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REVIEW ARTICLE

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The TRAP complex (SSR1–SSR4): mechanistic roles and therapeutic opportunities

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ABSTRACT

Background: Esophageal squamous cell carcinoma (ESCC) is a highly aggressive cancer with a poor prognosis, and its molecular mechanisms remain unclear. Our previous research identified the signal sequence receptor subunit delta (SSR4) of the TRAP complex as a potential ESCC biomarker. The TRAP complex, composed of SSR1, SSR2, SSR3, and SSR4, is essential for protein translocation, folding, and quality control, crucial for cellular balance. While individual TRAP subunits have been studied, a comprehensive understanding of their roles in human diseases is lacking.

Aim: This review synthesizes current evidence on the TRAP complex and its subunits (SSR1-SSR4) to clarify their roles in tumor progression and other diseases, identify knowledge gaps, and evaluate their potential as therapeutic targets.

Results: The study shows that TRAP subunit genes are significantly upregulated in various cancers, influencing tumor progression and immune infiltration, with some subunits showing different responses to chemotherapy. A pan-cancer analysis highlights their roles, while SSR3 and SSR4 mutations are linked to congenital glycosylation disorders. SSR1 and SSR3 are essential for glucose metabolism and are associated with diabetes risk. The interaction between TRAP and endoplasmic reticulum stress suggests potential therapeutic applications.

Conclusion: This review emphasizes the crucial roles of the TRAP complex and its subunits (SSR1-SSR4) in various diseases, highlighting their potential as therapeutic targets and biomarkers. Future research should focus on understanding the mechanisms through integrated experimental and multi-omics approaches, defining subunit interactions, and exploring structure-based drug design for clinical applications.

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Introduction

Esophageal squamous cell carcinoma (ESCC) is a malignant tumor with high morbidity and mortality rates worldwide. According to epidemiological studies, ESCC accounts for approximately 90% of the 456,000 new cases of esophageal cancer each year [1]. The 5-year survival rate of patients with ESCC is usually <20% [2], mainly because of its strong invasiveness, easy recurrence, and early lymph node metastasis. Studies have shown that although the risk of lymph node metastasis in patients with T1 ESCC is low, it is increasing, especially in cases of deep submucosal infiltration [3]. Lymph node positivity is an independent prognostic factor in ESCC [4]. Researchers are exploring new treatment strategies and biomarkers to improve the prognosis of patients with ESCC. Immunotherapy shows promise for ESCC, especially the use of immune checkpoint inhibitors [5,6]. Furthermore, new biomarkers associated with immune infiltration have been identified, which may contribute to early diagnosis and treatment decisions, helping to improve patient prognosis [7].

Lugol's iodine staining is an important method for the endoscopic diagnosis of ESCC. The esophageal squamous epithelium can present a powder-staining sign owing to the lack of glycogen in the lesion,

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and the biological basis of this phenomenon is abnormal glucose metabolism [8,9]. Glycolytic reprogramming, a hallmark of early carcinogenesis, plays a pivotal role in ESCC pathogenesis [10]. Therefore, we established a prognostic model for ESCC based on a glucose metabolism-related gene set, including four model genes [11]. For subsequent studies, we screened signal sequence receptor subunit delta (SSR4) from the model genes. First, we verified the high expression of SSR4 in ESCC tissues at both the mRNA and protein levels. By collecting clinical samples, we analyzed the correlation between SSR4 and clinicopathological features as well as immune infiltration [12]. The selection of SSR4 was particularly intriguing because, beyond its role in our metabolic model, it encodes a critical subunit of the translocon-associated protein (TRAP) complex, a key regulator of protein biogenesis within the endoplasmic reticulum [13]. The TRAP complex is a crucial entity in cellular biology, consisting of four subunits: signal sequence receptor subunit alpha (SSR1/TRAPα), signal sequence receptor subunit beta (SSR2/TRAPβ), SSR3 signal sequence receptor subunit gamma (SSR3/TRAPγ), and SSR4/TRAPδ [13]. Relevant studies have explored the phenotypes and biological functions of these genes, not only in ESCC but also in other malignant tumors and non-tumor diseases, such as metabolic diseases. In 2020, Russo et al. summarized the functions of the TRAP complex from several aspects; however, this review focused more on its structural properties without elucidating more details of the four genes encoding the four subunits [14]. The literature on this aspect is rarely summarized.

Therefore, this review aims to systematically integrate contemporary clinical and basic research evidence to synthesize mechanistic insights regarding the roles of the TRAP complex and its subunits (SSR1–SSR4) in both oncogenesis and non-neoplastic diseases. Through this integration, we seek to identify existing knowledge gaps and assess the potential of these components as therapeutic targets across diverse organ systems, thereby establishing a foundational framework for future research. To this end, we first systematically evaluate the current evidence for each TRAP subunit (SSR1–SSR4) in oncogenesis and non-neoplastic diseases.

Search strategy, inclusion, and exclusion criteria

The search strategy contained medical subject headings and words for TRAP, SSR1, SSR2, SSR3, and SSR4. The detailed search strategy, inclusion, and exclusion criteria for use in MEDLINE *via* PubMed are listed in Supplemental Table S1. Our initial search yielded 298 records. After removing duplicates and screening titles and abstracts, 91 full-text articles were assessed for eligibility. Ultimately, 79 studies that met the inclusion criteria were included in this comprehensive review. The key characteristics of the included studies, categorized by the primary TRAP subunit investigated and disease context, are summarized in Tables 1 and 2.

SSR1

High expression of SSR1 reportedly indicates poor prognosis in patients with breast cancer, colon cancer, and hepatocellular carcinoma (HCC). Furthermore, SSR1 was independently associated with advanced TNM stage, suggesting the potential application of tissue-specific prognostic markers [15–17]. From the bioinformatic analysis, it was observed that SSR1 may promote cell proliferation by activating several pathways, such as the TGF-β pathway in HCC [16]. Both KEGG and GSEA analyses showed that the gene set of SSR1 high-expression samples was significantly enriched in the TGF-β signaling pathway [16]. This pathway, however, remains unverified as there is no experimental confirmation. Based on its function within the TRAP complex in the ER, we speculate that SSR1 is associated with the maturation and secretion of TGF-β ligands. Furthermore, SSR1 knockdown has been shown to inhibit tumor activity (proliferation and migration) [17]. In contrast, elevated SSR1 expression promotes HCC metastasis through the induction of epithelial–mesenchymal transition (EMT) and is negatively correlated with Th2 cell infiltration, suggesting regulation of the immune microenvironment [18]. However, healthy cells can present with TAP-independent SSR1 peptides under inflammatory conditions, suggesting that SSR1-based immunotherapy should carefully verify antigen expression in healthy tissues to avoid toxic reactions [19]. Therefore, while multiple reports consistently indicate SSR1's pro-tumorigenic functions [16–18], future studies should aim to standardize experimental conditions and utilize large, multi-center cohorts to validate these observations, strengthening the evidence base. More specific strategies (see below) are warranted.

Table 1. The summary of SSR1, SSR2, SSR3, and SSR4 genes in cancers.

Gene	Disease	Oncogenic/ protective	Pathway	Prognostic/ predictive	Source of evidence	References
SSR1	Breast cancer /CRC	Oncogenic	–	Prognostic biomarker	Bioinformatics	[15]
SSR1	HCC	Oncogenic	–	Prognostic biomarker Predictive biomarker	Bioinformatics/*In vitro*	[16,17]
SSR1	HCC	Oncogenic	EMT pathway	Prognostic biomarker Predictive biomarker	Bioinformatics/*In vitro*	[18]
SSR1	HSCC	Oncogenic	RP11-156L14.1-miR-548ao-3p-SSR1 axis	–	Bioinformatics/ *In vitro/In vivo*	[19]
SSR1	GBM	Oncogenic	PBX2-circTLK1-miR-452-5p-SSR1-JAK/ STAT axis	–	Bioinformatics/ *In vitro/In vivo*	[20]
SSR2	HCC	Oncogenic	Hippo pathway	Prognostic biomarker Predictive biomarker	Bioinformatics/ *In vitro/In vivo*	[21]
SSR2	HCC	Oncogenic	–	Prognostic biomarker Predictive biomarker	Bioinformatics/*In vitro*	[22]
SSR2	HCC	Oncogenic	–	Prognostic biomarker Predictive biomarker	Bioinformatics/ *In vitro/In vivo*	[23]
SSR2	HCC	Oncogenic	EMT pathway	Prognostic biomarker Predictive biomarker	Bioinformatics/ *In vitro/In vivo*	[24]
SSR2	HCC	Oncogenic	SNHG14-miR-876-5p-SSR2 axis	Prognostic biomarker	Bioinformatics/*In vitro*	[25]
SSR2	GC	Oncogenic	RP11-874J12.4-miR-3972-SSR2 axis	–	Bioinformatics/*In vitro*	[26]
SSR2	Melanoma	Oncogenic	ER-stress-UPR-XBP1s-SSR2 axis	Prognostic biomarker Predictive biomarker	Bioinformatics/*In vitro*	[27]
SSR3	HCC	Oncogenic	–	Prognostic biomarker	Bioinformatics	[28,29]
SSR3	CRC	Oncogenic	–	Prognostic biomarker Predictive biomarker	Bioinformatics	[30]
SSR3	HNSCC	Oncogenic	–	Prognostic biomarker	Bioinformatics	[31]
SSR3	Pan-cancer	Oncogenic	Positive correlation with PD-L1, TGF-β	Prognostic biomarker Predictive biomarker	Bioinformatics/*In vitro*	[32]
SSR3	Breast cancer /GBM	Protective	Regulation of the TRAP-SSR3-IRE1α axis	Predictive biomarker	Bioinformatics/ *In vitro/In vivo*	[33]
SSR4	COAD	Protective	–	Prognostic biomarker	Bioinformatics	[34]
SSR4	CRC	Oncogenic	Cell cycle (S/G1); ROS accumulation	–	*In vitro*	[35]
SSR4	ESCC	Oncogenic	–	Prognostic biomarker	Bioinformatics	[11,12]
SSR4	GC	Oncogenic	Regulate the expression of NDUFB11 and ATP6AP1	Prognostic biomarker	*In vitro/In vivo*	[36]

Notes: The pathways presented in this table only show those that have been verified by wet experiments, and pathways acquired from only the bioinformatics analysis are not displayed. TRAP, translocon-associated protein complex; SSR1, signal sequence receptor subunit alpha; SSR2, signal sequence receptor subunit beta; SSR3, signal sequence receptor subunit gamma; SSR4, signal sequence receptor subunit delta; COAD, colon adenocarcinoma; CRC, colorectal cancer; ROS, reactive oxygen species; HCC, hepatocellular carcinoma; HNSCC, head and neck squamous cell carcinoma; GBM, glioblastoma multiforme; ESCC, esophageal squamous cell carcinoma; GC, gastric cancer; EMT, epithelial–mesenchymal transition; HSCC, hypopharyngeal squamous cell carcinoma; UPR, unfolded protein response; XBP1s, X-Box Binding Protein 1s; ER, endoplasmic reticulum.

Interestingly, lncRNA RP11-156L14.1 upregulates SSR1 expression by competitively binding to miR-548ao-3p, driving hypopharyngeal squamous cell carcinoma proliferation and migration [20]. In addition, circTLK1 upregulates SSR1 expression by adsorbing miR-452-5p and activating the JAK/STAT signaling pathway to promote glioma development [21].

SSR1 also plays critical roles in non-oncological diseases. For example, in patients with Parkinson's disease, the level of SSR1 in peripheral blood was negatively correlated with the loss of dopaminergic neurons in the substantia nigra [22]. A diagnostic model of intervertebral disc degeneration based on glycolysis-related genes (including SSR1) showed that high SSR1 expression was associated with CD8+ T cell infiltration, suggesting a role for immune metabolic interactions in degeneration [23], which is consistent with the results of Guo et al. [24].

Notably, in 2012, a large-scale genome-wide association analysis (133,010 individuals without diabetes) found that SSR1 adjacent loci were associated with blood glucose regulation, suggesting that SSR1 may indirectly affect metabolic pathways; however, the mechanism remains to be elucidated [25]. In one relatively small sample study (5,777 patients with type 2 diabetes and 7,956 individuals with normal fasting glucose levels), the SSR1 gene polymorphism (rs9505118) was found to be associated with decreased β-cell function; however, there was no significant association in gestational diabetes mellitus [26], a conclusion similar to that of Muntean et al. [27]. Deletion of the TRAP complex (including SSR1) resulted in a decrease in insulin precursor synthesis, and overexpression of TRAPα could partially restore β-cell function, revealing the key role of SSR1 in insulin biosynthesis [28]. In addition, as a stress-response molecule in adipocytes deficient in FABP4, SSR1 is involved in maintaining endoplasmic reticulum (ER) homeostasis [29]. Through m6A modification, circSSR1 promotes SSR1 protein translation and activates the ER stress-dependent pyroptosis pathway to drive pulmonary hypertension [30].

SSR2

Valuable insights into the molecular pathways involving SSR2 in tumor progression have been reported. SSR2 is highly expressed in HCC tissues at both the mRNA and protein levels [31–35]. A significant positive correlation between the expression of SSR2 genes and clinical TNM stage was found in HCC [32], which was associated with poor disease-free survival and overall survival [31–34]. As determined by the bioinformatic analysis, SSR2 is positioned as a co-expression partner of a member of the Ras-related in brain family, which may indirectly affect tumor biology, especially the regulation of HCC by participating in cellular processes such as the regulation of vesicle transport, which may represent a key mechanism by which tumor cells upregulate inhibitory factors (PD-L1, TGF-β) to suppress the function of immune cells [35]. Phenotypically, SSR2 promotes the proliferation, migration, and invasion of HCC cells, and knocking down SSR2 can inhibit G2/M phase transformation, induce HCC cell apoptosis [33] through modulating EMT [34]. Furthermore, overexpression of SSR2 reversed the suppressive roles of SNHG14 depletion in HCC by acting as a sponge for miR-876-5p [36]. Moreover, knockdown of SSR2 significantly enhanced the sensitivity of HCC to cisplatin by activating the Hippo pathway (inhibiting YAP dephosphorylation), and subsequent animal experiments confirmed that the SSR2/Hippo axis is a new target for overcoming chemotherapy resistance [31].

In gastric cancer, RP11-874J12.4 knockdown markedly inhibited cancer cell growth *in vivo*, which was associated with increased tumor expression of miR-3972 and decreased expression of SSR2, and enhanced the resistance of gastric cancer cells to cisplatin [37]. The potential of SSR2 as a drug-resistance target in melanoma is also worth noting [38].

In a murine model of SSR2 deficiency, aberrant syncytiotrophoblast cells within the placenta resulted in cardiac developmental anomalies. This study was the first to establish that SSR2 deficiency induces congenital heart disease *via* placental-embryo interactions [39].

SSR3

SSR3 is highly expressed in HCC, is positively correlated with tumor size, TNM stage, and differentiation, and is an independent marker of poor prognosis [40]. Thus, SSR3 may accelerate HCC progression by promoting HCC cell proliferation [41]. A colorectal cancer metastasis prediction model based on SSR3 and other genes was constructed, and SSR3 was found to promote metastasis by regulating the ER protein processing pathway [42,43]. Furthermore, a panel of molecular prognostic markers, including SSR3 and two other genes, was identified for head and neck squamous cell carcinoma; however, further validation did not focus on the SSR3 gene [44].

Through pan-cancer analysis, Hu et al. reported that the SSR3 gene plays a vital role in various human cancers. Specifically, high expression of SSR3 was associated with the upregulation of PD-1 and a decrease in CD8+ T cell infiltration, suggesting that it negatively regulates the response to immunotherapy [45]. Furthermore, it is indicated that high levels of SSR3 enhance the sensitivity of breast cancer and glioblastoma to paclitaxel by regulating IRE1α phosphorylation [46].

Similarly, the role of SSR3 in non-tumorous diseases cannot be ignored. In 2011, Yamaguchi et al. reported that SSR3 is required for vascular network formation in mouse placentas [47]. The SSR3 mutation is the cause of a novel congenital glycosylation disorder (TRAPγ-CDG) [48], leading to the defect of ER glycoprotein transport and the asymmetric deletion of N-glycosylation sites in the chorionic plate region, confirming its key role in protein quality control [49]. Co-localization of fat distribution GWAS signals and SSR3 expression is associated with metabolic syndrome, suggesting a potential role in the regulation of adipose tissue function [50].

In further research, it was found that SSR3 was rapidly upregulated in a high-glucose environment and promoted the transport of insulin precursors across the ER membrane; knocking out SSR3 blocked glucose-induced insulin synthesis (reduced by 50%) [28]. Furthermore, SSR3 expression was found to be associated with abnormal plantar pressure distribution and may be used as an early biomarker for diabetic foot ulcers without a deeper exploration of the underlying mechanism [51]. Recently, a chronic obstructive pulmonary disease protein biomarker identified by comparing 40 patients and 10 healthy controls, SSR3, is indicated to inhibit Th17 cell differentiation [52].

SSR4

There are few reports on the specific role of SSR4 in cancers. He et al. indicated that SSR4 is highly expressed in colon adenocarcinoma and is associated with advanced TNM staging and plasma cell infiltration [53], highlighting its potential as a prognostic biomarker. Notably, researchers have evaluated the impact of SSR4 on colon adenocarcinoma, mainly focusing on plasma cells. Combining the expression of SSR4 and the number of plasma cells, it was found that patients with high expression had longer overall survival. This was the first study to confirm SSR4 as a potential oncogene in colorectal cancer cells. SSR4 knockdown significantly inhibited cancer cell proliferation, induced cell cycle arrest (S/G1 phase) and apoptosis, and inhibited anchorage-independent growth [54]. In ESCC, SSR4 was detected based on a prognostic model and correlated with the clinical characteristics and immune infiltration [11,12]. Concerning overall survival in ESCC, SSR4 was an independent risk factor for prognosis, which was supported by the results of the univariate analysis. Based on public databases, high SSR4 expression was associated with poor overall and disease-free survival. Lower SSR4 expression indicated higher survival in our study; therefore, a long-term follow-up is necessary. Recently, Li et al. conducted *in vivo* and *in vitro* experiments, finding that SSR4 modulates the expression of NDUFB11 and ATP6AP1, thereby enhancing the functionality of mitochondrial respiratory chain complex I and complex V. This enhancement facilitates mitochondrial oxidative phosphorylation, contributing to the progression of gastric cancer [55].

A-to-I RNA editing was reported to be significantly enriched at the ubiquitination sites of the SSR4 gene, which is related to the clinical characteristics of tumors (such as SSR4 gene editing) and the activation of immune response pathways, providing clues for subsequent mechanistic exploration [56].

SSR4-congenital disorders of glycosylation (SSR4–CDG) is a rare, X-linked subtype of congenital disorders of glycosylation (CDG), primarily affecting male patients, and is caused by pathogenic variants in the SSR4 gene [57]. Several studies have suggested that SSR4 mutations can affect multiple organ development through *N*-glycosylation defects and SSR4–CDG, which manifest as a broad spectrum of clinical features, including neurological dysfunction (hypotonia, developmental delay, microcephaly, and neurodevelopmental abnormalities), connective tissue defects (skin redundancy and joint hypermobility), and cardiovascular involvement (congenital heart disease and non-ischemic cardiomyopathy). Additional phenotypes include laryngeal abnormalities, congenital diaphragmatic defects, growth retardation, glycosylation abnormalities (e.g. altered serum transferrin levels), oculomotor disturbances (nystagmus), and gastrointestinal manifestations (congenital diarrhea) (Figure 1) [57–65]. Thus, SSR4 is essential for

maintaining *N*-glycosylation homeostasis, and gene mutations can lead to glycosylation disorders. A variety of SSR4 gene variations have been found, including missense variation, deletion, and splicing variation [57,59,65–67]. For example, a study found a new typical splicing variant c.67 + 2T > C in a CDG-ly family [65], which resulted in the retention of 19 bp in the first 46 bp of intron 1 by identifying the false splicing site. These gene mutations lead to dysfunction of the TRAP complex, which in turn affects the N-linked glycosylation process [58]. With the development of high-throughput sequencing technology, gene sequencing has become an important tool to identify the pathogenic variation of the SSR4 gene [66,67].

Interestingly, the expression of the SSR4 gene was significantly upregulated in the inflammatory state, that is, during ER stress, and was co-expressed with the ER stress marker X-box binding protein1 (XBP1) [68]. This suggests that SSR4 is a key responsive component of the TRAP complex under stress conditions. The mechanism by which the TRAP complex (including SSR4) dynamically coordinates *N*-linked glycosylation quality control under ER stress is detailed in the following section [69].

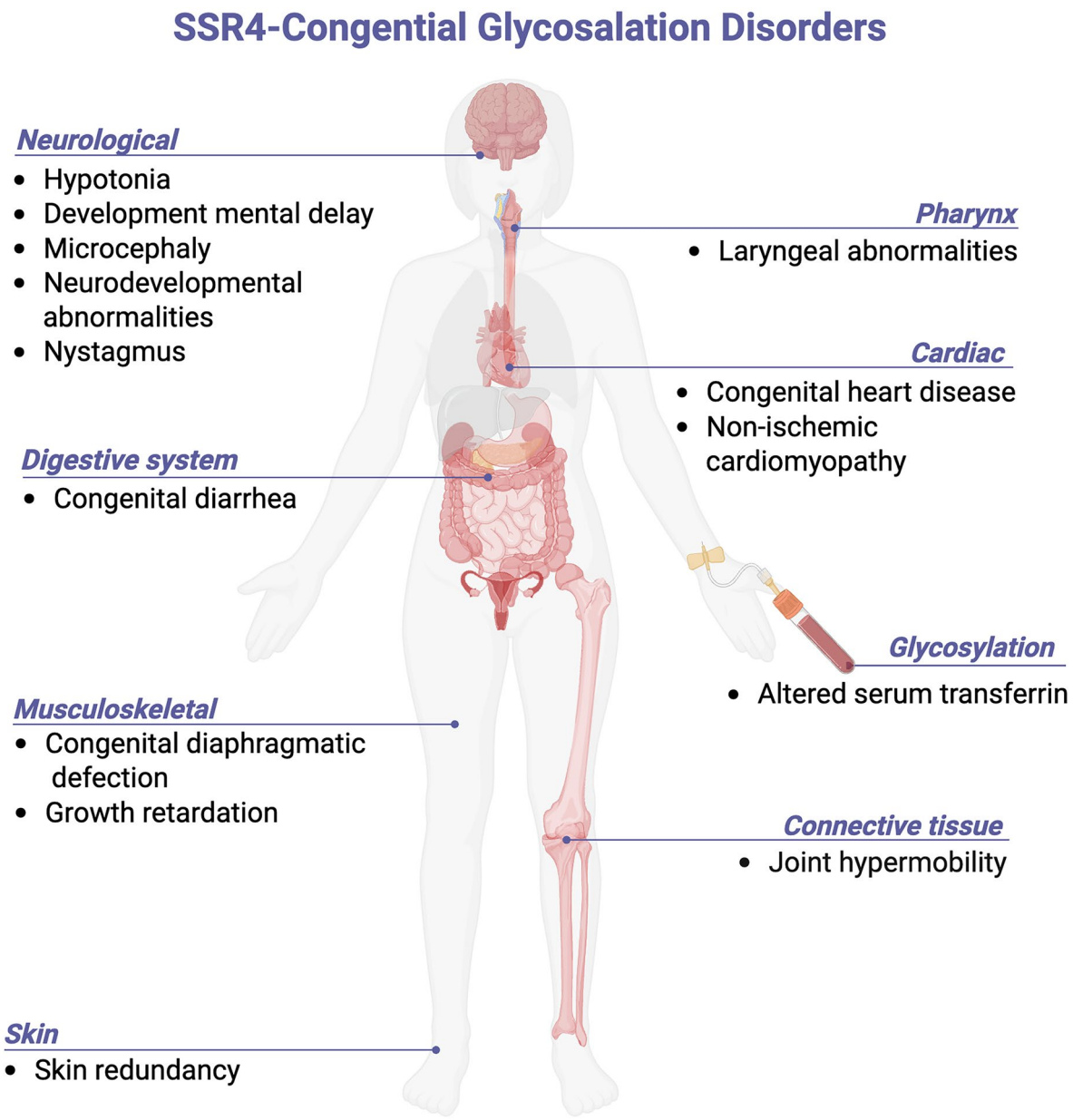

Figure 1. Summary of clinical features of SSR4-congenital glycosylation disorders. *Notes:* SSR4, signal sequence receptor subunit delta.

Collectively, the evidence above underscores distinct yet overlapping functions of individual TRAP subunits. The following section provides an integrated summary and pan-cancer perspective of these findings.

Summary of SSR1, SSR2, SSR3, and SSR4

Functions of the above genes in non-tumor diseases and the pan-cancer analysis are summarized in Figures 2 and 3, respectively. The pan-cancer analysis elucidated a complex expression landscape across the TRAP subunits. Notably, SSR1, SSR3, and SSR4 exhibited a consistent oncogenic pattern characterized by overexpression in tumor tissues relative to their normal counterparts (Figure 3A,C,D). In contrast, SSR2 emerged as a significant exception, displaying reduced expression in the majority of cancer types (Figure 3B). Interestingly, in HCC (LIHC in the figure), the SSR2 has a higher expression than in normal patients, which is in line with the cited research [31–35]. The observed phenomenon indicates that SSR2 may have varying functions across different types of cancer. These figures may help intuitively display the roles of

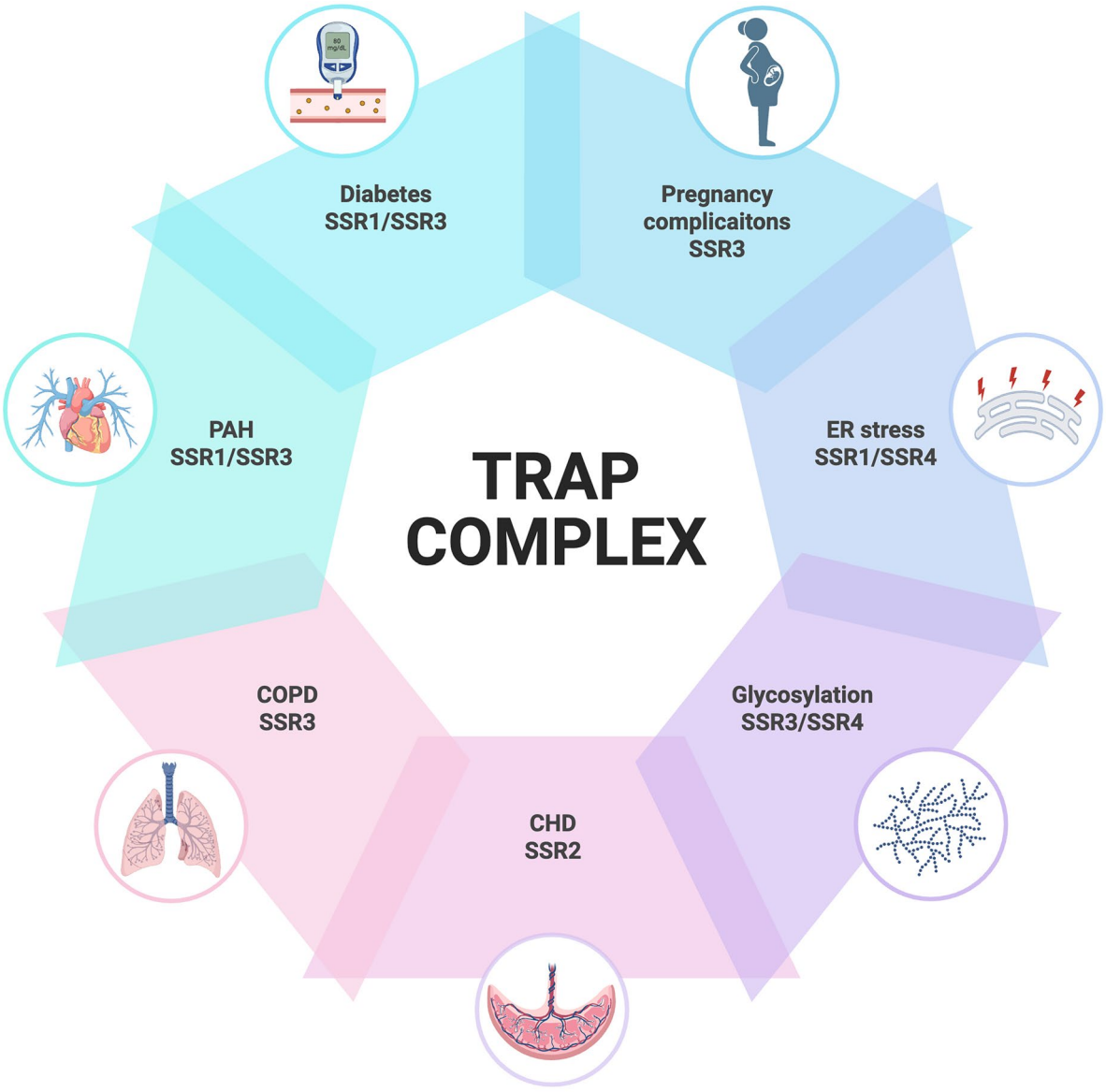

Figure 2. Summary of the role of the TRAP-complex genes in non-tumor diseases. *Notes:* TRAP, translocon-associated protein complex; SSR1, signal sequence receptor subunit alpha; SSR2, signal sequence receptor subunit beta; SSR3, signal sequence receptor subunit gamma; SSR4, signal sequence receptor subunit delta; COPD, chronic obstructive pulmonary disease; PAH, pulmonary arterial hypertension; CHD, congenital heart disease; ER, endoplasmic reticulum.

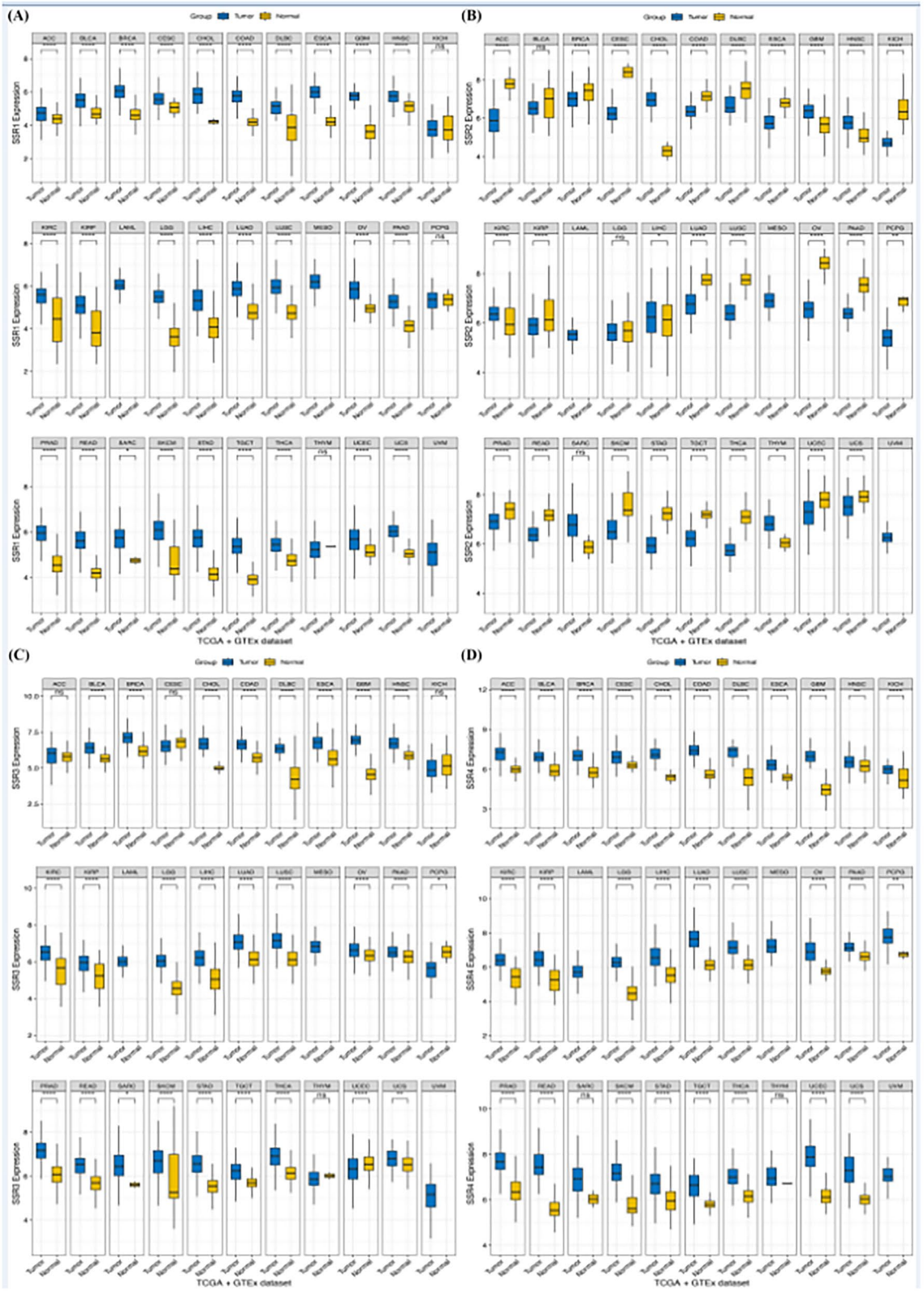

Figure 3. Pan-cancer analysis of the four genes. **(A)** SSR1; **(B)** SSR2; **(C)** SSR3; **(D)** SSR4.

subunits. Table 1 presents a comprehensive summary of the SSR1–SSR4 genes, detailing their associated diseases, pathways, and roles as oncogenic or protective, predictive, and prognostic biomarkers across various cancer types. Figure 4 and Table 2 provide a comprehensive overview of the primary functions of these four genes, encompassing their oncogenic, immunologic, and metabolic roles.

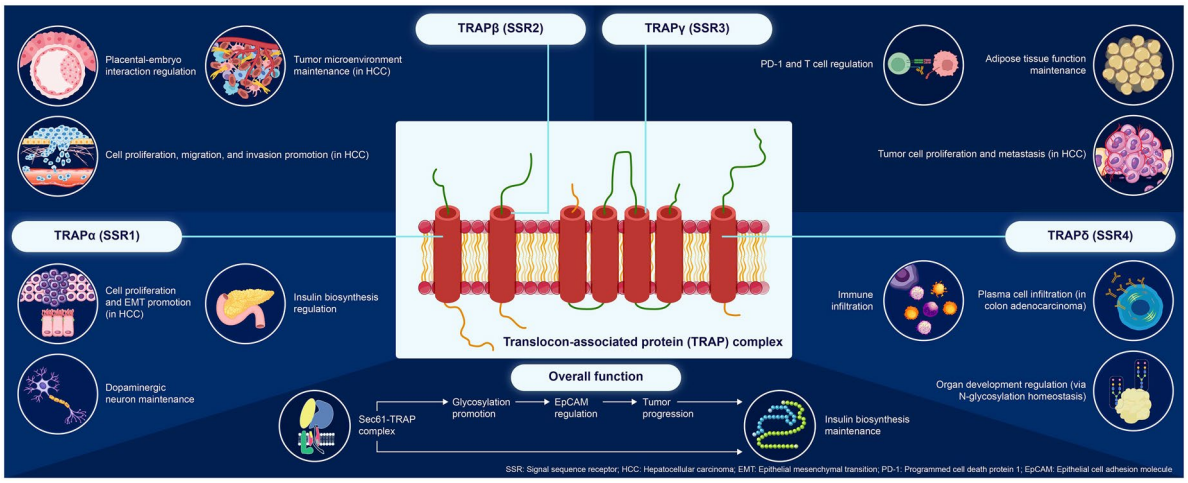

Figure 4. Summary of major functions of SSR1–SSR4. *Notes:* TRAP, translocon-associated protein complex; SSR1, signal sequence receptor subunit alpha; SSR2, signal sequence receptor subunit beta; SSR3, signal sequence receptor subunit gamma; SSR4, signal sequence receptor subunit delta.

Table 2. Roles of SSR1, SSR2, SSR3, and SSR4 genes in different aspects.

Function	SSR1	SSR2	SSR3	SSR4
Oncogenic	Up-regulation [15–18] Correlation with clinical characteristics [16,17] Promote cell proliferation, migration [17–19]	Up-regulation [21–23,27] Correlation with clinical characteristics [23] Promote cell proliferation, migration, induce cell apoptosis [21,23] Sensitivity to cisplatin [21,26] Resistance to BRAF inhibitors [27]	Up-regulation [28–31] Correlation with clinical characteristics [28,31] Promote cell proliferation, migration [29,30] Susceptibility to paclitaxel [33]	Up-regulation [12,34–36] Correlation with clinical characteristics [12,34] Promote cell proliferation, arrest cell cycle, inhibit cell apoptosis [35] Facilitate mitochondrial oxidative phosphorylation [36]
Immunologic	Immune infiltration association [18,39,40] Defined as an independent antigen [37]	Immune infiltration association [22]	Immunotherapy response [32] Inhibit Th17 cell differentiation [55]	Immune infiltration association [12,34]
Metabolic	Glucose metabolism/ diabetes [41–44] ER homeostasis [45,46]	Induce congenital heart disease *via* placental-embryo interactions [48]	SSR3–CDG [50–53] Glucose metabolism/ diabetes [44,54]	SSR4–CDG [57–68]

Notes: SSR1, signal sequence receptor subunit alpha; SSR2, signal sequence receptor subunit beta; SSR3, signal sequence receptor subunit gamma; SSR4, signal sequence receptor subunit delta; SSR4–CDG, SSR4-congenital disorders of glycosylation; ER, endoplasmic reticulum.

Having delineated the roles of individual subunits, we now focus on the integrated function of the TRAP complex as a whole.

TRAP complex

As the core auxiliary component of the ER transporter (Sec61), the TRAP complex regulates protein co-translational transport, glycosylation, and membrane integration through various mechanisms. In 2020, Russo et al. summarized the functions of the TRAP complex from several aspects [13]. TRAP is a heterotetrameric complex, including four subunits: α (SSR1), β (SSR2), γ (SSR3), and δ (SSR4), all of which are ER membrane proteins. Among them, α, β, and δ are single transmembrane proteins (type I), and γ is a four-transmembrane protein (no signal peptide) [70]. During the process of co-translational protein transport, TRAP binds to Sec61 (a heterotrimer complex including Sec61α, Sec61β, and Sec61γ) at a stoichiometric ratio of 1:1 to maintain the open state of the channel and assists in the transport of substrate proteins with weak hydrophobicity or glycine/proline-rich signal peptides [71–73]. Using cryo-electron tomography, the molecular structure of the TRAP complex was analyzed, and the spatial arrangement of its four subunits (SSR1, SSR2, SSR3, and SSR4) was determined, revealing the key role of TRAP in membrane protein biosynthesis and glycosylation [69]. Furthermore, the dynamic binding of the TRAP

complex to the ribosome–Sec61 complex has been observed using cryo-electron microscopy [69,74]. The TRAP complex facilitates Sec61 channel opening by bending the luminal loop of the ER membrane and directly interacting with nascent polypeptides to promote the co-translational insertion of transmembrane proteins, revealing the key structural support role of TRAP in nascent peptide chain insertion and membrane protein biosynthesis [75].

Functional defects in the TRAP complex lead to several diseases, such as CDG, abnormal insulin secretion, and tumor progression. The specific mechanisms by which the TRAP complex is associated with these diseases are described below.

The TRAP complex promotes the opening of the Sec61 channel by recognizing glycine and proline residues in the preproinsulin signal sequence and is an essential factor for insulin biosynthesis [76]. Among these, Sec61α2 is the main channel for proinsulin co-translational transport, and its deletion leads to the accumulation of unreleased full-length proinsulin on the ribosome, affecting blood glucose homeostasis [77]. CK147 binds deep inside the channel next to the plug helix, thus identifying a new Sec61 target site for the development of translocation inhibitors [78]. As discussed earlier, the TRAP complex maintains N-glycosylation quality under ER stress by regulating the activity of the BiP chaperone protein, and its deletion restores glycosylation homeostasis *via* the UBE2J1-dependent pathway [79]. In the early stages of TRAP subunit deletion, BiP binds to SSR1 and SSR2, interferes with their interactions, and inhibits their glycosylation. Knockdown of BiP by siRNA restored the glycosylation ability of SSR3- and SSR4-deficient cells, indicating that BiP activity is an important regulator of TRAP complex function. Following ER stress relief (such as the late stage of SSR3 or SSR4 deletion), the dissociation of BiP and SSR1/SSR2 restores their interaction, thereby reactivating glycosylation [80]. In triple-negative breast cancer, the TRAP complex does not show a difference in subtype distribution from inflammatory or non-inflammatory breast cancer, suggesting that the molecular heterogeneity of triple-negative breast cancer may be independent of TRAP function [80]. In carcinoma tissue, epithelial cell adhesion molecule (EpCAM) is excessively glycosylated, and its cancer-promoting role largely relies on the extent of glycosylation [81]. Wang et al. found that by maintaining the stability of the Sec61–TRAP complex, BAP31 promotes EpCAM to enter the ER cavity and be glycosylated in gastric cancer, and the antibody VH-F12 may block tumor cell proliferation by inhibiting TRAP function through the AKT-PI3K-mTOR signaling pathway [79], suggesting that the potential value of Sec61–TRAP complex can be used as a molecular target for the treatment of gastric cancer.

Taken together, beyond its role in basal protein translocation, the TRAP complex is a critical modulator of the cellular response to ER stress, ensuring proteo-stasis under pathological conditions. First, the TRAP complex is a key component for the cell's response to ER stress, assisting in the translocation of substrate proteins, which is essential for maintaining proteostasis. For instance, it facilitates the opening of the Sec61α2 channel, the main channel for proinsulin co-translational transport, and the Sec61–TRAP function is critical for alleviating metabolic ER stress. Second, once the body is under persistent or severe ER stress, the chaperone protein Bip could bind to the subunits, thereby interfering with their interactions and directly inhibiting the glycosylation function of the TRAP complex. This inhibition is dynamic and reversible; knocking down BiP could restore the glycosylation ability of cells, proving that BiP acts as a decisive switch controlling TRAP complex function.

The crosstalk suggests its therapeutic potential in both tumorigenic and non-tumorigenic pathologies. Under normal physiological conditions, its stable function is crucial for maintaining homeostasis, exemplified by the regulation of blood glucose levels. Conversely, in oncogenic contexts, its hyperactive stabilization contributes to tumorigenesis, primarily through the excessive glycosylation of pro-oncogenic proteins. Consequently, targeting its function constitutes a rational strategy for cancer therapy.

The mechanistic insights into the function of the TRAP complex reveal several potential avenues for therapeutic intervention. Firstly, the direct targeting of the Sec61/TRAP translocon using small-molecule inhibitors, such as CADA derivatives that modulate the TRAP–Sec61 interaction [78], presents a viable strategy for disrupting the synthesis of oncogenic and pro-survival proteins in cancer cells. Secondly, considering the pivotal role of the TRAP complex in regulating ER stress, modulators of ER stress pathways, such as IRE1α kinase inhibitors, could be leveraged to synergize with TRAP-dependent processes or to selectively target cancer cells exhibiting elevated ER stress levels. Additionally, given that aberrant glycosylation facilitated by TRAP functionality contributes to tumor progression, as seen in the

glycosylation of EpCAM in gastric cancer [79], targeting specific glycosylation enzymes or glycan-receptor interactions may offer therapeutic advantages. Nevertheless, these strategies necessitate a careful assessment of therapeutic windows due to the essential role of the TRAP complex in normal cellular physiology.

Perspectives and limitations

Despite the promising insights discussed above, several challenges and limitations must be addressed to translate these findings into clinical applications. Firstly, a significant limitation of the current study is its extensive dependence on bioinformatic analyses and/or *in vitro* studies. It is crucial to perform experimental validation of these findings through the use of *in vivo* models, such as conditional knockout mice for each TRAP subunit in specific tissues or patient-derived xenograft models. Furthermore, the integration of multi-omics data, including proteomics, phosphoproteomics, and glycoproteomics, with functional genetics in these models will be indispensable for advancing beyond mere correlations to establish causal mechanistic links between TRAP subunit expression, molecular pathways, and disease phenotypes. Secondly, our focus on delineating the oncogenic roles of TRAP subunits may introduce an inherent selection bias, as negative or null findings might be underreported in the literature (publication bias). For instance, we noticed SSR2 is highly expressed in HCC cells in both research pan-cancer analyses and promotes tumor progression, suggesting its oncogenic role. Nevertheless, its role in other cancers (higher in normal tissue) needs to be interpreted with caution. Meanwhile, high expression of SSR4 presented inconsistent trends in the overall survival in different tumors. This paradox highlights the complex nature of these genes, which may exert opposing functions in different cellular or immune contexts. Furthermore, though some studies have been undertaken, the role of the TRAP complex in various tissues remains inconclusive. The ablation of a single subunit results in a range of outcomes, suggesting that each isoform of the TRAP complex may fulfill distinct functions or that the knockout of one subunit may disrupt the integrity of the entire complex. This aspect warrants further mechanistic exploration. The structure of the TRAP complex has been described in detail using cryo-electron microscopy [82]. Perhaps the most significant gap is the lack of consideration for the functional interactions and potential synergy between the four subunits. The TRAP complex functions as a heterotetrameric unit [70,71,75], yet most studies focus on individual subunits in isolation. The phenotypic consequences of ablating a single subunit may stem from destabilizing the entire complex rather than the loss of that subunit's unique function. Therefore, future research should shift towards studying the complex as a whole. Do the subunits exhibit functional redundancy or unique roles? Is there synergy in their regulation of Sec61 channel activity or glycosylation quality control? Addressing these questions will require integrated approaches, such as studying the assembly and stoichiometry of the complex in different diseases and developing models that simultaneously modulate multiple subunits. We hope that the work summarized in this review will provide inspiration for further exploration of its biochemical mechanisms.

Overall, this review summarizes the critical involvement of the TRAP complex subunits in oncogenesis and non-neoplastic diseases, highlighting their therapeutic potential. In future endeavors, translational research should prioritize several critical areas: (i) biomarker development: This involves rigorously validating the prognostic and predictive value of TRAP subunits within large, multi-center clinical cohorts, as well as investigating their presence in liquid biopsies for non-invasive monitoring purposes. (ii) druggability assessment: This requires a systematic evaluation of the 'druggability' of TRAP subunits and their interactions, employing structural biology for rational drug design and high-throughput screening to identify small-molecule modulators. (iii) immunotherapeutic strategies: This entails exploring the potential of TRAP subunit-derived peptides as neoantigens for cancer vaccines or adoptive cell therapies, while meticulously assessing on-target, off-tumor toxicity. (iv) combination therapies: This involves examining combinations of TRAP-targeting strategies with existing modalities such as chemotherapy, radiotherapy, or immunotherapy to overcome resistance and enhance efficacy. Addressing these priorities will be crucial in fully realizing the therapeutic potential of the TRAP complex. Alternatively, future efforts should focus on validating these strategies in advanced pre-clinical models, such as patient-derived organoids. Clinical studies are warranted to enable the assessment of the efficacy of drugs and the monitoring of drug side effects by allowing the public to conduct phase IV clinical trials.

Conclusions

In conclusion, this review underscores the pivotal roles of the TRAP complex and its subunits (SSR1–SSR4) across a wide disease spectrum, highlighting their significant potential as therapeutic targets and biomarkers. Translating this knowledge into clinical applications will require future efforts to elucidate the underlying mechanisms through integrated experimental and multi-omics approaches, define functional interactions between subunits, and explore structure-based drug design.

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