Targeting ICMT: A promising strategy in cancer treatment (Review)

JINGHONG HU, YING XIAO and JINGYI TANG

School of Pharmacy and Bioengineering, Chongqing University of Technology, Chongqing 400054, P.R. China

Received November 13, 2025; Accepted January 20, 2026

DOI: 10.3892/ol.2026.15506

Abstract. Protein prenylation is a prevalent post-translational modification of proteins, pivotal in regulating their biological functions. It influences critical cellular processes such as signal transduction, cell cycle control and apoptosis. Isoprenylcysteine carboxymethyltransferase (ICMT) serves as the terminal enzyme in this pathway, catalyzing the methylation of proteins containing-CAAX or -CXC motifs, thereby modulating their subcellular localization and biological activity. Accumulating evidence indicates that ICMT inhibition disrupts key malignant phenotypes, such as tumor cell proliferation, migration and invasion, and attenuates the functional dependency of RAS proteins on prenylation. Consequently, ICMT has emerged as an important regulator of cancer-associated signaling and a potential therapeutic target. This review summarizes current knowledge on ICMT-mediated protein modification, its regulatory mechanisms and its roles in cancer progression, with the aim of highlighting recent advances and discussing the therapeutic implications of targeting ICMT in oncology.

Correspondence to: Dr Jingyi Tang, School of Pharmacy and Bioengineering, Chongqing University of Technology, 69 Hongguang Avenue, Banan, Chongqing 400054, P.R. China
E-mail: jingyitang@cqut.edu.cn

Abbreviations: FTase, farnesyltransferase; GGTase I, geranylgeranyltransferase I; RCE1, Ras-converting enzyme 1; ICMT, isoprenylcysteine carboxymethyltransferase; RhoA, Ras homolog family member A; PDA, pancreatic ductal adenocarcinoma; PanIN, pancreatic intraepithelial neoplasia; BNIP3, BCL2/adenovirus E1B 19 kDa-interacting protein 3; EMT, epithelial-mesenchymal transition; CSCs, cancer stem cells; TAZ, transcriptional co-activator with PDZ-binding motif; IRAK, interleukin-1 receptor-associated kinase; MAPK, mitogen-activated protein kinase; MAPKK, mitogen-activated protein kinase kinase; AP-1, activator protein 1; PFKFB4, 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 4; CDC42, cell division cycle 42; HGPS, Hutchinson-Gilford progeria syndrome; RTKs, receptor tyrosine kinases

Key words: ICMT, pancreatic cancer, breast cancer, RAS, Rho, Rab

Contents

1. Introduction
2. Structure and function of ICMT
3. ICMT in cancer therapy
4. Role of ICMT in pancreatic cancer
5. Role of ICMT in breast cancer
6. Regulation of ICMT in other cancers
7. Molecular mechanisms of ICMT regulation in cancers
8. ICMT's regulation in other diseases
9. Discussion

1. Introduction

Protein prenylation is an essential post-translational modification that regulates the function of specific proteins involved in eukaryotic cell biology, particularly those implicated in tumor initiation and progression. This modification primarily occurs on CAAX motifs and involves three key steps: First, a 15-carbon (farnesyl) or 20-carbon (geranyl) isoprenoid lipid is covalently attached to a cysteine residue by protein farnesyltransferase (FTase) or protein geranylgeranyltransferase I (GGTase I), for instance: The HRAS can only be FTase catalytic, but KRAS and NRAS can be catalyzed by FTase and GGTase I (1). Second, the-AAX tripeptide is cleaved by Ras-converting enzyme 1 (RCE1), a protease that catalyzes endoproteolytic hydrolysis (2,3). Finally, isoprenylcysteine carboxymethyltransferase (ICMT) catalyzes the methylation of the cysteine-terminal α-carboxylic acid, completing the modification (4), as indicated in Fig. 1. The processing of CAAX proteins has attracted substantial attention due to the pivotal role of mutant Ras proteins in cancer development. Despite the potential of FTase inhibitors in cancer therapy, their efficacy is limited by the compensatory activation of GGTase I when FTase is inhibited, highlighting the need for alternative therapeutic strategies (5,6). ICMT, however, uniquely modifies CAAX proteins, making it a more promising target. In RCE1-deficient fibroblasts, Ras mislocalization and markedly reduced cell growth are observed, and RCE1-deficient mice typically die in late gestation or shortly after birth (7). By contrast, ICMT-deficient mice exhibit more pronounced phenotypic defects, including severe growth retardation during embryonic development and lethality by embryonic day 10.5-11.5 (8). These findings underscore the irreplaceable role of ICMT in cellular homeostasis. As such, targeting ICMT may offer a novel approach for cancer treatment by disrupting the modification and localization of CAAX proteins, such as Ras, thus inhibiting tumor cell proliferation and migration. This emerging strategy presents new avenues for therapeutic intervention in cancer.

To systematically summarize the ICMT-related findings, the PubMed (https://pubmed.ncbi.nlm.nih.gov/) and X-MOL (https://www.x-mol.com/) databases were searched without a lower date limit through December 2025, sorting results 'most recent first', and Boolean logic coupled with MeSH terms was used to link 'prenylcysteine carboxyl methyltransferase' to breast, pancreatic, gastric, hepatocellular and epithelial ovarian cancers as well as non-tumor diseases, RAS family, Ras homolog gene family, member A (RhoA), Rab GTPases, apoptosis, autophagy, cell cycle, migration, invasion, breast-cancer stemness and DNA-damage repair, retaining only full-length, data-complete original studies while excluding abstracts, conference papers, letters, duplicates and articles loosely connected to ICMT regulation and disease.

Fig. 2 systematically illustrates the research milestones of ICMT. The journey began in 1978 with the discovery of the farnesyl-like isoprene moiety in fungal rhodotorucine A, providing the first evidence of cysteine-linked thioether bonding (9). By 1988, the confirmation of human RAS protein farnesylation established a critical link between post-translational modification and oncogenesis (10,11). The 1990s saw the elucidation of the 'CAAX' modification cascade-catalyzed by FTase/GGTase I, RCE1 and ICMT, positioning ICMT as the final essential step (2,12-15). Functional breakthroughs occurred in 2004 and 2010, demonstrating that ICMT deficiency or inhibition suppresses K-Ras/B-Raf-mediated transformation and triggers autophagy-dependent apoptosis (16,17). More recent advances in 2015 and 2021 expanded its role to mitochondrial metabolic reprogramming and DNA damage repair (18,19). Recently, findings published in 2024 reveal that ICMT promotes invasive pseudopodia and metastasis, underscoring its multifaceted regulatory roles in tumor progression (20). Building upon these evolutionary milestones, this review offers a holistic perspective on the biochemical intricacies of ICMT-driven modifications and their complex regulatory networks. We seek to delineate how recent mechanistic breakthroughs can be leveraged to develop ICMT-targeted interventions, thereby offering a forward-looking perspective on its therapeutic viability in oncology.

2. Structure and function of ICMT

The direct homologue of ICMT in *Saccharomyces cerevisiae*, STE14p, was the first enzyme of this class to be cloned and sequenced, establishing it as a founding member of the eukaryotic protein methyltransferase family (21). Subsequently, a human homologue of STE14 was identified, sharing significant sequence similarity with its yeast counterpart (21). The human and mouse genes were subsequently designated ICMT2 and ICMT, respectively. ICMT is composed of eight transmembrane α-helices (M1-M8), predominantly located within the endoplasmic reticulum membrane. Notably, the M1-M3 region is unique to animal ICMT, where it interacts closely with M4 and the M4-M5 junction (15,21). These regions are stabilized within the transmembrane domain through interactions between M1, M2 and M3, as well as between the M6-M7 and M5-M6 junctions. The largest cytoplasmic region of ICMT contains the AdoHcy binding site, which is defined by an extension of M8 and the M6-M7 linkage (22). Genetic deletion of M1 and M2 leads to inactivation of human ICMT (23).

Protein isoprenylation is a critical post-translational modification that enables proteins bearing-CAAX or -CXC motifs to acquire their full biological activity after transcription and translation (24). ICMT serves as the terminal enzyme in this process, catalyzing the methylation of isoprenylated proteins, with major substrates including Ras proteins, various Rho GTPases and the γ-subunit of G proteins (1). In summary, ICMT, as a key isoprenyl-cysteine carboxymethyltransferase, plays a vital role within the eukaryotic protein methyltransferase family. Its unique transmembrane structure and functional domains facilitate its stable residence in the endoplasmic reticulum membrane, where it catalyzes the isoprenylation modification of numerous critical proteins, thereby influencing their biological functions. In this review, the comprehensive role of ICMT in regulating different diseases and their progression will be discussed, particularly for cancer.

3. ICMT in cancer therapy

Mutations in Ras genes are among the most common genetic alterations in human cancers, occurring in ~30% of cancer cases (25). Protein isoprenylation is a crucial post-translational modification that allows proteins with -CAAX or -CXC motifs to achieve their full biological function. ICMT catalyzes the final step in this process, methylating isoprenylated proteins. However, current targeted therapies aimed at disrupting the isoprenylation process face significant challenges.

Although inhibitors of farnesyltransferase can block the isoprenylation of certain Ras proteins (e.g., KRAS and NRAS), these proteins can still be modified through the alternative geranylgeranylation pathway, resulting in drug resistance (6). While concurrent inhibition of FTase and GGTase I has been shown to block the isoprenylation of oncogenic Ki-Ras4B in animal models, the dose required to achieve effective anti-tumor efficacy causes rapid animal mortality (26). Furthermore, inhibition of RCE1 in the second step of isoprenylation has shown variable inhibitory effects in different tissues (27,28). This variability can lead to severe side effects, including disruption of normal visual and cardiac cell functions, and may even promote the development of acute myeloid leukemia (1,29).

Given these limitations, targeting the methylation step catalyzed by ICMT-the final step in the isoprenylation pathway-may represent a more effective and specific approach for cancer therapy. By focusing on the methylation of isoprenylated proteins, such as Ras, it may be possible to reduce resistance and minimize off-target effects, offering a promising therapeutic strategy (30).

The expression of ICMT in various cancers has garnered significant attention due to the broad spectrum of ICMT substrates. However, significantly higher expression levels were observed in testicular and prostate cancers, while the lowest expression was noted in adrenal cancer. This pattern

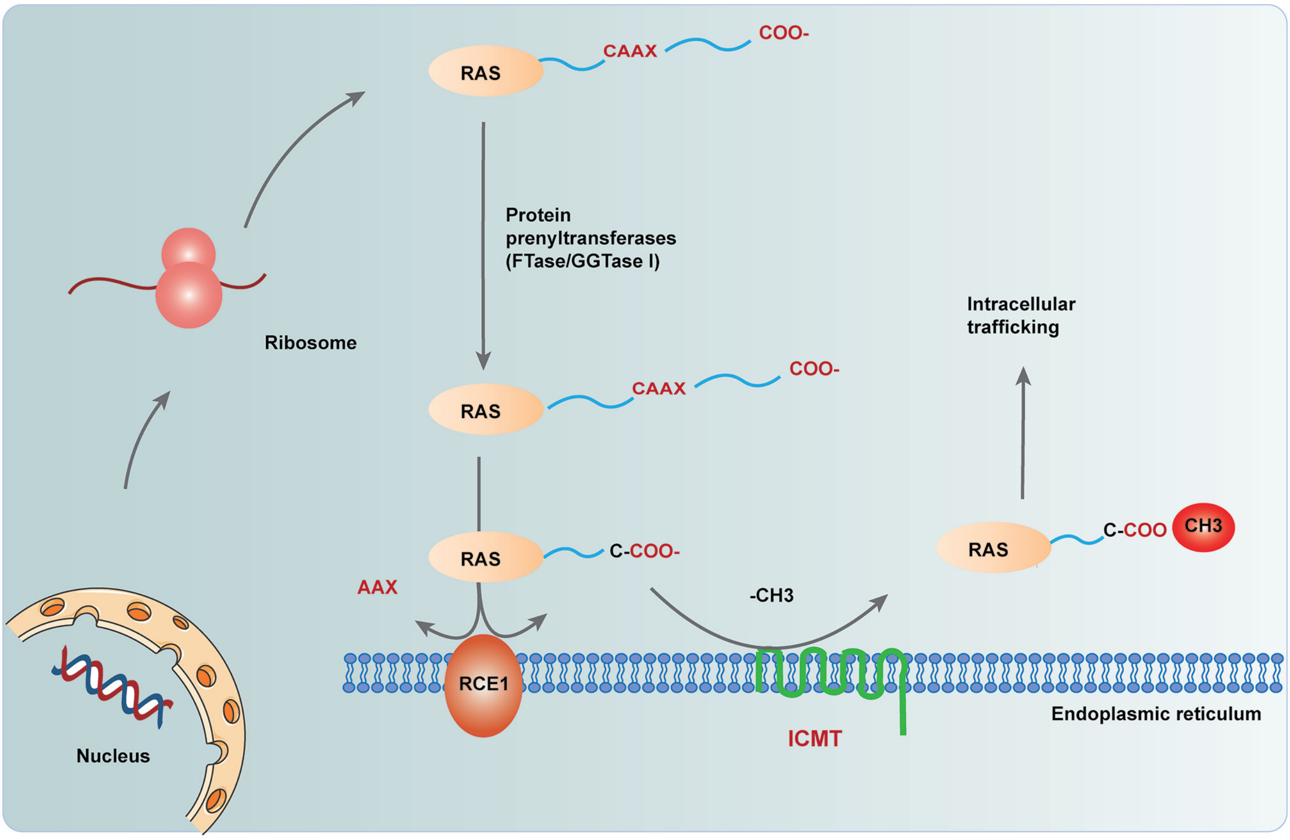

Figure 1. Three steps of CAAX protein prenylation. After the RAS gene is transcribed and translated on the ribosome, it is anchored to the endoplasmic reticulum membrane for further modification. First, a 15-carbon (farnesyl) or 20-carbon (geranyl) isoprenoid lipid is covalently attached to a cysteine residue by protein FTase or GGTase I. Subsequently, the -AAX tripeptide is cleaved by RCE1, a protease that catalyzes endoproteolytic hydrolysis. Finally, ICMT catalyzes the methylation of the cysteine-terminal α-carboxylic acid, completing the modification. FTase, farnesyltransferase; GGTase I, geranlygeranyltransferase I; RCE1, Ras-converting enzyme 1; ICMT, isoprenylcysteine carboxymethyltransferase.

suggests that while ICMT impacts a wide range of cancer cells, its expression varies considerably across different cancers (20,31). Notably, the variability in ICMT expression within the same cancer type implies that its function may not be determined solely by its abundance in the cell. Instead, it is likely influenced by the role of ICMT's substrates and their ability to regulate relevant cellular processes, as indicated in Fig. 3. The following content will mainly focus on ICMT-regulated cancer development, according to different cancer types, especially pancreatic cancer and breast cancer. Also, some critical substrates of ICMT will be discussed in this review.

4. Role of ICMT in pancreatic cancer

ICMT regulates the initiation of pancreatic cancer. Human pancreatic ductal adenocarcinoma (PDA) is characterized by oncogenic KRAS mutations, which occur in >90% of PDAC cases (32). Activating mutations in the KRAS proto-oncogene have been identified in patients with pancreatic intraepithelial neoplasia (PanIN), indicating the significant role of KRAS mutations in the pathogenesis of PDA (33). Court *et al* (34) developed a Pdx1-Cre, LSL-KrasG12D mouse model with ICMT knockout at the embryonic stage and demonstrated that the progression from PanIN to PDA was significantly accelerated in ICMT-deficient pancreata. Similarly, in a Notch1-deficient mouse model, the effects of Notch1 and ICMT deficiency were comparable, suggesting that both may influence pancreatic cancer development through a shared pathway, potentially due to the dependence of the Notch1 signaling pathway on ICMT activity. By contrast, in a mouse model without Kras-induced carcinogenesis, ICMT deficiency alone did not result in tumor formation, indicating that ICMT deficiency alone is insufficient to drive pancreatic tumorigenesis (34). On the other hand, in a pancreatic cancer cell model, the ICMT inhibitor compound 8.12 not only induced cell cycle arrest and inhibited anchorage-independent growth in HepG2 and PC3 cells, but also promoted autophagy by dose-dependently increasing light chain 3 (LC3)-II levels in both cell types (35). In summary, while ICMT inhibition accelerates tumor progression in animal models, it shows promising therapeutic effects in cellular models, highlighting the differential impact of ICMT inhibition depending on the model used.

ICMT regulates apoptosis and autophagy in pancreatic cancer. Autophagy is a highly conserved intracellular degradation process that maintains cellular homeostasis by degrading damaged, misfolded or aged proteins and organelles via the lysosomal system (36-38). While apoptosis, a programmed cell death process, is activated by death signals and can be mediated through extrinsic receptor-dependent pathways or intrinsic mitochondrial pathways (39,40). Mitochondrial

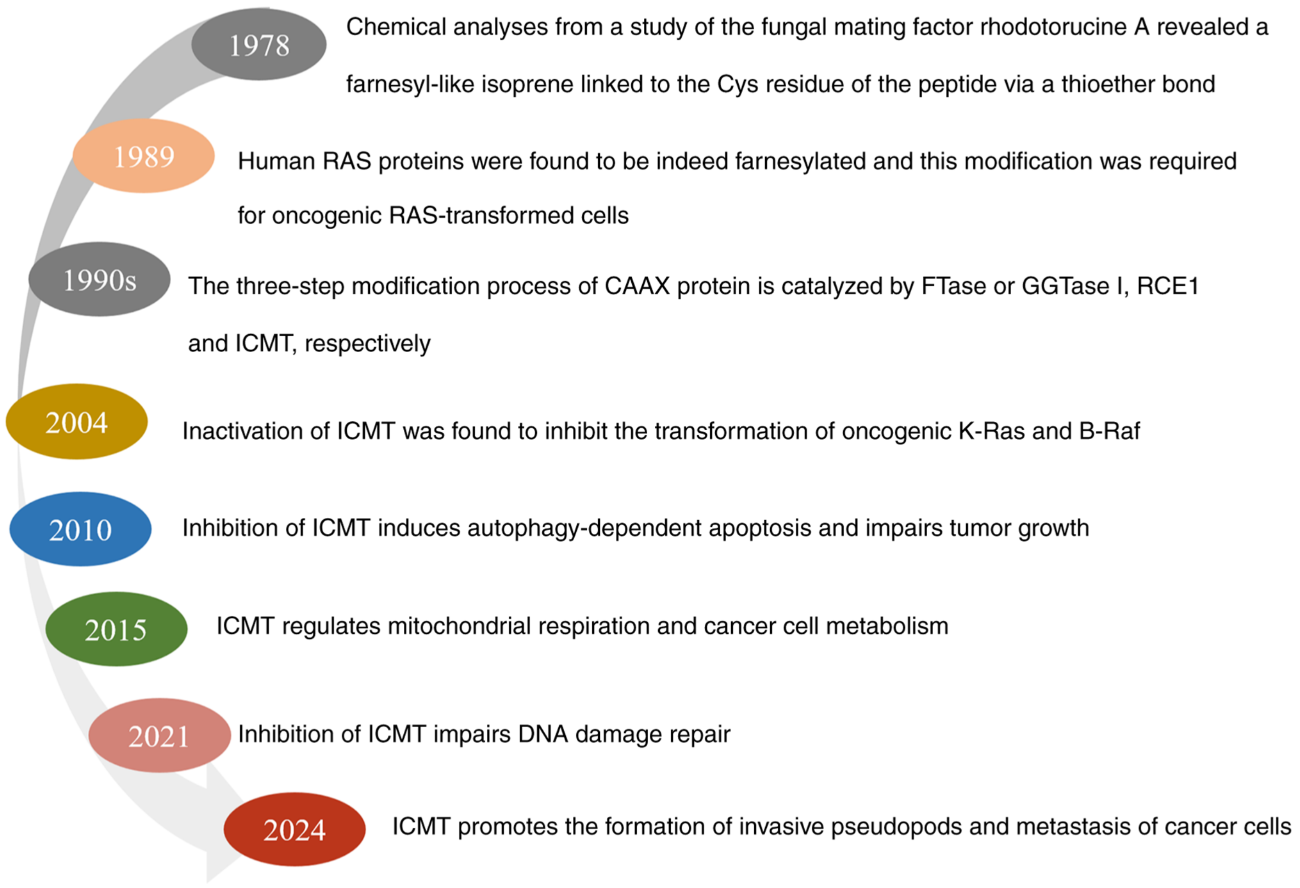

Figure 2. Timeline of ICMT research. In 1978, chemical analyses from a study on fungal mating factor rhodotorucine A revealed a farnesyl-like isoprene linked to the Cys residue of the peptide via a thioether bond (9); in 1988, human RAS proteins were found to be indeed farnesylated and this modification was required for oncogenic RAS-transformed cells (10,11); in the 1990s, the three-step modification process of CAAX protein was reported to be catalyzed by FTase or GGTase I, RCE1 and ICMT, respectively (2,12-15); in 2004, inactivation of ICMT was found to inhibit the transformation of oncogenic K-Ras and B-Raf (16); in 2010, inhibition of ICMT was indicated to induce autophagy-dependent apoptosis and impair tumor growth (17); in 2015, ICMT was reported to regulate mitochondrial respiration and cancer cell metabolism (18); in 2021, inhibition of ICMT was indicated to impair DNA damage repair (19); in 2024, ICMT was found to promote the formation of invasive pseudopods and metastasis of cancer cells (20). FTase, farnesyltransferase; GGTase I, geranlygeranyltransferase I; RCE1, Ras-converting enzyme 1; ICMT, isoprenylcysteine carboxymethyltransferase.

respiration plays a pivotal role in tumor cell survival (41). Since Warburg *et al* (42) first established the link between mitochondria and cancer via the Warburg effect in the 1920s, subsequent investigations have consistently demonstrated that targeted inhibition of mitochondrial respiration can potently suppress tumor progression and reverse therapeutic resistance (43,44). ICMT was also recently reported to play a critical role in regulating cell survival and death through its influence on apoptosis and autophagy. In sensitive pancreatic cancer cells, inhibition of ICMT led to mitochondrial respiratory defects and cellular energy depletion, resulting in significant upregulation of p21. However, cells resistant to ICMT inhibition did not show mitochondrial dysfunction or alterations in p21 signaling, and instead, apoptosis was induced through p21-activated BCL2/adenovirus E1B 19 kDa-interacting protein 3 (BNIP3) expression, rather than autophagy (45). Treatment of HepG2 cells with an ICMT inhibitor caused a marked increase in LC3-II protein levels, with LC3-II translocation to autophagosomes, which is a widely used indicator of autophagy induction. These findings suggest that ICMT inhibition triggers autophagy in pancreatic cancer cells by increasing LC3-II levels (17). Thus, inhibition of ICMT appears to have a negative effect on tumor cell survival, inducing autophagy and potentially contributing to therapeutic efficacy.

ICMT regulates the cell cycle in pancreatic cancer. The cell cycle is a tightly regulated process through which cells divide, ensuring accurate replication and distribution of genetic material. Dysregulation of the cell cycle can lead to uncontrolled cell proliferation, a hallmark of cancer (46,47). ICMT directly influences cell cycle progression by regulating the expression and activity of cell cycle-related proteins (45). Inhibition of ICMT in pancreatic cancer cells led to cell cycle arrest and apoptosis via the p21 and p21-regulated BNIP3 pathway (45). Further experiments showed that treatment of HepG2 cells with ICMT inhibitors resulted in a significant increase in the proportion of cells in the G1 phase, along with enhanced cell death, especially with prolonged treatment. Notably, the activity of caspase 3 was significantly increased in the cell lysates, and there was a marked elevation in p27 protein levels (17). These results collectively confirm that ICMT inhibition effectively induces cell cycle arrest and promotes apoptosis in HepG2 cells. Therefore, in pancreatic cancer cells, ICMT inhibition

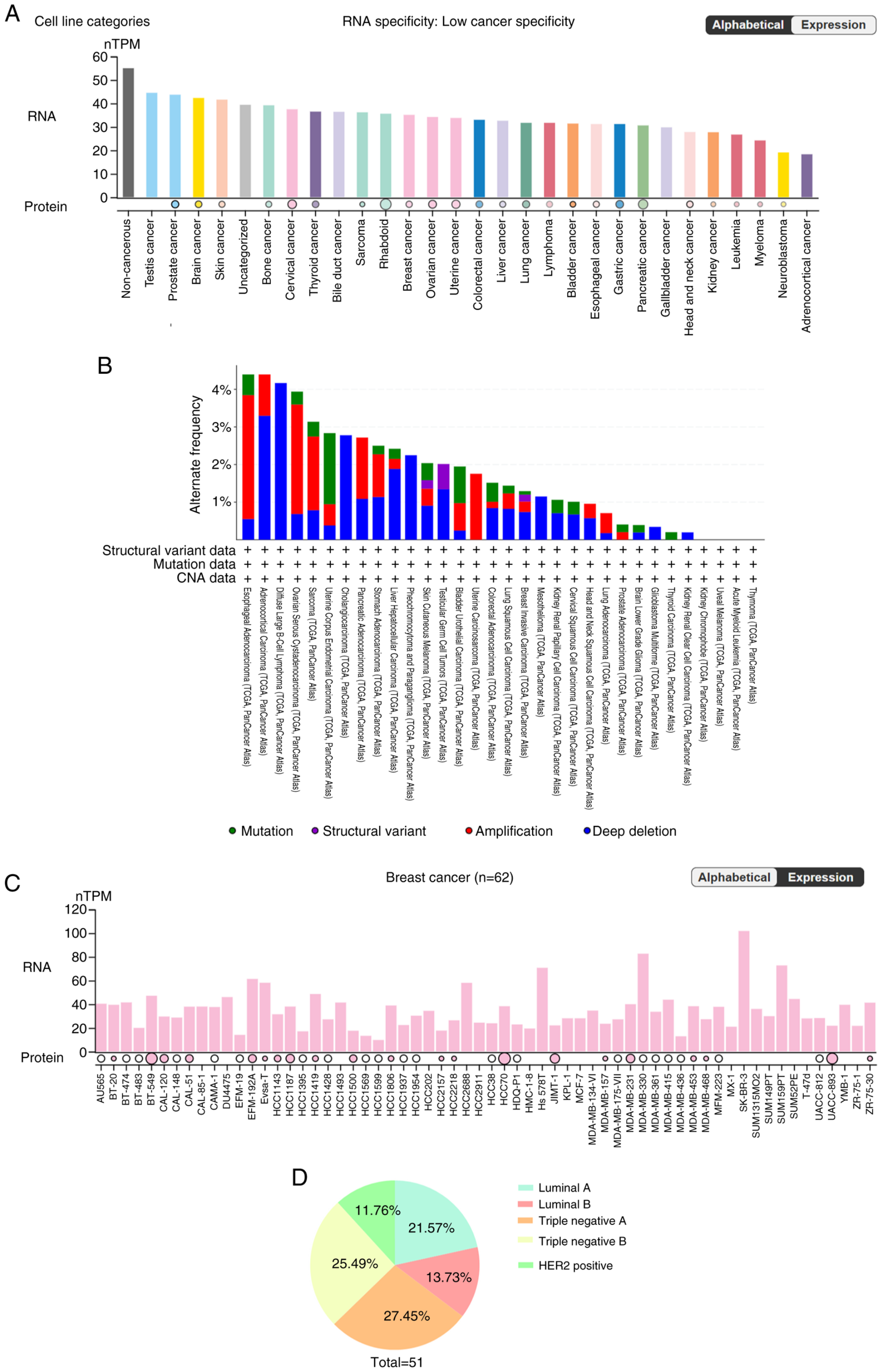

Figure 3. Expression pattern of ICMT in different cancer types and breast cancer cell lines. (A) Expression of ICMT in 30 cancer types. It is expressed significantly higher in testicular and prostate cancers, but lowest in adrenal cancer. The data were generated using the Human Protein Atlas (https://www.proteinatlas.org). (B) Expression of ICMT in 30 cancer types. The data were generated using cBioPortal (https://www.cbioportal.org). (C) Expression of ICMT in different breast cancer cells. The expression of ICMT was the highest in SK-BR-3 and MDA-MB-330 cells. The data were generated using Human Protein Atlas (https://www.proteinatlas.org). (D) Pie chart illustrating the proportion of ICMT expression in luminal A, luminal B, HER2 positive, triple negative A and triple negative B. Among them, triple negative A and B and luminal A accounted for ~20%. ICMT, isoprenylcysteine carboxymethyltransferase; TCGA, The Cancer Genome Atlas.

not only induces cell cycle arrest but also triggers apoptosis through multiple pathways, providing a solid foundation for understanding the role of ICMT in cell cycle regulation and highlighting it as a potential therapeutic target for pancreatic cancer.

5. Role of ICMT in breast cancer

ICMT regulates breast cancer tumorigenesis. ICMT plays a crucial regulatory role in the initiation and transformation of breast cancer. Lau *et al* (48) investigated the effect of ICMT on KRAS mutant (G12V) cells by constructing an HME1-shp53 cell model. Their results showed that deletion of ICMT inhibited colony formation, while restoration of ICMT expression re-established this ability, indicating that ICMT is critical for KRAS-driven cancer progression (48). In KRAS-transfected fibroblasts, the absence of carboxymethylation led to rapid turnover of RhoA and upregulation of the cyclin-dependent kinase inhibitor p21Cip1. Of note, deletion of the p21Cip1 gene abolished the effects of ICMT inactivation on cell growth and KRAS-induced soft agar colony formation, suggesting that ICMT influences cell growth and KRAS transformation through interaction with p21Cip1 (16). In summary, ICMT is essential for the initiation and maintenance of KRAS-driven cancers, and its loss significantly impairs cell transformation and colony formation.

ICMT regulates autophagy and apoptosis in breast cancer. Studies have reported that inhibiting ICMT in breast cancer can induce autophagy and apoptosis, like the phenotypes observed in pancreatic cancer. Autophagy and apoptosis often work synergistically to induce cancer cell death, particularly during chemotherapy or radiotherapy in breast cancers, and typically occur in cells with intact apoptotic pathways (49,50). Inhibition of ICMT impairs the function of mitochondrial complexes I, II and III in cancer cells, leading to decreased ATP production and depletion of tricarboxylic acid cycle metabolites. This disruption inhibits cell growth and metabolism, triggering a significant autophagic response (18). Treatment with the ICMT inhibitor Cysmethynil led to a significant increase in intracellular LC3-II levels and the formation of autophagic lysosomes, indicating that ICMT inhibition induces autophagic cell death (51). These findings suggest that ICMT affects both autophagy and apoptosis, underlining its potential as a therapeutic target for cancer treatment by modulating mitochondrial function and cellular metabolism.

ICMT regulates breast cancer migration and invasion. Cancer metastasis involves several steps: *In situ* tumor growth, angiogenesis, epithelial-mesenchymal transition (EMT), invasion, endocytosis, circulation, exocytosis, dormancy and metastatic growth (52). In the highly metastatic human breast cancer cell line MDA-MB-231, inhibition of ICMT significantly reduced cell adhesion and spreading ability. Further experiments showed that ICMT inhibition also impaired cell migration, suggesting that ICMT plays a key role in promoting the migratory and invasive abilities of breast cancer cells (53). Integrin β3 is strongly associated with invasiveness and cancer lethality in various tissues (54,55). In the breast cancer cell line MCF-7, forced expression of integrin β3 led to a more polarized cellular morphology, increased levels of phosphorylated focal adhesion kinase and enhanced actin stress fiber formation. However, these effects were completely reversed upon ICMT inhibition, indicating that the function of integrin β3 in promoting cancer cell polarity and migration is dependent on ICMT activity (56). These findings underscore the importance of ICMT in regulating the migration and invasion of breast cancer cells, highlighting it as a potential therapeutic target in breast cancer metastasis.

ICMT regulates breast cancer stem cells (CSCs). CSCs are a subpopulation of tumor cells with stem cell-like properties. They have a significantly higher proliferative capacity compared to other cancer cells within the same tumor and play an essential role in tumor initiation, progression and recurrence (57-59). CSCs are characterized by high tumorigenicity, drug resistance, unlimited self-renewal capacity and dysregulated cell cycles, making them a major contributor to cancer lethality (60). CSCs are prevalent in all types of cancer, with metastatic breast cancer being particularly enriched in CSCs (58). In the developing organism, activation of the Yes-associated protein (YAP)/transcriptional co-activator with PDZ-binding motif (TAZ) pathway imparts stem cell-like properties to cells, triggering uncontrolled proliferation and tumor formation (61,62). Positive interactions between KRAS and YAP/TAZ have been observed in several cancer types (63,64). For instance, inhibition of ICMT reduced the self-renewal capacity of KRAS-driven breast cancer cells, with silencing ICMT leading to a significant reduction in TAZ protein levels and loss of self-renewal potential. This effect could be reversed by overexpressing mutant KRAS, demonstrating that ICMT modifies KRAS regulation of TAZ stability and function (65). These findings highlight the crucial role of ICMT in regulating the stemness of cancer cells and its interaction with KRAS and YAP/TAZ, providing a new therapeutic perspective for targeting CSCs.

ICMT regulates the cell cycle in breast cancer. ICMT has been reported to regulate cell cycle progression in various cancer cell types, including breast cancer. Treatment of cancer cells with ICMT inhibitors has been shown to increase the proportion of cells in G1 phase, with elevated p27 levels and reduced cyclin D1 levels, suggesting cell cycle arrest at G1 (51). Further investigation revealed that loss of ICMT function results in cell cycle arrest at the G2/M phase, as evidenced by increased levels of phosphorylated CDC2 (Thr15) and cyclin B1, confirming that ICMT-deficient cells are arrested at G2/M (19). Additionally, ICMT deletion in cancer cells decreased cyclin D1 levels and increased p27 levels, leading to G0/G1 phase arrest (66). These results suggest that ICMT regulates cell cycle progression, and its loss leads to abnormal cell cycle arrest, which could be exploited for therapeutic purposes in breast cancer.

ICMT regulates DNA damage repair in breast cancer. DNA integrity is essential for normal cellular function and stability, and DNA damage, whether caused by environmental factors or endogenous toxic agents such as free radicals, can compromise genome stability and contribute to cancer development (67,68). DNA repair mechanisms are complex processes that ensure the repair of DNA damage to maintain genomic stability. These mechanisms include base excision repair, nucleotide excision repair, mismatch repair and double-strand break repair (DSBR), with DSBR further subdivided into non-homologous end joining and homologous recombination (69,70). In MDA-MB-231 breast cancer cells, deletion of ICMT resulted in massive apoptosis and a significant increase in p-γH2AX and cleaved caspase 7 levels, indicating that ICMT deletion induced DNA damage and cell death. p-γH2AX persisted in ICMT-deficient cells following DNA damage, whereas it rapidly decreased in control cells, further confirming that ICMT loss impairs DNA damage repair (19). These findings provide new insights into the role of ICMT in DNA repair and its critical function in maintaining genomic stability in breast cancer cells.

6. Regulation of ICMT in other cancers

Gastric cancer. ICMT is not only strongly associated with breast cancer but also plays a role in various other cancers. Although the incidence and mortality rates of gastric cancer have declined over the past 50 years, it remains the fifth most diagnosed cancer worldwide and the third leading cause of cancer-related deaths globally (71,72). In 2022, Ma *et al* (73) demonstrated that licoricidin downregulated ICMT expression and inhibited gastric cancer growth. Notably, active Ras GTP levels were significantly reduced in tumors treated with glycyrrhizin in a dose-dependent manner compared to controls. Furthermore, the inactivation of Ras effectively blocked Raf and Erk phosphorylation in the glycyrrhizin-treated group, preventing the activation of downstream signaling pathways essential for cancer progression. These results highlight the potential anticancer activity of glycyrrhizin through the ICMT/Ras pathway, suggesting that ICMT inhibition may be a valuable therapeutic strategy for gastric cancer treatment (73). Thus, by inhibiting ICMT, glycyrrhizin shows promising synergistic effects in gastric cancer therapy.

Hepatocellular carcinoma (HCC). HCC is the fourth most common cancer globally and the third leading cause of cancer-related deaths in China (74). In 2019, Xu *et al* (75) reported that ICMT protein levels were significantly higher in ~70% of HCC tissues and cell lines compared to their normal counterparts. ICMT was shown to suppress the growth and migration of Adriamycin-resistant HCC cells while inducing apoptosis. Conversely, overexpression of ICMT promoted the growth and migration of normal hepatocytes. Inhibition of ICMT suppressed Ras/Raf/Mek/Erk signaling and EMT in HCC cells, suggesting that ICMT plays an essential role in HCC biology (75). Therefore, targeting ICMT may help suppress the development and progression of HCC.

Epithelial ovarian cancer. Epithelial ovarian cancer is the leading cause of gynecological cancer-related deaths among women worldwide (76). In 2018, Liu *et al* (77) found that upregulation of ICMT expression in malignant ovarian tissues compared to normal ovarian tissues is a common phenomenon in ovarian epithelial cancer. Additionally, SKOV3 and TOV-112D cells, which exhibit lower ICMT expression, were significantly more sensitive to paclitaxel and cisplatin treatment than PA1, Caov3, and SW626 cells, which express higher levels of ICMT (77). These findings suggest that ICMT contributes to the efficacy of chemotherapy drugs, enhancing the therapeutic effects of standard treatments.

7. Molecular mechanisms of ICMT regulation in cancers

ICMT is a key protein methyltransferase that modulates numerous substrates through diverse regulatory mechanisms. The following discusses the major molecular mechanisms by which ICMT exerts its effects, particularly focusing on Ras and its regulation in cancer. In this chapter, the major pathways of mutant Ras and related RAS inhibitors are discussed, and they are also presented in Fig. 4 and Table I.

Ras. Ras proteins are small GTP-binding proteins that belong to the Ras superfamily. Active Ras proteins have significant roles in cell growth, differentiation, cytoskeletal dynamics, protein transport and secretion (78). They are localized to the plasma membrane and regulate various cellular functions (79). Ras proteins undergo post-translational modifications at their C-terminal CAAX motifs, including farnesylation, proteolytic cleavage and carboxymethylation, which facilitate their membrane affinity (31). Ras proteins are crucial components of the MAPK signaling pathway; when activated, Ras transduces signals via RAF kinase, MEK kinase and MAPK (e.g., ERK), regulating cell proliferation (80). ICMT inhibition prevents Ras translocation to the plasma membrane, thereby inhibiting Ras activity, which has therapeutic potential for Ras-driven tumorigenesis (81). ICMT regulates the interleukin-1 receptor-associated kinase (IRAK)-mitogen-activated protein kinase kinase (MAPKK)-MAPK-activator protein 1 (AP-1) pathway involved in inflammation in a Ras-dependent manner (82). Furthermore, ICMT interacts with 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 4 (PFKFB4), influencing the RAS/AKT pathway and cell migration (83). An ICMT inhibitor, UCM-1336, induces Ras mislocalization, reduces GTP-loaded Ras activity, inhibits the PI3K/AKT and MEK/ERK pathways, and promotes autophagy and apoptosis (84). In glioblastoma cells, ICMT inhibition reduced Ras-GTP levels and decreased the phosphorylation of Raf, ERK, p90RSK, Akt and mTOR, suggesting that the Ras/Raf/Mek and Ras/PI3K/Akt/mTOR pathways are inhibited by ICMT inhibition (85). These findings suggest that ICMT drives tumor development by interacting with Ras, and its inhibition disrupts Ras localization and downstream signaling, offering therapeutic implications for Ras-associated cancers.

Rho. The Rho subfamily, a member of the Ras superfamily, plays a critical role in regulating cell signaling pathways involved in cell proliferation, differentiation, migration and morphology (86). Rho proteins are processed through the prenylation modification, and their activity impacts various cellular processes. A previous study by Bergo *et al* (16) showed that ICMT inactivation inhibited cell growth and K-Ras-induced oncogenic transformation in both soft agar assays and nude mouse models. This was accompanied by a significant increase in the Ras/Erk1/2 dependence of p21(Cip1), possibly due to reduced levels of RhoA.

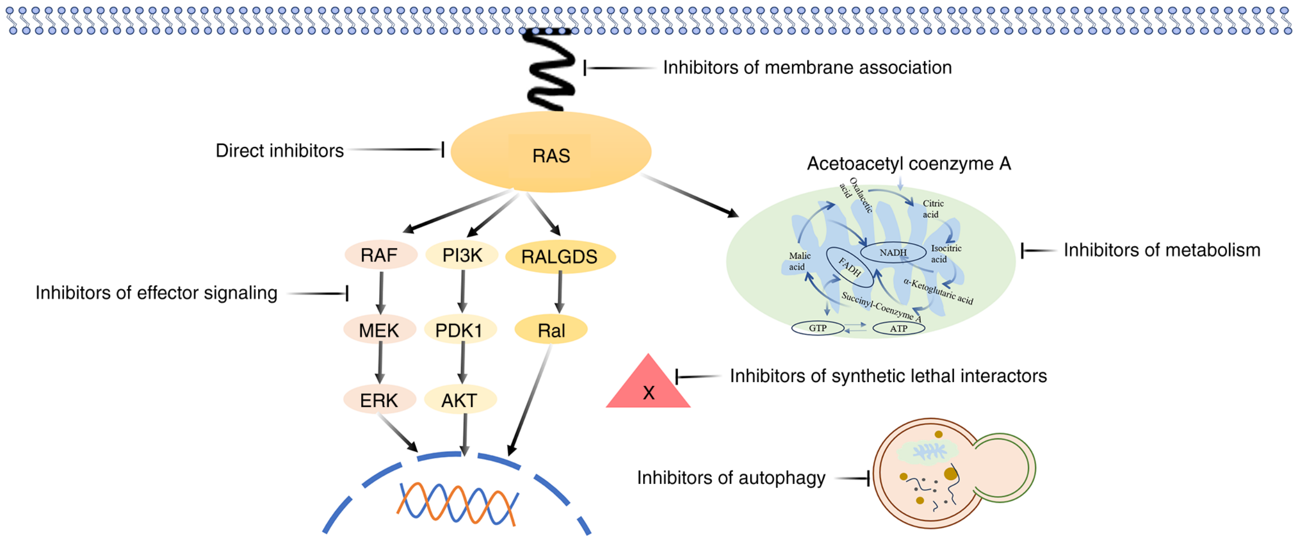

Figure 4. Summary of critical inhibitors targeting Ras according to its molecular mechanism. Ras serves as a crucial signaling node that coordinates multiple cellular processes through three major effector pathways. The RAS-MAPK pathway, activated by receptor tyrosine kinases (RTKs), transduces signals through the RAF-MEK-ERK cascade to regulate cell proliferation and differentiation. Simultaneously, the PI3K-AKT pathway promotes cell survival and growth by converting PIP2 to PIP3 through PI3K, which subsequently activates AKT to inhibit apoptotic signals. Additionally, the RALGDS pathway modulates cytoskeletal dynamics and vesicular trafficking, thereby influencing cell migration and secretory functions. RTKs, receptor tyrosine kinases; MAPK, mitogen-activated protein kinase; RAF, rapidly accelerated fibrosarcoma kinase; MEK, MAPK kinase; ERK, extracellular signal-regulated kinase; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; PIP3, phosphatidylinositol 3,4,5-trisphosphate; RALGDS, ral guanine nucleotide dissociation stimulator.

Papaharalambus *et al* (87) discovered that ICMT inhibition affects the interaction between Rac1 and its inhibitor, Rho guanine nucleotide dissociation inhibitor (RhoGDI). In ICMT-deficient cells, lower levels of Rho proteins were observed (88). ICMT inhibition in MDA-MB-231 cells significantly impaired thrombin- and EGF-induced activation of Rho and Rac, and increased RhoGDI binding to RhoA and Rac1. Overexpression of RhoGTPases partially rescued the migratory impairment caused by ICMT inhibition, likely due to the involvement of other Rho proteins such as cell division cycle 42 (CDC42) (53). These findings indicate that ICMT inhibition disrupts RhoA and Rac activation, impairing cell morphology, adhesion and migration, and that these effects can be partially rescued by exogenous expression of RhoA or Rac1. ICMT, therefore, plays a crucial role in RhoA and Rac activation, affecting cellular processes critical to cancer metastasis.

Rab. Rab GTPases represent the largest subfamily of small GTPases within the Ras family, with nearly 70 members (89). Activated Rab proteins regulate the trafficking of specific proteins to cellular compartments and organelles, playing a central role in membrane trafficking. ICMT deficiency causes mislocalization of GFP-RAB7 and GFP-RAB8 from the inner membrane to the cytoplasmic lysate, enhancing their binding to RABGDI and reducing their GTP-bound state. This results in defective Notch1 processing and mislocalization (90). RAB4A, involved in integrin β3 recycling, is crucial for cell migration in response to pro-migratory stimuli like platelet-derived growth factor (PDGF) (91,92). Knockdown of ICMT in MDA-MB-231 and HT-1080 cells reduced the basal and PDGF-stimulated localization of integrin β3 and RAB4 at the cell membrane, suggesting that ICMT regulates the function of RAB4A in integrin β3 recycling and cell migration (56). In conclusion, ICMT affects the localization and activity of Rab proteins, influencing the Notch signaling pathway and cell migration, with significant implications for cancer metastasis.

8. ICMT's regulation in other diseases

In addition to its significant role in cancer, ICMT has been implicated in a range of other diseases. For example, ICMT inhibitors such as cysmethynil and 3-methoxy-N-[2-2,2,6,6-tetramethyl-4-phenyltetrahydropyran-4-yl) ethyl] aniline (MTPA) have been shown to attenuate the lipopolysaccharide-induced ICMT/Ras/AP-1 signaling pathway, thereby inhibiting inflammatory responses (93). Marín-Ramos *et al* (84) reported a potent ICMT inhibitor, compound 3, which significantly impaired membrane binding of four Ras isoforms, leading to reduced Ras activity and inhibition of downstream Ras signaling pathways, ultimately improving survival in an *in vivo* model of acute myeloid leukemia. Similarly, compound C75, another potent ICMT inhibitor, delayed the progression of acute myeloid leukemia, blocked the methylation of progerin, disrupted its interaction with AKT and enhanced AKT signaling (94). In Hutchinson-Gilford progeria syndrome (HGPS) cells and Zmpste24-deficient mouse fibroblasts, compound C75 stimulated growth and development by targeting progerin mislocalization and activating AKT signaling (95). Furthermore, ICMT inhibitor UCM-13207 significantly improved the proliferative capacity of HGPS fibroblasts, reduced progerin localization to the nuclear membrane, decreased DNA damage, increased cell viability, and notably improved body weight and lifespan while reducing tissue senescence in mice (96). In diabetes, knockdown of ICMT

Table I. Summary of classification, mechanism of action and study phase of inhibitors targeting the Ras signaling pathway.

Ras-related pathway	Inhibitor class	Drug name	Mechanism of action	Study phase
Ras membrane localization	Inhibitors of membrane association	GGTI-298	Disruption of Ras membrane localization	Preclinical
		GGTI-2154	Disruption of Ras membrane localization	Preclinical
		UCM-1336	Disruption of Ras membrane localization	Preclinical
Direct Ras inhibition	Direct inhibitors	ARS-853	Targeting of mutant Ras proteins	Preclinical
		AMG510	Targeting of mutant Ras proteins	Preclinical
		MRTX849	Targeting of mutant Ras proteins	Preclinical
		SCH-54292	Targeting of mutant Ras proteins	Preclinical
		RMC6236	Targeting of mutant Ras proteins	Preclinical
RAS-MAPK effector pathway	Inhibitors of effector signaling-MEK inhibitor	GDC-0623	Inhibiting of MEK in the RAF-MEK-ERK cascade	Preclinical
	Inhibitors of effector signaling-Raf inhibitor	Dabrafenib	Inhibiting of Raf in the RAF-MEK-ERK cascade	Clinical
PI3K-AKT effector pathway	Inhibitors of effector signaling-PI3K inhibitor	INCB 0504655	Inhibiting of PI3K to block PIP2 to PIP3 conversion	Clinical
		GDC 0084	Inhibiting of PI3K to block PIP2 to PIP3 conversion	Clinical
RALGDS effector pathway	Inhibitors of effector Signaling-Ral inhibitor	RBC8	Inhibiting of Ral in the RALGDS pathway	Preclinical
Metabolic intervention	Inhibitors of metabolism	GLS	Targeting of metabolic vulnerabilities	Preclinical
		Phenformin	Exploitation of metabolic vulnerabilities (biguanide class)	Preclinical
		Metformin	Exploitation of metabolic vulnerabilities (biguanide class)	Clinical
Synthetic lethal interactions	Inhibitors of synthetic lethal interactors	Trametinib	Targeting of synthetic lethal interactions	Clinical
		PD032590	Targeting of synthetic lethal interactions	Clinical
Autophagy modulation	Inhibitors of autophagy	Hydroxychloroquine	Modulation of autophagy	Clinical
		Flunarizine	Modulation of autophagy	Clinical

MEK, MAPK kinase; MAPK, mitogen-activated protein kinase; PI3K, phosphatidylinositol 3-kinase; PIP2, phosphatidylinositol 4,5-bisphosphate; RALGDS, ral guanine nucleotide dissociation stimulator.

attenuated glucose-induced insulin secretion and Rac1 activation, as well as reactive oxygen species (ROS) production, suggesting that ICMT regulates glucose-induced insulin secretion, Rac1 activation and ROS production through its methylation of Rac1 (97). These findings highlight the broad therapeutic potential of ICMT inhibition, not only in cancer but also in a variety of other diseases.

9. Discussion

Enzymes that post-translationally modify the CAAX motif of Ras proteins have long been considered promising targets for anti-Ras drug discovery. After several preclinical studies demonstrated that ICMT is essential for KRAS-mediated cellular transformation and *in vivo* tumorigenesis (16,81), and with evidence suggesting that pharmacological inhibition of ICMT blocks Ras-dependent transformation (30,94), ICMT has emerged as a valuable drug target. For example, in pancreatic cancer, ICMT inhibition induces mitochondrial dysfunction, leading to cell death (45). Additionally, ICMT deficiency results in cell-cycle arrest, further driving cell death (17). However, in the Pdx1-Cre, LSL-KrasG12D mouse model of pancreatic cancer, ICMT knockout unexpectedly accelerated tumor progression. This may be due to the involvement of multiple ICMT substrates in the pancreas, with differential expression of these substrates potentially explaining why ICMT may act as a tumor suppressor in certain tissues (e.g., pancreas) but not others (e.g., bone marrow). Accumulating evidence indicates that depletion of Ras family members in mice leads to profound developmental abnormalities, frequently resulting in embryonic or neonatal lethality. These phenotypes include pulmonary immaturity, as well as cardiac and placental defects (98-100). Within the Rho GTPase family, CDC42 is essential for meiosis and the establishment of cell polarity, whereas Rac1 is required for gastrulation and epiblast survival; loss of either gene results in early embryonic lethality (101-103). Similarly, Rab family GTPases play indispensable roles during development. Genetic ablation of Rab proteins in mice commonly causes early embryonic lethality-for example, Rab1a deletion induces developmental arrest. Notably, distinct subtype-specific effects have been observed among Rab5 isoforms: Homozygous deletion of Rab5a or Rab5b is compatible with viability, whereas loss of Rab5c is lethal, and Rab5c heterozygous mice exhibit hematopoietic and metabolic abnormalities (104,105). Furthermore, the acceleration of PanINs in the absence of ICMT could be due to enhanced stromal responses, including increased inflammatory cell infiltration and fibrosis in ICMT-deficient pancreata expressing KRASG12D (81). Collectively, these essential developmental functions underscore that ICMT-catalyzed prenylation is indispensable for the survival and homeostasis of multiple tissues; consequently, its early global loss in the Pdx1-Cre; LSL-KrasG12D model is likely to unleash context-specific stress and compensatory hyperplasia that accelerate PanIN formation-highlighting the need to weigh developmental toxicity against tumor-suppressive potential when timing ICMT inhibition in pancreatic cancer therapy. Besides, the roles of ICMT substrates other than Ras should be carefully considered in future therapeutic strategies for pancreatic cancer. Furthermore, the bulk of current work relies on fully transformed, established tumor lines, indirectly suggesting that ICMT is actionable only as a therapeutic target, not as a candidate for cancer prevention. In conclusion, ICMT has considerable potential for the development of novel therapeutic approaches for pancreatic cancer, and targeting ICMT or its substrates offers promising avenues for treatment.

The research on ICMT extends beyond pancreatic cancer, with significant implications for other cancers, such as breast cancer. ICMT has been shown to influence the transformation of cells with Ras mutations (48) and plays a crucial role in regulating cancer cell invasion and metastasis. By targeting RhoA, one of ICMT's substrates, cancer cell migration and metastasis can be modulated (53,56). Furthermore, ICMT inhibition leads to mitochondrial dysfunction, which triggers cellular autophagy and apoptosis (18). ICMT also impacts cell cycle regulation and DNA damage repair (19,56). In breast cancer, combining ICMT inhibition with existing therapies such as radiotherapy, chemotherapy or targeted therapies (e.g., carboplatin) could enhance the anti-tumor effect and improve prognosis.

ICMT's substrates are diverse, and its regulatory mechanisms extend to Ras, RhoA, and Rab proteins. For instance, ICMT interacts with PFKFB4 to influence the RAS/AKT pathway and cell migration (83), and inhibition of ICMT impairs thrombin-mediated RhoA and Rac activation, leading to disrupted cell migration (53). ICMT also regulates the mislocalization of Rab proteins, such as Rab7 and Rab8, which impacts the Notch signaling pathway and cellular processes like migration (90). Future studies should explore additional signaling pathways and mechanisms of action related to ICMT to fully understand its therapeutic potential.

Although the observed phenotypes are largely driven by canonical ICMT substrates, synergistic contributions from additional, less-characterized substrates cannot be excluded. Hypomethylated CDC42 disrupts cytoskeletal dynamics in MDA-MB-231 cells and precipitates mitotic errors (53); RAB-focused experiments in KRAS-mutant breast-cancer models reveal that ICMT inhibition simultaneously cripples RAS-dependent metastatic signaling (56); yet even KRAS-wild-type lines accumulate γH2AX-positive DNA damage after ICMT knockdown, pointing to RAS-independent routes to genomic instability (19). To determine whether these outcomes reflect single- or multi-substrate perturbation, future work should couple single-cell multi-omics with a stepwise HMEC transformation cell model in which individual prenylated proteins (KRAS, RhoA, RAB4, etc.) can be toggled on or off while ICMT is acutely inhibited. Such precision-controlled systems will clarify which combinations of hypomethylated substrates must be co-targeted to maximize therapeutic efficacy.

Beyond pancreatic and breast cancer, ICMT has promising applications in the treatment of other cancers. For example, licoricidin has shown promising anti-gastric cancer activity through the ICMT/Ras pathway (73), while in HCC, ICMT inhibition impaired cell growth and migration, and induced apoptosis (75). KRAS also requires palmitoylation to reinforce its membrane anchoring function, so future therapeutic strategies could consider combination therapies targeting this modification (106). ICMT also has important roles in non-cancer diseases, including inflammation, acute myeloid leukemia and premature aging (93-95). At present, the small-molecule ICMT inhibitor cysmethynil has low aqueous solubility and remains in the pre-clinical stage; therefore, no clinical data are available to support a therapeutic window. However, published studies allow us to speculate: In a Hutchinson-Gilford progeria mouse model (95,96,107), ICMT knockdown produced no overt toxicity, yet targeting the second step of prenylation (e.g., RCE1) sensitizes retinal neurons (28,108), so ICMT inhibition may have potential for clinical treatment with low toxicity, but might elicit similar side effects. Overall, ICMT inhibition demonstrates significant therapeutic potential in both cancer and other diseases, and its targeted inhibition is expected to contribute to advancements in human healthcare in the future.

Besides its therapeutic potential as a single-agent target, ICMT holds considerable promise in combination treatment strategies. The immediate argument is a mechanistic fit with poly(ADP-ribose) polymerase (PARP) inhibitors: By silencing multiple DNA-repair circuits, ICMT inhibition imposes a 'BRCAness' state on otherwise BRCA-proficient breast cancers, converting them into PARP-inhibitor-responsive tumors (19,109,110). This synthetic-lethal logic can be extended further. So far, current research cannot exclude the possibility that concomitant blockade of the YAP arm of the Hippo pathway may elicit synthetic-lethal interactions in specific breast-CSC contexts; although, in one KRAS-mutant pancreatic and one KRAS-mutant breast cancer line, the Hippo-YAP axis did not emerge as the decisive downstream effector of the ICMT-KRAS module, broadening the cell-line panel or interrogating non-KRAS-mutant tumors could still uncover settings in which YAP co-inhibition is genuinely synthetically lethal (65,111-113) Likewise, the line-to-line variability in ICMT-mediated cell-cycle arrest positions ICMT inhibitors as natural partners for cyclin-dependent kinases or other cell-cycle checkpoints blockers (17,19,35,45,51).

Mechanistically, ICMT suppression appears to kill by stripping cancer cells of their redundant repair and survival modules, such as ICMT deletion causing 'BRCAness' (19). However, the metabolic adaptations that might eventually restore viability, and thus drive acquired resistance, remain largely uncharted. Building clinically relevant, drug-resistant models to map these escape routes should be a high-priority follow-up for ICMT inhibitor clinical study. For the biomarker development field, a validated predictor of ICMT-inhibitor benefit is still limited. ICMT transcript or protein levels display no systematic elevation in tumors vs. matched normal tissues and vary widely across cancer types, depriving clinicians of a straightforward expression-based biomarker. Attention therefore centers on tumors whose oncogenic circuitry is already wired through ICMT substrates-RAS-mutant cancers, lesions with hyper-active RAS signaling and metastases addicted to Rho-family GTPases-rather than on ICMT abundance *per se*. Future ICMT-directed trials must therefore embed parallel biomarker-discovery arms that link pharmacodynamic readouts to multi-omic signatures, ensuring that patients are selected for the dependency state created by the enzyme rather than for the enzyme itself (30,109,114).

Acknowledgements

The authors would like to thank Dr Gang Xiang (School of Pharmacy and Bioengineering, Chongqing University of Technology, Chongqing, China) for providing the website resources for this article and Professor Tingxiu Xiang (Chongqing Key Laboratory for the Mechanism and Intervention of Cancer Metastasis, Chongqing University Cancer Hospital, Chongqing University, Chongqing, China), who gave suggestions for the content.

Funding

This work was supported by Science and Technology Research Program of Chongqing Municipal Education Commission (grant no. KJQN202501152) and the Scientific Research Foundation of Chongqing University of Technology (to JT).

Availability of data and materials

Not applicable.

Authors' contributions

JH contributed to the drafting of the manuscript and literature search. YX contributed to drafting the manuscript and provided some of the images included. JT proposed ideas, provided the framework of the manuscript and made revisions. All authors have read and approved the final 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.

References

1. Wang M and Casey PJ: Protein prenylation: Unique fats make their mark on biology. Nat Rev Mol Cell Biol 17: 110-122, 2016.
2. Boyartchuk VL, Ashby MN and Rine J: Modulation of Ras and a-factor function by carboxyl-terminal proteolysis. Science 275: 1796-1800, 1997.
3. Freije JM, Blay P, Pendás AM, Cadiñanos J, Crespo P and López-Otín C: Identification and chromosomal location of two human genes encoding enzymes potentially involved in proteolytic maturation of farnesylated proteins. Genomics 58: 270-280, 1999.
4. Gutierrez L, Magee AI, Marshall CJ and Hancock JF: Post-translational processing of p21ras is two-step and involves carboxyl-methylation and carboxy-terminal proteolysis. EMBO J 8: 1093-1098, 1989.
5. James G, Goldstein JL and Brown MS: Resistance of K-RasBV12 proteins to farnesyltransferase inhibitors in Rat1 cells. Proc Natl Acad Sci USA 93: 4454-4458, 1996.
6. Whyte DB, Kirschmeier P, Hockenberry TN, Nunez-Oliva I, James L, Catino JJ, Bishop WR and Pai JK: K- and N-Ras are geranylgeranylated in cells treated with farnesyl protein transferase inhibitors. J Biol Chem 272: 14459-14464, 1997.
7. Bergo MO, Ambroziak P, Gregory C, George A, Otto JC, Kim E, Nagase H, Casey PJ, Balmain A and Young SG: Absence of the CAAX endoprotease Rce1: Effects on cell growth and transformation. Mol Cell Biol 22: 171-181, 2002.
8. Bergo MO, Leung GK, Ambroziak P, Otto JC, Casey PJ, Gomes AQ, Seabra MC and Young SG: Isoprenylcysteine carboxyl methyltransferase deficiency in mice. J Biol Chem 276: 5841-5845, 2001.
9. Kamiya Y, Sakurai A, Tamura S and Takahashi N: Structure of rhodotorucine A, a novel lipopeptide, inducing mating tube formation in Rhodosporidium toruloides. Biochem Biophys Res Commun 83: 1077-1083, 1978.
10. Casey PJ, Solski PA, Der CJ and Buss JE: p21ras is modified by a farnesyl isoprenoid. Proc Natl Acad Sci USA 86: 8323-8327, 1989.
11. Clarke S, Vogel JP, Deschenes RJ and Stock J: Posttranslational modification of the Ha-ras oncogene protein: Evidence for a third class of protein carboxyl methyltransferases. Proc Natl Acad Sci USA 85: 4643-4647, 1988.

12. Reiss Y, Goldstein JL, Seabra MC, Casey PJ and Brown MS: Inhibition of purified p21ras farnesyl: Protein transferase by Cys-AAX tetrapeptides. Cell 62: 81-88, 1990.
13. Seabra MC, Reiss Y, Casey PJ, Brown MS and Goldstein JL: Protein farnesyltransferase and geranylgeranyltransferase share a common alpha subunit. Cell 65: 429-434, 1991.
14. Otto JC, Kim E, Young SG and Casey PJ: Cloning and characterization of a mammalian prenyl protein-specific protease. J Biol Chem 274: 8379-8382, 1999.
15. Dai Q, Choy E, Chiu V, Romano J, Slivka SR, Steitz SA, Michaelis S and Philips MR: Mammalian prenylcysteine carboxyl methyltransferase is in the endoplasmic reticulum. J Biol Chem 273: 15030-15034, 1998.
16. Bergo MO, Gavino BJ, Hong C, Beigneux AP, McMahon M, Casey PJ and Young SG: Inactivation of Icmt inhibits transformation by oncogenic K-Ras and B-Raf. J Clin Invest 113: 539-550, 2004.
17. Wang M, Hossain MS, Tan W, Coolman B, Zhou J, Liu S and Casey PJ: Inhibition of isoprenylcysteine carboxylmethyltransferase induces autophagic-dependent apoptosis and impairs tumor growth. Oncogene 29: 4959-4970, 2010.
18. Teh JT, Zhu WL, Ilkayeva OR, Li Y, Gooding J, Casey PJ, Summers SA, Newgard CB and Wang M: Isoprenylcysteine carboxylmethyltransferase regulates mitochondrial respiration and cancer cell metabolism. Oncogene 34: 3296-3304, 2015.
19. Tang J, Casey PJ and Wang M: Suppression of isoprenylcysteine carboxylmethyltransferase compromises DNA damage repair. Life Sci Alliance 4: e202101144, 2021.
20. Borini Etichetti C, Arel Zalazar E, Di Benedetto C, Cocordano N, Valente S, Bicciato S, Menacho-Márquez M, Larocca MC and Girardini J: Isoprenylcysteine carboxyl methyltransferase (ICMT) promotes invadopodia formation and metastasis in cancer cells. Biochimie 222: 28-36, 2024.
21. Bergo MO, Leung GK, Ambroziak P, Otto JC, Casey PJ and Young SG: Targeted inactivation of the isoprenylcysteine carboxyl methyltransferase gene causes mislocalization of K-Ras in mammalian cells. J Biol Chem 275: 17605-17610, 2000.
22. Diver MM, Pedi L, Koide A, Koide S and Long SB: Atomic structure of the eukaryotic intramembrane RAS methyltransferase ICMT. Nature 553: 526-529, 2018.
23. Diver MM and Long SB: Mutational analysis of the integral membrane methyltransferase isoprenylcysteine carboxyl methyltransferase (ICMT) reveals potential substrate binding sites. J Biol Chem 289: 26007-26020, 2014.
24. Zhang FL and Casey PJ: Protein prenylation: Molecular mechanisms and functional consequences. Annu Rev Biochem 65: 241-269, 1996.
25. Cox AD, Der CJ and Philips MR: Targeting RAS membrane association: Back to the future for Anti-RAS drug discovery? Clin Cancer Res 21: 1819-1827, 2015.
26. deSolms SJ, Ciccarone TM, MacTough SC, Shaw AW, Buser CA, Ellis-Hutchings M, Fernandes C, Hamilton KA, Huber HE, Kohl NE, *et al*: Dual protein farnesyltransferase-geranylgeranyltransferase-I inhibitors as potential cancer chemotherapeutic agents. J Med Chem 46: 2973-2984, 2003.
27. Ma C, Yang Y, Xu L, Tu W, Chen F and Wang J: Rce1 suppresses invasion and metastasis of hepatocellular carcinoma via epithelial-mesenchymal transition induced by the TGF-β1/H-Ras signaling pathway. J Cell Physiol 235: 2506-2520, 2020.
28. Aiyagari AL, Taylor BR, Aurora V, Young SG and Shannon KM: Hematologic effects of inactivating the Ras processing enzyme Rce1. Blood 101: 2250-2252, 2003.
29. Karlsson C, Akula MK, Staffas A, Cisowski J, Sayin VI, Ibrahim MX, Lindahl P and Bergo MO: Knockout of the RAS endoprotease RCE1 accelerates myeloid leukemia by downregulating GADD45b. Leukemia 35: 606-609, 2021.
30. Winter-Vann AM, Baron RA, Wong W, dela Cruz J, York JD, Gooden DM, Bergo MO, Young SG, Toone EJ and Casey PJ: A small-molecule inhibitor of isoprenylcysteine carboxyl methyltransferase with antitumor activity in cancer cells. Proc Natl Acad Sci USA 102: 4336-4341, 2005.
31. Wright LP and Philips MR: Thematic review series: Lipid posttranslational modifications. CAAX modification and membrane targeting of Ras. J Lipid Res 47: 883-891, 2006.
32. Kurniansyah N, Goodman MO, Khan AT, Wang J, Feofanova E, Bis JC, Wiggins KL, Huffman JE, Kelly T, Elfassy T, *et al*: Evaluating the use of blood pressure polygenic risk scores across race/ethnic background groups. Nat Commun 14: 3202, 2023.
33. Almoguera C, Shibata D, Forrester K, Martin J, Arnheim N and Perucho M: Most human carcinomas of the exocrine pancreas contain mutant c-K-ras genes. Cell 53: 549-554, 1988.
34. Court H, Amoyel M, Hackman M, Lee KE, Xu R, Miller G, Bar-Sagi D, Bach EA, Bergö MO and Philips MR: Isoprenylcysteine carboxylmethyltransferase deficiency exacerbates KRAS-driven pancreatic neoplasia via Notch suppression. J Clin Invest 123: 4681-4694, 2013.
35. Lau HY, Ramanujulu PM, Guo D, Yang T, Wirawan M, Casey PJ, Go ML and Wang M: An improved isoprenylcysteine carboxylmethyltransferase inhibitor induces cancer cell death and attenuates tumor growth in vivo. Cancer Biol Ther 15: 1280-1291, 2014.
36. Glick D, Barth S and Macleod KF: Autophagy: Cellular and molecular mechanisms. J Pathol 221: 3-12, 2010.
37. Yamamoto H, Zhang S and Mizushima N: Autophagy genes in biology and disease. Nat Rev Genet 24: 382-400, 2023.
38. Gómez-Virgilio L, Silva-Lucero MD, Flores-Morelos DS, Gallardo-Nieto J, Lopez-Toledo G, Abarca-Fernandez AM, Zacapala-Gómez AE, Luna-Muñoz J, Montiel-Sosa F, Soto-Rojas LO, *et al*: Autophagy: A key regulator of homeostasis and disease: An overview of molecular mechanisms and modulators. Cells 11: 2262, 2022.
39. Nagata S and Golstein P: The fas death factor. Science 267: 1449-1456, 1995.
40. Yang J, Liu X, Bhalla K, Kim CN, Ibrado AM, Cai J, Peng TI, Jones DP and Wang X: Prevention of apoptosis by Bcl-2: Release of cytochrome c from mitochondria blocked. Science 275: 1129-1132, 1997.
41. Wang J, Zhang A, Wu M and Qin S: Manipulating mitochondrial electron flow: A novel approach to enhance tumor immunogenicity. Mol Biomed 5: 10, 2024.
42. Warburg O, Wind F and Negelein E: The metabolism of tumors in the body. J Gen Physiol 8: 519-530, 1927.
43. Wang X, Xu Z, Wang J, Wu C, Zhang L, Qian C, Luo Y, Gu Y, Wong WT and Xiang D: A Mitochondria-targeted biomimetic nanomedicine capable of reversing drug resistance in colorectal cancer through mitochondrial dysfunction. Adv Sci (Weinh) 12: e2410630, 2025.
44. Feng J, Lian Z, Xia X, Lu Y, Hu K, Zhang Y, Liu Y, Hu L, Yuan K, Sun Z, *et al*: Targeting metabolic vulnerability in mitochondria conquers MEK inhibitor resistance in KRAS-mutant lung cancer. Acta Pharm Sin B 13: 1145-1163, 2023.
45. Manu KA, Chai TF, Teh JT, Zhu WL, Casey PJ and Wang M: Inhibition of isoprenylcysteine carboxylmethyltransferase induces Cell-Cycle Arrest and Apoptosis through p21 and p21-Regulated BNIP3 induction in pancreatic cancer. Mol Cancer Ther 16: 914-923, 2017.
46. Hanahan D and Weinberg RA: Hallmarks of cancer: The next generation. Cell 144: 646-674, 2011.
47. Cavalu S, Abdelhamid AM, Saber S, Elmorsy EA Hamad RS, Abdel-Reheim MA, Yahya G and Salama MM: Cell cycle machinery in oncology: A comprehensive review of therapeutic targets. FASEB J 38: e23734, 2024.
48. Lau HY, Tang J, Casey PJ and Wang M: Isoprenylcysteine carboxylmethyltransferase is critical for malignant transformation and tumor maintenance by all RAS isoforms. Oncogene 36: 3934-3942, 2017.
49. Gewirtz DA, Hilliker ML and Wilson EN: Promotion of autophagy as a mechanism for radiation sensitization of breast tumor cells. Radiother Oncol 92: 323-328, 2009.
50. Seyrek K, Wohlfromm F, Espe J and Lavrik IN: The cross-talk of autophagy and apoptosis in breast carcinoma: Implications for novel therapies? Biochem J 479: 1581-1608, 2022.
51. Wang M, Tan W, Zhou J, Leow J, Go M, Lee HS and Casey PJ: A small molecule inhibitor of isoprenylcysteine carboxymethyltransferase induces autophagic cell death in PC3 prostate cancer cells. J Biol Chem 283: 18678-18684, 2008.
52. Ziemys A, Yokoi K, Kai M, Liu YT, Kojic M, Simic V, Milosevic M, Holder A and Ferrari M: Progression-dependent transport heterogeneity of breast cancer liver metastases as a factor in therapeutic resistance. J Control Release 291: 99-105, 2018.
53. Cushman I and Casey PJ: Role of isoprenylcysteine carboxylmethyltransferase-catalyzed methylation in Rho function and migration. J Biol Chem 284: 27964-27973, 2009.
54. Wen S, Hou Y, Fu L, Xi L, Yang D, Zhao M, Qin Y, Sun K, Teng Y and Liu M: Cancer-associated fibroblast (CAF)-derived IL32 promotes breast cancer cell invasion and metastasis via integrin β3-p38 MAPK signalling. Cancer Lett 442: 320-332, 2019.
55. Wei L, Zhou Q, Tian H, Su Y, Fu GH and Sun T: Integrin β3 promotes cardiomyocyte proliferation and attenuates hypoxia-induced apoptosis via regulating the PTEN/Akt/mTOR and ERK1/2 pathways. Int J Biol Sci 16: 644-654, 2020.

56. Do MT, Chai TF, Casey PJ and Wang M: Isoprenylcysteine carboxylmethyltransferase function is essential for RAB4A-mediated integrin β3 recycling, cell migration and cancer metastasis. Oncogene 36: 5757-5767, 2017.
57. Bonnet D and Dick JE: Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat Med 3: 730-737, 1997.
58. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ and Clarke MF: Prospective identification of tumorigenic breast cancer cells. Proc Natl Acad Sci USA 100: 3983-3988, 2003.
59. Singh SK, Hawkins C, Clarke ID, Squire JA, Bayani J, Hide T, Henkelman RM, Cusimano MD and Dirks PB: Identification of human brain tumour initiating cells. Nature 432: 396-401, 2004.
60. Clarke MF, Dick JE, Dirks PB, Eaves CJ, Jamieson CH, Jones DL, Visvader J, Weissman IL and Wahl GM: Cancer stem cells-perspectives on current status and future directions: AACR Workshop on cancer stem cells. Cancer Res 66: 9339-9344, 2006.
61. Zanconato F, Cordenonsi M and Piccolo S: YAP/TAZ at the roots of cancer. Cancer Cell 29: 783-803, 2016.
62. Cordenonsi M, Zanconato F, Azzolin L, Forcato M, Rosato A, Frasson C, Inui M, Montagner M, Parenti AR, Poletti A, *et al*: The Hippo transducer TAZ confers cancer stem cell-related traits on breast cancer cells. Cell 147: 759-772, 2011.
63. Shao DD, Xue W, Krall EB, Bhutkar A, Piccioni F, Wang X, Schinzel AC, Sood S, Rosenbluh J, Kim JW, *et al*: KRAS and YAP1 converge to regulate EMT and tumor survival. Cell 158: 171-184, 2014.
64. Zhang W, Nandakumar N, Shi Y, Manzano M, Smith A, Graham G, Gupta S, Vietsch EE, Laughlin SZ, Wadhwa M, *et al*: Downstream of mutant KRAS, the transcription regulator YAP is essential for neoplastic progression to pancreatic ductal adenocarcinoma. Sci Signal 7: ra42, 2014.
65. Chai TF, Manu KA, Casey PJ and Wang M: Isoprenylcysteine carboxylmethyltransferase is required for the impact of mutant KRAS on TAZ protein level and cancer cell self-renewal. Oncogene 39: 5373-5389, 2020.
66. Wang S, Wang W, Zhang S, Yang F, Qiu J, Guo Q, Zheng J and Chen Z: Isoprenylcysteine carboxyl methyltransferase promotes the progression of tongue squamous cell carcinoma via the K-Ras and RhoA signaling pathways. Arch Oral Biol 134: 105320, 2022.
67. Lin L, Cheng X and Yin D: Aberrant DNA methylation in esophageal squamous cell carcinoma: Biological and clinical implications. Front Oncol 10: 549850, 2020.
68. Klintman J, Appleby N, Stamatopoulos B, Ridout K, Eyre TA, Robbe P, Pascua LL, Knight SJL, Dreau H, Cabes M, *et al*: Genomic and transcriptomic correlates of Richter transformation in chronic lymphocytic leukemia. Blood 137: 2800-2816, 2021.
69. Richardson C, Moynahan ME and Jasin M: Homologous recombination between heterologs during repair of a double-strand break. Suppression of translocations in normal cells. Ann N Y Acad Sci 886: 183-186, 1999.
70. Iliakis G, Wang Y, Guan J and Wang H: DNA damage checkpoint control in cells exposed to ionizing radiation. Oncogene 22: 5834-5847, 2003.
71. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 68: 394-424, 2018.
72. Ajani JA, D'Amico TA, Bentrem DJ, Chao J, Cooke D, Corvera C, Das P, Enzinger PC, Enzler T, Fanta P, *et al*: Gastric cancer, version 2.2022, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 20: 167-192, 2022.
73. Ma H, Wu F, Bai Y, Wang T, Ma S, Guo L, Liu G, Leng G, Kong Y and Zhang Y: Licoricidin combats gastric cancer by targeting the ICMT/Ras pathway in vitro and in vivo. Front Pharmacol 13: 972825, 2022.
74. Bray F, Laversanne M, Sung H, Ferlay J, Siegel RL, Soerjomataram I and Jemal A: Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 74: 229-263, 2024.
75. Xu J, Zhu Y, Wang F, Zhou Y, Xia G and Xu W: ICMT contributes to hepatocellular carcinoma growth, survival, migration and chemoresistance via multiple oncogenic pathways. Biochem Biophys Res Commun 518: 584-589, 2019.
76. Siegel RL, Miller KD and Jemal A: Cancer statistics, 2015. CA Cancer J Clin 65: 5-29, 2015.
77. Liu Q, Chen J, Fu B, Dai J, Zhao Y and Lai L: Isoprenylcysteine carboxylmethyltransferase regulates ovarian cancer cell response to chemotherapy and Ras activation. Biochem Biophys Res Commun 501: 556-562, 2018.
78. Bourne HR, Sanders DA and McCormick F: The GTPase superfamily: A conserved switch for diverse cell functions. Nature 348: 125-132, 1990.
79. Takashima A and Faller DV: Targeting the RAS oncogene. Expert Opin Ther Targets 17: 507-531, 2013.
80. Seger R and Krebs EG: The MAPK signaling cascade. FASEB J 9: 726-735, 1995.
81. Wahlstrom AM, Cutts BA, Liu M, Lindskog A, Karlsson C, Sjogren AK, Andersson KM, Young SG and Bergo MO: Inactivating Icmt ameliorates K-RAS-induced myeloproliferative disease. Blood 112: 1357-1365, 2008.
82. Yang WS, Kim HG, Kim E, Han SY, Aziz N, Yi YS, Kim S, Lee Y, Yoo BC, Han JW, *et al*: Isoprenylcysteine carboxyl methyltransferase and its substrate ras are critical players regulating TLR-Mediated inflammatory responses. Cells 9: 1216, 2020.
83. Sittewelle M, Kappès V, Zhou C, Lécuyer D and Monsoro-Burq AH: PFKFB4 interacts with ICMT and activates RAS/AKT signaling-dependent cell migration in melanoma. Life Sci Alliance 5: e202201377, 2022.
84. Marín-Ramos NI, Balabasquer M, Ortega-Nogales FJ, Torrecillas IR, Gil-Ordóñez A, Marcos-Ramiro B, Aguilar-Garrido P, Cushman I, Romero A, Medrano FJ, *et al*: A potent isoprenylcysteine carboxylmethyltransferase (ICMT) inhibitor improves survival in Ras-Driven acute myeloid leukemia. J Med Chem 62: 6035-6046, 2019.
85. Wan W, Xiao W, Pan W, Chen L, Liu Z and Xu J: Isoprenylcysteine carboxyl methyltransferase is critical for glioblastoma growth and survival by activating Ras/Raf/Mek/Erk. Cancer Chemother Pharmacol 89: 401-411, 2022.
86. Colicelli J: Human RAS superfamily proteins and related GTPases. Sci STKE 2004: Re13, 2004.
87. Papaharalambus C, Sajjad W, Syed A, Zhang C, Bergo MO, Alexander RW and Ahmad M: Tumor necrosis factor alpha stimulation of Rac1 activity. Role of isoprenylcysteine carboxylmethyltransferase. J Biol Chem 280: 18790-18796, 2005.
88. Cushman I and Casey PJ: RHO methylation matters: A role for isoprenylcysteine carboxylmethyltransferase in cell migration and adhesion. Cell Adh Migr 5: 11-15, 2011.
89. Schwartz SL, Cao C, Pylypenko O, Rak A and Wandinger-Ness A: Rab GTPases at a glance. J Cell Sci 120: 3905-3910, 2007.
90. Court H, Ahearn IM, Amoyel M, Bach EA and Philips MR: Regulation of NOTCH signaling by RAB7 and RAB8 requires carboxyl methylation by ICMT. J Cell Biol 216: 4165-4182, 2017.
91. Roberts M, Barry S, Woods A, van der Sluijs P and Norman J: PDGF-regulated rab4-dependent recycling of alphavbeta3 integrin from early endosomes is necessary for cell adhesion and spreading. Curr Biol 11: 1392-1402, 2001.
92. White DP, Caswell PT and Norman JC: Alpha v beta3 and alpha5beta1 integrin recycling pathways dictate downstream Rho kinase signaling to regulate persistent cell migration. J Cell Biol 177: 515-525, 2007.
93. Yang WS, Kim HG, Lee Y, Yoon K, Kim S, Kim JH and Cho JY: Isoprenylcysteine carboxyl methyltransferase inhibitors exerts anti-inflammatory activity. Biochem Pharmacol 182: 114219, 2020.
94. Judd WR, Slattum PM, Hoang KC, Bhoite L, Valppu L, Alberts G, Brown B, Roth B, Ostanin K, Huang L, *et al*: Discovery and SAR of methylated tetrahydropyranyl derivatives as inhibitors of isoprenylcysteine carboxyl methyltransferase (ICMT). J Med Chem 54: 5031-5047, 2011.
95. Chen X, Yao H, Kashif M, Revêchon G, Eriksson M, Hu J, Wang T, Liu Y, Tüksammel E, Strömblad S, *et al*: A small-molecule ICMT inhibitor delays senescence of Hutchinson-Gilford progeria syndrome cells. Elife 10: e63284, 2021.
96. Marcos-Ramiro B, Gil-Ordóñez A, Marín-Ramos NI, Ortega-Nogales FJ, Balabasquer M, Gonzalo P, Khiar-Fernández N, Rolas L, Barkaway A, Nourshargh S, *et al*: Isoprenylcysteine Carboxylmethyltransferase-Based Therapy for Hutchinson-Gilford Progeria Syndrome. ACS Cent Sci 7: 1300-1310, 2021.
97. Jayaram B, Syed I, Singh A, Subasinghe W, Kyathanahalli CN and Kowluru A: Isoprenylcysteine carboxyl methyltransferase facilitates glucose-induced Rac1 activation, ROS generation and insulin secretion in INS 832/13 β-cells. Islets 3: 48-57, 2011.
98. Koera K, Nakamura K, Nakao K, Miyoshi J, Toyoshima K, Hatta T, Otani H, Aiba A and Katsuki M: K-ras is essential for the development of the mouse embryo. Oncogene 15: 1151-1159, 1997.

99. Nakamura K, Ichise H, Nakao K, Hatta T, Otani H, Sakagami H, Kondo H and Katsuki M: Partial functional overlap of the three ras genes in mouse embryonic development. Oncogene 27: 2961-2968, 2008.
100. Fuentes-Mateos R, Jimeno D, Gómez C, Calzada N, Fernández-Medarde A and Santos E: Concomitant deletion of HRAS and NRAS leads to pulmonary immaturity, respiratory failure and neonatal death in mice. Cell Death Dis 10: 838, 2019.
101. Cui XS, Li XY and Kim NH: Cdc42 is implicated in polarity during meiotic resumption and blastocyst formation in the mouse. Mol Reprod Dev 74: 785-794, 2007.
102. Sugihara K, Nakatsuji N, Nakamura K, Nakao K, Hashimoto R, Otani H, Sakagami H, Kondo H, Nozawa S, Aiba A, *et al*: Rac1 is required for the formation of three germ layers during gastrulation. Oncogene 17: 3427-3433, 1998.
103. He X, Liu J, Qi Y, Brakebusch C, Chrostek-Grashoff A, Edgar D, Yurchenco PD, Corbett SA, Lowry SF, Graham AM, *et al*: Rac1 is essential for basement membrane-dependent epiblast survival. Mol Cell Biol 30: 3569-3581, 2010.
104. Dickinson ME, Flenniken AM, Ji X, Teboul L, Wong MD, White JK, Meehan TF, Weninger WJ, Westerberg H, Adissu H, *et al*: High-throughput discovery of novel developmental phenotypes. Nature 537: 508-514, 2016.
105. Wu Y, Yang D and Chen GY: Targeted disruption of Rab1a causes early embryonic lethality. Int J Mol Med 49: 46, 2022.
106. Dekker FJ, Rocks O, Vartak N, Menninger S, Hedberg C, Balamurugan R, Wetzel S, Renner S, Gerauer M, Schölermann B, *et al*: Small-molecule inhibition of APT1 affects Ras localization and signaling. Nat Chem Biol 6: 449-456, 2010.
107. Ibrahim MX, Sayin VI, Akula M, Liu M, Fong LG, Young SG and Bergo MO: Targeting isoprenylcysteine methylation ameliorates disease in a mouse model of progeria. Science 340: 1330-1333, 2013.
108. Bergo MO, Lieu HD, Gavino BJ, Ambroziak P, Otto JC, Casey PJ, Walker QM and Young SG: On the physiological importance of endoproteolysis of CAAX proteins: Heart-specific RCE1 knockout mice develop a lethal cardiomyopathy. J Biol Chem 279: 4729-4736, 2004.
109. Wang MT, Holderfield M, Galeas J, Delrosario R, To MD, Balmain A and McCormick F: K-Ras promotes tumorigenicity through suppression of Non-canonical wnt signaling. Cell 163: 1237-1251, 2015.
110. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, Santarosa M, Dillon KJ, Hickson I, Knights C, *et al*: Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 434: 917-921, 2005.
111. Sinnett-Smith J, Anwar T, Reed EF, Teper Y, Eibl G and Rozengurt E: Opposite effects of src family kinases on YAP and ERK activation in pancreatic cancer cells: Implications for targeted therapy. Mol Cancer Ther 21: 1652-1662, 2022.
112. Wang H, Tao Y, Han J, Shen J, Mu H, Wang Z, Wang J, Jin X, Zhang Q, Yang Y, *et al*: Disrupting YAP1-mediated glutamine metabolism induces synthetic lethality alongside ODC1 inhibition in osteosarcoma. Cell Oncol (Dordr) 47: 1845-1861, 2024.
113. Ren F, Yi Y, Lu T, Liu X, Cui G, Huang S, Parada LF and Chen J: Synthetic lethality through Gsk3β inhibition in glioma stem cells via the WNT-WWC1-YAP axis. Oncogene 44: 2427-2439, 2025.
114. Vasan N, Baselga J and Hyman DM: A view on drug resistance in cancer. Nature 575: 299-309, 2019.