, proteins and nucleic acids) are enriched, the oncogenic signaling pathway directly enhances nutrient acquisition and promotes tumor cell proliferation, which is inextricably linked to the regulatory role of SAR1B in lipid transport.

Experimental results have shown that SAR1B is overexpressed in CRC cells. Knocking out SAR1B can inhibit the

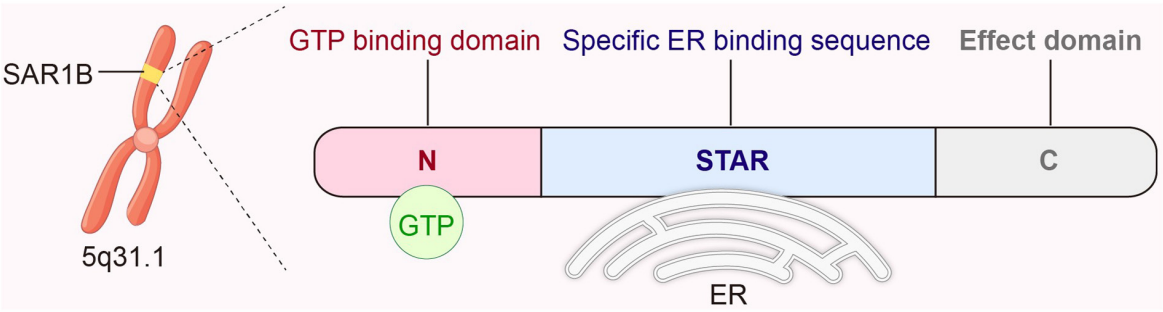

Figure 1. Schematic diagram of the SAR1B gene structure. SAR1B, secretion associated Ras related GTPase 1B; ER, endoplasmic reticulum.

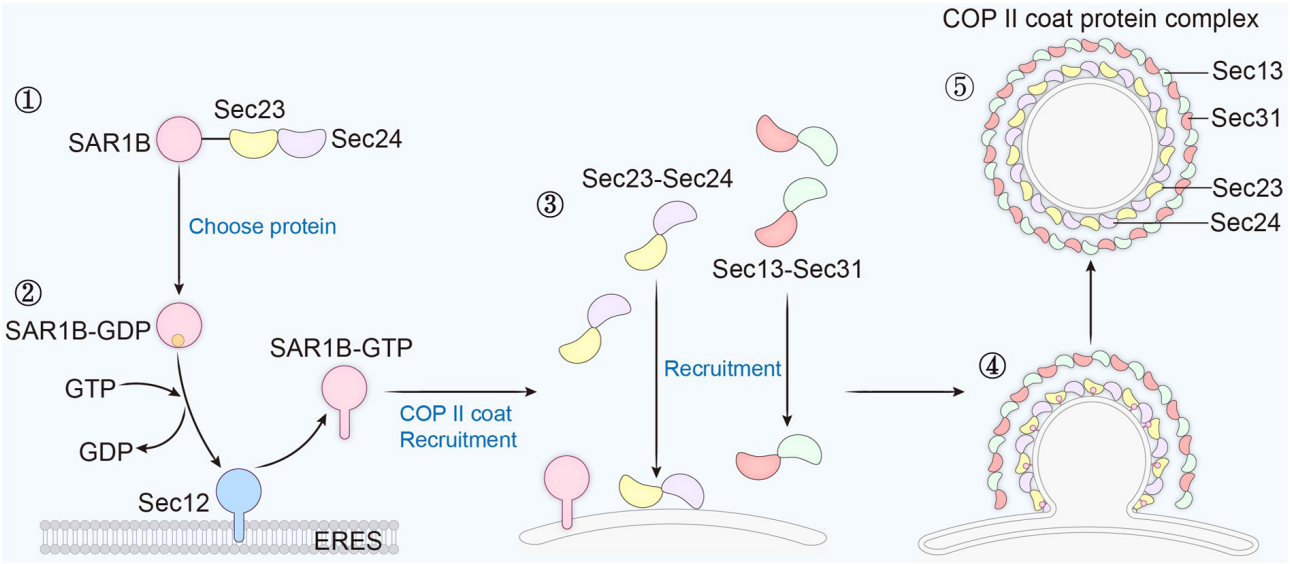

Figure 2. Schematic diagram of the synthesis of COPII coat protein complex at the endoplasmic reticulum exit sites mediated by SAR1B. COPII, coat protein complex II; SAR1B, secretion associated Ras related GTPase 1B; ERES, endoplasmic reticulum exit sites.

proliferation of CRC cells and induce apoptosis in RKO cells. This suggests that SAR1B may promote the proliferation of CRC cells and has a certain tumor-inducing effect (11). This may be related to the fact that SAR1B serves as a hub for lipid metabolism in tumor cells.

In addition, SAR1B can also affects lipid metabolism in tumor cells by regulating the transport of lipoproteins. SAR1B regulates lipoprotein delivery in concert with surfeit locus protein 4 (SURF4), a cargo receptor that is localized in the ER membrane. Several lipoproteins, including chymotrypsin, very low-density lipoprotein, and its transformation product low-density lipoprotein (LDL), transport insoluble lipids within the apolipoprotein envelope. There is evidence that SURF4 is involved in the transport of lipoproteins, and knockdown of SURF4 in hepatocytes drastically reduces plasma total cholesterol and triglyceride levels (12). LDL is the main carrier of cholesterol, cholesterol is an important structural component of cell membranes, malignant tumor cells proliferate rapidly and require a large amount of cholesterol to form new cell membranes, and the binding of LDL to its LDL receptor can deliver cholesterol to tumor cells and provide raw materials for cell membrane synthesis in rapidly proliferating tumor cells.

Cholesterol plays a crucial role in maintaining the integrity and function of cell membranes on the one hand. On the other hand, when cholesterol is in excess, it can lead to cytotoxicity. Cholesterol is an amphiphilic sterol molecule; SREBF1/sterol regulatory element-binding transcription factor 1 (SREBP-1) is a key lipogenic transcription factor and plays a critical role in maintaining cholesterol homeostasis in tumor cells (13). The activation of the PI3K/Akt/mTOR signaling pathway can induce the transcription of SREBPs and promote cholesterol uptake and synthesis to meet the needs of tumor cells (14). It has been confirmed that the deficiency of SAR1B can lead to a decrease in the level of SREBP-1, resulting in reduced lipogenesis (15). Therefore, SAR1B can indirectly regulate cholesterol homeostasis in tumor cells and play different roles at different stages of tumor progression.

The small intestine is an important site for transporting dietary fat in the form of lipoproteins. The lipolytic products generated by the digestion of food are absorbed by small intestinal epithelial cells. Chylomicrons, triglyceride-rich lipoproteins, and dietary lipid carriers produced by the processing of enterocytes will transfer dietary fat into the bloodstream through the lymphatic system for the body to utilize (15). Genetic defects in SAR1B will inhibit the transport of chylomicrons within enterocytes from the ER to the Golgi apparatus. As a result, the lipids and fat-soluble vitamins absorbed in the form of chylomicrons cannot be released into

the bloodstream, leading to a large amount of lipid accumulation in enterocytes. It has been shown that knocking out SAR1B in the human colorectal adenocarcinoma cell line Caco-2/15, which secretes chylomicrons, disrupts lipid homeostasis and leads to lipid accumulation (10). The deficiency of SAR1B not only interferes with lipid homeostasis in enterocytes, but lipid accumulation has also been observed in SAR1B-deficient livers (12). Cells with lipid metabolism disorders typically exhibit enhanced fatty acid synthesis, increased lipid uptake, and inhibited oxidation. This then gives rise to lipotoxicity, which causes oxidative stress. Oxidative stress promotes DNA damage in cancer, further leading to malignancy and carcinogenesis (14), and can trigger a series of intracellular signaling cascades, exacerbating tumor progression. Lipid accumulation can also enhance the downstream pro-cancer signal transduction by forming lipid rafts to enrich growth factor receptors (such as EGFR and HER2). It can be observed that SAR1B has a certain anticancer effect in some cases, although the specific mechanism remains to be explored.

SAR1B also regulates the formation of lipid droplets. Lipid droplets are intracellular organelles that are present in numerous types of cells and are generated after budding from the ER via the COPII vesicle pathway. Lipids stored in lipid droplets in tumor cells will provide energy support to tumor cells and are involved in the regulation of cell membrane production and signaling. In addition, lipid droplets can sequester chemotherapeutic drugs, reducing the effective concentration of drugs in tumor cells and making tumor cells resistant to chemotherapeutic drugs. The core of lipid droplets consists of triacylglycerol surrounded by phospholipid monolayers and surface proteins such as perilipin 2 (PLIN2). It has been shown that SAR1B mutations will result in reduced PLIN2 expression and can lead to mis-localization of PLIN2, which affects the morphology and integrity of lipid droplets and their ability to uptake and store lipids (16).

4. SAR1B responds to stress and regulates autophagy levels in cells

Unlike the physiological mechanism of SAR1B-mediated COPII vesicle formation, SAR1B can also regulate the level of cellular autophagy to maintain cellular homeostasis by forming the precursor components of autophagosome membranes under stress. Autophagy is a type of self-protection function during cellular stress, which is like a 'cleaner' of the cell, capable of removing damaged organelles (for example, mitochondria and ER), misfolded or aggregated proteins, as well as invasive pathogens. In this way, SAR1B can ensure the cell's stability in the presence of nutrients. Consequently, it guarantees cell survival under unfavorable conditions, such as nutrient deficiency and oxidative stress. Moreover, autophagy plays a key role in the development of organisms, immunity, aging, and the onset and progression of a variety of diseases (for example, neurodegenerative diseases and cancer) (17). The core of autophagy is the formation of autophagosomes. Autophagosomes are double-membrane vesicles produced during autophagy. They encapsulate aged or damaged organelles, proteins and other substances, and transport them to lysosomes for degradation. The resulting macromolecules are then recycled and reused. Autophagosome membranes are mainly obtained from the ER-Golgi transport system, and membrane precursors of autophagosomes are generated by membrane reorganization.

Under stress conditions such as starvation, the ER will generate two important sites: ER-Golgi intermediate compartment (ERGIC) and ER exit sites (ERES). Under normal homeostasis, ERGIC and ERES accomplish vesicular transport of proteins through SAR1-mediated generation of the COPII shell protein complex. Sec12 is an activator of COPII vesicle formation. In stress environments such as starvation, it can trigger the formation of a special type of COPII vesicle, known as ERGIC-COPII vesicles or derivative COPII vesicles. The formation and assembly of derivative COPII vesicles are also regulated by SAR1B. A key step in autophagosome biogenesis is the lipidation of microtubule-associated protein 1 light chain 3 (LC3) to generate the autophagosome membrane, and these derivative vesicles will serve as the membrane template for LC3 lipidation. The formation of derivative COPII vesicles is triggered by membrane contact, ER can form different membrane contacts with different organelles, such as mitochondria, to realize intercellular information transfer (18). Derived COPII vesicles are localized in ERGIC, and SEC12 is localized in ERES. Starvation-induced ERES enlarges and becomes tightly apposed to ERGIC and undergoes a membrane contact, which is typically <2 nm (19). Close membrane contact enables Sec12 located at the ERES to trans-activate the assembly of COPII on the ERGIC, triggers the generation of derivative COPII vesicles here, and further regulates the formation of autophagosomes (19). Subsequently, derivative vesicles generated at the ERGIC site can assume normal protein transport functions or continue to be used to generate autophagosome membrane precursors. It has been experimentally demonstrated that both the size and SEC12 of ERGIC are affected by starvation (20) (Fig. 3). Meanwhile, experiments have indicated that the overexpression of the Sar1 mutant protein leads to the inhibition of autophagosome formation, and knocking down Sar1 can reduce autophagosome formation (21). In an experiment searching for drugs against liver cancer drug resistance, knocking down SAR1B in liver tumor-initiating stem-like cells inhibited the formation of the autophagy-related gene LC3 II. When SAR1B was re-expressed, the inhibition of LC3 II formation was relieved, which supports the involvement of SAR1B in the formation of autophagosomes in tumor cells (22). Other families of small G proteins are also involved in this process. Following the formation of membrane precursors, the lipid composition of autophagosome membranes and the modification of membrane proteins are regulated by Rab family small GTPases (23,24). In addition, after their formation, intact autophagosomes approach lysosomes through microtubule networks and fuse with them to form autophagic lysosomes, which begin to degrade autophagosome contents and remove damaged organelles and aged proteins. The stability of the fusion process is regulated by Rho family small GTPases through the regulation of the cytoskeleton and affects the transport of autophagosomes within the cell, while Ras family small GTPases promote the expression of autophagy-related genes (25-28).

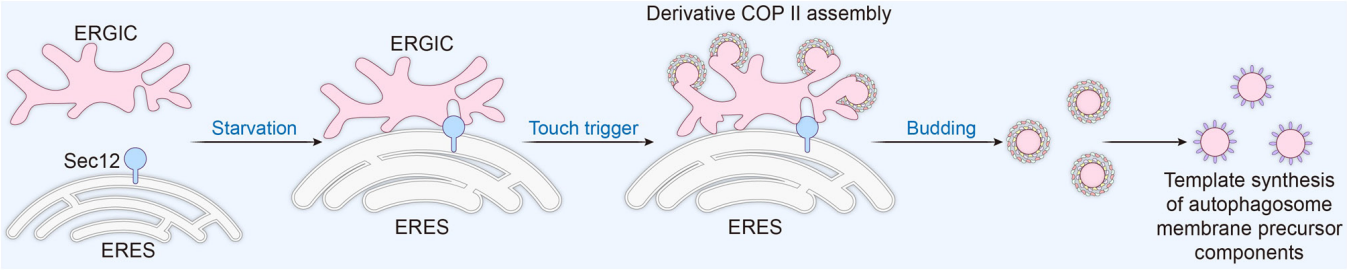

Figure 3. At the endoplasmic reticulum exit sites, membrane apposition with the ERGIC triggers the formation of COPII vesicles, which serve as templates for the formation of autophagosome membrane precursor components. ER, endoplasmic reticulum; ERGIC, ER-Golgi intermediate compartment; COPII, coat protein complex II; ERES, ER exit sites.

In states such as viral infection or oxidation, the intracellular protein structure is damaged. When a large number of proteins are misfolded or unfolded, they accumulate in the ER and cannot be transported out normally, causing a dysregulation of the ER homeostasis, which is termed ER stress (29). The deletion of SAR1B expression also induces an accumulation of proteins in the ER, which may result in the saturation of the ER's folding capacity (30). At this point, the body triggers an adaptive mechanism, that is, unfolded protein response, which restores ER homeostasis and exerts cytoprotective effects by attenuating protein translation, increasing the ER folding capacity, and increasing the ER protein degradation capacity. Unfolded protein response induces SAR1B expression, thus accelerating protein transport. However, in case of excessive or prolonged ER stress, autophagy is induced. Autophagy helps the cells to remove unfolded proteins and damaged ER, thereby relieving the ER stress, protecting the cell function, and preventing cell death (29).

Autophagy has contradictory effects on tumor cells and tumor progression. Autophagy can inhibit tumors in the early stages of tumorigenesis and maintain the genomic stability of cells by removing carcinogens and damaged components from the cells. Moreover, in the late stage of tumor development, autophagy can help tumor cells survive in harsh environments such as nutrient deficiency and hypoxia, provide tumor cells with necessary nutrients and energy, and promote tumor growth and metastasis (31). The application of SAR1B to regulate the autophagy level of tumor cells in different periods is particularly important and deserves further investigation.

5. SAR1B gene is involved in tumor cell signaling

SAR1B is involved in regulating the tumor Wnt/β-catenin signaling pathway and affects tumor migration. SAR1B is associated with the transduction of several tumor cell signaling pathways. Among them, SAR1B is involved in Wnt protein secretion of the Wnt/β-catenin signaling pathway. Aberrant activation of this signaling pathway is closely associated with the development of numerous tumors, and 90% of CRCs show β-catenin overexpression. Wnt is a secreted glycoprotein that is transported extracellularly via COPII vesicles to play its role, and it is essential for embryonic development and morphogenesis of adult tissues (32). Wnt is secreted into vesicles to control the output of functional ligands through the ER mechanism, and Wntless is an important intermediate in this pathway and a key regulator of Wnt protein secretion; its aberrant expression level affects Wnt signaling. Wnt ligand secretion mediator (Wls) enters the ER and binds to SEC12 and SAR1B, thereby synergistically initiating the assembly of the COPII complex. Wls is also able to bind to Wnt, facilitating its own interaction with SEC12 and SAR1B in the ER, while regulating the movement of mature Wnt vesicles out of the ER to the cell surface to perform their functions. Although the underlying mechanism remains unclear, Wnt-Wls binding in the ER may affect Wls-SEC12 binding through a change in Wls conformation that stabilizes Wls-SEC12 binding or exposes more SEC12 binding sites (33). When the Wnt molecule is defective in palmitoylation, this process is compromised, and the output of functional ligands is limited, potentially leading to the development of certain diseases (33). Abnormalities of SAR1B in this process lead to impaired Wnt secretion, while the downstream β-catenin continues to accumulate and activate downstream target genes. As a result, the cells gain the ability to proliferate indefinitely, which is also an important basis for tumorigenesis (Fig. 4).

The Arf subfamily proteins to which SAR1B belongs, as well as their GEF and GAP, are aberrantly expressed in different cancer cell types and human cancers through their involvement in regulating actin remodeling. In sequencing data from The Cancer Genome Atlas, the most common Arf genetic alterations are gene amplification in prostate, breast, squamous lung, esophageal and ovarian cancers, as well as invasive metastatic potential in glioblastomas, uveal melanomas, breast, colon, prostate and laryngeal squamous cell cancers, among others. Deletions of the Arf GTPase genome in cancer also occur, albeit more rarely (34).

SAR1B and the other members of the Arf subfamily are also capable of influencing the migration process of tumor cells through EMT. β-catenin is a key regulator of EMT, a biological process that causes epithelial cells to lose polarity and intercellular junctions and acquire mesenchymal cell properties. It confers the ability to metastasize and invade, and plays an important role in embryonic development, tissue repair and tumor metastasis. Most β-catenin is located on the cell membrane of epithelial cells. Under normal physiological conditions, intracellular β-catenin is at low levels and binds to E-cadherin (CDH1) to form a complex that anchors it to the actin cytoskeleton, enhancing intercellular adhesion and maintaining the integrity and stability of epithelial tissue. Once this binding is disrupted, intercellular adhesion is weakened, the polarity and organization of epithelial cells are affected, and cells are more

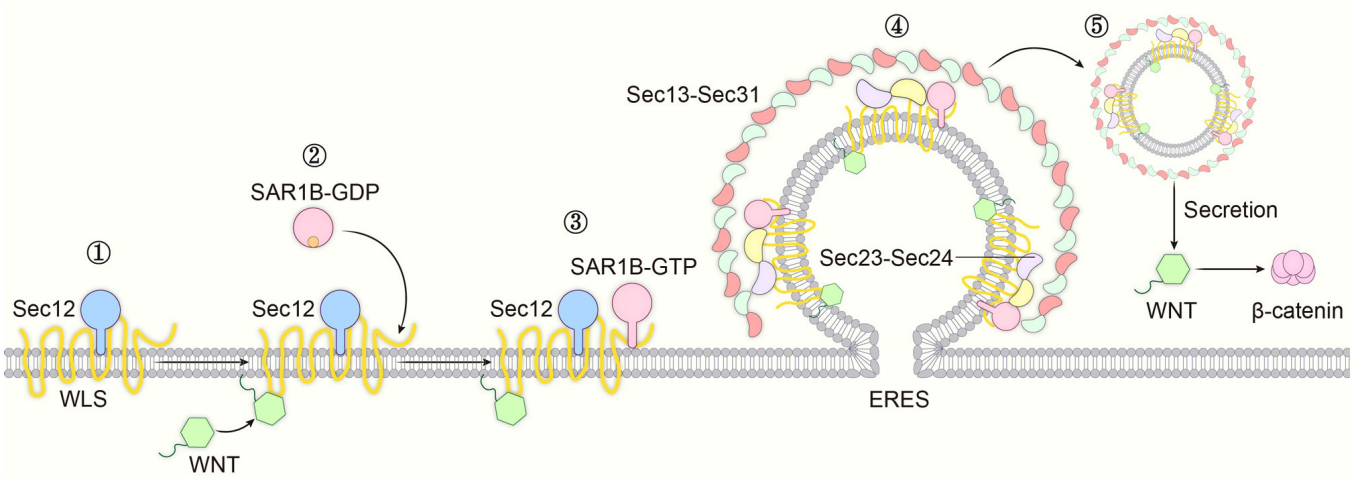

Figure 4. WNT is secreted via the SAR1B pathway and participates in the Wnt/β-catenin signaling pathway. SAR1B, secretion associated Ras related GTPase 1B; ERES, ER exit sites.

likely to detach from epithelial tissues, which is important in the process of tumor cell invasion and metastasis. In a variety of tumors, such as breast, colorectal and gastric cancers, the reduced expression of CDH1 is accompanied by abnormal activation and nuclear accumulation of β-catenin, which is closely related to tumor aggressiveness and poor prognosis (35). Experiments have shown that knockdown of SAR1B in CRC cells enhances the migration and invasion abilities of CRC cells and simultaneously leads to a significant reduction in the levels of the epithelial marker CDH1 and an increase in the mRNA expression of the mesenchymal marker vimentin. These findings suggested that the cells shifted towards a more mesenchymal phenotype. Therefore, SAR1B may inhibit the motility and metastasis of CRC cells by regulating EMT. Meanwhile, the deficiency of SAR1B can also stimulate EMT and promote cell motility and Transwell invasion (36). Lower levels of SAR1B mRNA expression were significantly associated with reduced survival and advanced disease stage in patients with CRC, patients with high expression of SAR1B have an improved prognosis, revealing a potential role for SAR1B in inhibiting CRC progression. SAR1B may serve as a prognostic biomarker and a potential inhibitor of metastasis in CRC tumor cells (36). Moreover, experiments have shown that SAR1A expression levels are elevated in patients with osteosarcoma, and SAR1A levels increase osteosarcoma lung metastasis. Furthermore, knocking down SAR1A can reduce the formation of platelet-like pseudopods in osteosarcoma cells, inhibit the EMT of osteosarcoma cells, and reduce the ability of osteosarcoma cells to invade and migrate (37). The function of SAR1A as a paralogous homolog of SAR1B, to some extent, also reveals the potential function of SAR1B.

As aforementioned, SAR1B can either promote or inhibit the proliferation of tumor cells by regulating lipid metabolism. Meanwhile, experiments have confirmed that SAR1B can promote the proliferation and inhibit the apoptosis of CRC cells. Additionally, SAR1B can suppress the migration and invasion of CRC by regulating EMT. It was found that SAR1B plays different roles at different stages of CRC development, bringing either positive or negative impacts on tumor cell activities. It is worth noting that numerous genes play different regulatory roles in the biological behavior of tumor cells within the same type of tumor. For example, Patched 1, a gene encoding a transmembrane protein, inhibits the proliferation of non-small cell LC (NSCLC) through its encoded protein. However, it also promotes the migration, invasion and adhesion of NSCLC cells through its 3'-untranslated region (38). A similar situation exists for the SAR1B gene in CRC cells. This interesting phenomenon is worthy of in-depth consideration and exploration.

SAR1B is involved in the regulation of the mTOR pathway

SAR1B as a leucine sensor for the mTOR signaling pathway. SAR1B is involved in the mTOR pathway through two pathways. The mTOR pathway is a key signaling pathway in cells. mTOR is a serine/threonine protein kinase that, together with a variety of regulatory-related proteins, form the mTOR complex 1 (mTORC1), which senses intracellular nutrients (for example, amino acids and glucose), energy levels, growth factors, and stress signals and promotes cell proliferation by regulating various aspects of protein synthesis, ribosome biogenesis and cell cycle progression (39). The small GTPase SAR1B plays a key role in the activation, signaling and functional regulation of the mTOR pathway.

Normally, mTOR helps cells proliferate, as well as and maintain their function and structure. However, abnormally high activity of mTOR may lead to excessive cell proliferation, which in turn may lead to the development of malignant solid tumors (for example, breast cancer, LC and ovarian cancer) and hematologic malignancies (for example, leukemia and lymphoma) (40). In addition, abnormalities of mTOR have been associated with the development of certain neurological diseases, such as cognitive impairment and Parkinson's disease (41). Sustained activation of the mTOR signaling pathway promotes cell proliferation and survival and inhibits autophagy. In neurological diseases, it leads to abnormal changes in neurons, interferes with the normal transmission and processing of neural signals, and thus affects the brain's information integration and

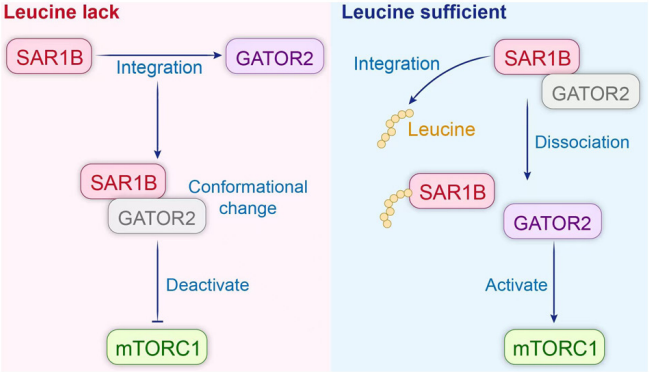

Figure 5. SAR1B acts as a leucine sensor and participates in the regulation of the mTOR signaling pathway by influencing the conformation of GATOR2. SAR1B, secretion associated Ras related GTPase 1B; GATOR2, GAP activity towards Rags 2.

cognitive functions. For example, it may cause increased neuronal excitability or excessive synaptic growth. Alternatively, it may result in the failure to clear unhelpful proteins in the brain through autophagy, leading to their deposition in the brain and damage to neuronal functions. As an illustration, the deposition of amyloid-β (Aβ) in the brain to form amyloid plaques causes Alzheimer's disease (42). In tumors, the continuous activation of mTOR is manifested as promoting the proliferation and metastasis of tumor cells. For instance, the abnormal activation of the PI3K-Akt-mTOR signaling pathway can promote tumor cell proliferation, survival, metabolic reprogramming and angiogenesis (43).

Leucine can act as an upstream regulator of the mTOR pathway, entering the cell via amino acid transporter carriers on the cell membrane and regulating the mTORC1 signaling pathway and subsequent protein synthesis processes (44). SAR1B can act as a leucine sensor to regulate mTORC1 signaling based on intracellular leucine levels. GAP activity towards Rags 2 (GATOR2) is an activator of mTORC1; SAR1B senses the intracellular leucine level through GATOR2 to regulate mTORC1 signaling. In the absence of leucine, SAR1B binds to GATOR2 and undergoes a conformational change, losing its activating function for mTORC1 and, thus, inhibiting mTORC1. Under leucine-sufficient conditions, SAR1B binds to leucine, undergoes a conformational change, and dissociates from GATOR2, which acts to activate mTORC1. Binding status does not affect their function in mTORC1 regulation (Fig. 5) (45). Knockdown of SAR1B renders mTORC1 insensitive to amino acid depletion and specifically affects the regulation of mTORC1 by leucine, without influencing other amino acids. Re-expression of SAR1B can restore the sensitivity of mTORC1 to leucine. The SAR1B mutant fails to bind to GATOR2 and loses its inhibitory effect on mTORC1 under leucine-deficient conditions. Therefore, it can be observed that SAR1B is essential for the inhibition of mTORC1 under leucine-deficient conditions, and the leucine-sensitive interaction between SAR1B and GATOR2 is crucial for the regulatory effect of SAR1B on mTORC1 (45).

Deficiency of the small GTPase SAR1B is associated with lung carcinogenesis. In a mouse lung *in situ* xenograft tumor model, deficiency of SAR1B and its homologue SAR1A eliminated leucine sensitivity and failed to inhibit mTORC1 and significantly promoted the mTORC1-dependent tumor growth. Immunohistochemical staining revealed higher levels of the anabolic marker pS6 and the proliferation marker Ki-67 and lower levels of the catabolic marker light chain 3B in SAR1A- and SAR1B-deficient tumors. Silencing of SAR1A and SAR1B in cells resulted in sustained activation of mTORC1, which in turn led to tumorigenesis. Bioinformatics analysis showed that SAR1B is frequently absent in human lung squamous cell carcinoma and lung adenocarcinoma, and that patients with cancer with lower levels of SAR1B expression have a poorer prognosis. Therefore, SAR1B is most likely a tumor suppressor in LC (45). The mechanism of cancer inhibition may be related to the modulation of leucine levels by SAR1B, which affects the mTOR signaling pathway. SAR1B can be used as a prognostic marker for LC, and compounds selectively targeting SAR1B-dependent mTORC1 signaling may have potential for use in the treatment of LC.

SAR1B regulates the formation of autophagosomal membrane precursors associated with the mTOR pathway. In addition to the core molecular mechanisms involved in the formation of autophagosomes and autophagosomal membranes, the complex signaling cascades that control autophagy are also particularly important. Among them, the mTOR pathway is the core but not the only one. mTORC1 regulates anabolism and catabolism to meet the needs of cell proliferation. In proliferating cells, highly active mTORC1 promotes the synthesis of biomolecules while inhibiting autophagy. When mTORC1 is activated, it can phosphorylate and inhibit autophagy-associated proteins, thereby inhibiting the formation of autophagosomes and the autophagic process involving the small GTPase SAR1B. By contrast, when the activity of mTORC1 is inhibited under nutrient-deficient or stress conditions, the autophagic process is activated, and cells can degrade and recycle intracellular proteins and organelles through the formation of autophagosomes to maintain cell survival and energy (46).

Dysregulation of mTORC1 is associated with autophagy-deficient diseases. Autophagy requires the involvement of COPII-derived vesicle transport, and vesicle generation is regulated by SAR1B. The mTOR inhibitor rapamycin can treat cancer by upregulating autophagy levels. Drugs have been successfully developed based on the GTP-binding ability of SAR1 and its ability to mediate vesicle formation to regulate autophagy levels. $CD133^+$ liver tumor-initiating stem cell-like cells isolated from mouse and human liver tumors drive early tumor initiation and recurrence and are chemo-resistant to mTOR inhibitors, which may lead to drug-resistant epilepsy and hepatocellular carcinoma recurrence. The chemo-sensitizing drug baicalein (BC), which was developed based on the resistance of hepatocellular carcinoma cells to mTOR inhibitors, can block mTOR inhibitor-induced autophagy through competitive inhibition of the GTP-binding ability of SAR1B GTPase, and thus has a chemo-sensitizing effect. BC binds and inhibits small GTPases involved in vesicle transport, and the binding of SAR1B to GTP is blocked. Without the binding of SAR1B to GTP, vesicles cannot be generated, the autophagosome membrane cannot be synthesized normally,

and autophagosome generation is reduced, thus inhibiting the autophagy process. BC-treated tumor tissues show a significant reduction of active SAR1B. Nanobead pull-down and mass spectrometry, biochemical binding assay and three-dimensional computational simulation, as well as activity analysis of BC binding site showed that the main binding site of BC is the NH 2-terminal motif of SAR1, which is responsible for the activation of SAR1 as well as involved in its interactions with GEF SEC12, including GEF-binding and GAP-binding. The BC-mediated SAR1B-dependent autophagy inhibition was attributed to its chemo-sensitizing effect; inhibition is the basis of its chemo-sensitizing effect. Therefore, SAR1B could be a novel target for anticancer effects in liver tumor-initiating stem cell-like cells and HCC cells that are resistant to mTORC1 inhibition (22).

6. Discussion and future perspectives

As a core regulator of COPII vesicle trafficking, SAR1B plays a role in tumor cell genesis, development, proliferation, migration, substance metabolism, autophagy level, signal transduction, and therapeutic resistance by mediating protein secretion. SAR1B has the potential to be used as a prognostic marker in lung and CRCs, and it has become a therapeutic target for drug resistance in hepatocellular carcinoma. SAR1B has been shown to promote cell proliferation and inhibit tumor cell metastasis in CRC cells, maintain cellular homeostasis by regulating autophagy and removing intracellular carcinogens under normal cellular stress, and help tumor cells regulate autophagy to ensure their survival under nutrient-deficient conditions and provide energy support to tumor cells by affecting their lipid metabolism. Therefore, SAR1B has opposite functions in various biological behaviors of malignant tumors. Of course, there are still some thorny issues to be resolved. The mechanism by which SAR1B promotes the proliferation of tumor cells in CRC, the mechanism through which SAR1B inhibits the proliferation of LC cells, the reason why it has completely opposite effects in different types of tumors, whether SAR1B inhibits mTORC1 and suppresses cancer proliferation regardless of the presence of leucine, and if the effect of SAR1B on the mTOR pathway can be observed in tumor types other than LC, remain unexplored. The application of the two sides of SAR1B, rational utilization of its cancer inhibitory function, and identification of therapeutic targets against its cancer-promoting mechanism have become major challenges in this field. In addition, whether SAR1B also mediates the transport of some proteins that are highly relevant to various biological behaviors of tumor cells remains unknown. Thus, further investigation is warranted to address these challenges.

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Authors' contributions

HL was responsible for establishing the framework of the manuscript. QY undertook the task of literature retrieval, composed the manuscript, and crafted the accompanying illustrations. GH, CL and ZL offered professional guidance and were actively involved in the meticulous revision and refinement of the article. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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