

MTCH2 in Metabolic Diseases, Neurodegenerative Diseases, Cancers, Embryonic Development and Reproduction

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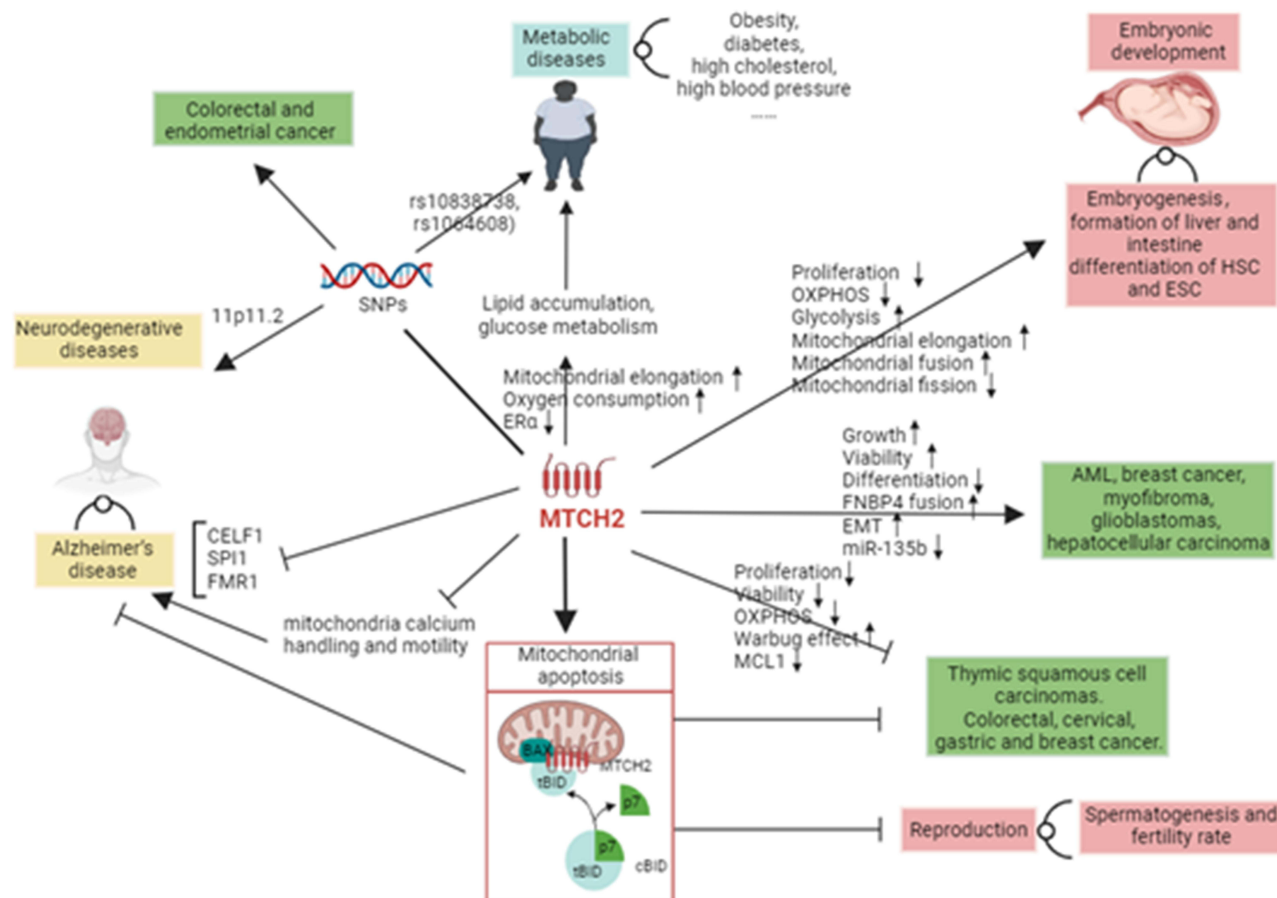
Abstract: Mitochondrial carrier homolog 2 (MTCH2) is a member of the solute carrier 25 family, located on the outer mitochondrial membrane. MTCH2 was first identified in 2000. The development in MTCH2 research is rapidly increasing. The most well-known role of MTCH2 is linking to the pro-apoptosis BID to facilitate mitochondrial apoptosis. Genetic variants in MTCH2 have been investigated for their association with metabolic and neurodegenerative diseases, however, no intervention or therapeutic suggestions were provided. Recent studies revealed the physiological and pathological function of MTCH2 in metabolic diseases, neurodegenerative diseases, cancers, embryonic development and reproduction via regulating mitochondrial apoptosis, metabolic shift between glycolysis and oxidative phosphorylation, mitochondrial fusion/fission, epithelial-mesenchymal transition, etc. This review endeavors to assess a total of 131 published articles to summarise the structure and physiological/pathological role of MTCH2, which has not previously been conducted. This review concludes that MTCH2 plays a crucial role in metabolic diseases, neurodegenerative diseases, cancers, embryonic development and reproduction, and the predominant molecular mechanism is regulation of mitochondrial function. This review gives a comprehensive state of current knowledge on MTCH2, which will promote the therapeutic research of MTCH2.

Keywords: Mimp, MTCH2, mitochondrial carrier homolog 2, BID, apoptosis

Introduction

Mitochondrial carrier homolog 2 (MTCH2) is a member of the solute carrier 25 family, an integral membrane protein known for the role of catalyzing the exchange of substrates across the inner mitochondrial membrane (IMM). MTCH2 is primarily located on the outer mitochondrial membrane (OMM) rather than the IMM, and functions as an insertase¹ and also a scramblase.^{2,3} The insertase allows the insertion of cytoplasmic α -helical protein into the outer mitochondrial membrane but not the transfer to the inner mitochondrial membrane.¹ The scramblase facilitates bidirectional lipid transport across cell membranes.⁴ The best-known role of MTCH2 is binding with truncated BID (tBID) to regulate mitochondrial apoptosis.⁵ Recent studies have demonstrated the physiological and pathological role of MTCH2 in metabolic diseases, neurodegenerative diseases, cancers, embryonic development and reproduction, and the predominant molecular mechanisms are regulating apoptosis, metabolic shift, mitochondrial elongation, epithelial-mesenchymal transition, etc. No review has summarised those findings with disease-oriented aspects, although a recent review article published in March 2024 concluded current studies on MTCH2 from a mechanism of action aspects. A thoughtful

Graphical Abstract



understanding of MTCH2 in health and diseases is helpful in guiding future research. Therefore, a total of 130 articles related to MTCH2 are systematically searched using PubMed databases, and the findings are summarised in this review. In the following sections, we will demonstrate the structure and pro-apoptosis role of MTCH2 and summarise the current studies of MTCH2 in metabolic diseases, neurodegenerative diseases, cancers, embryonic development and reproduction.

Structure Characteristics of MTCH2

MTCH2 was first identified as an uncharacterized protein of the putative open reading frames of CD34+ hematopoietic stem/progenitor cells by Zhu Chen⁸ and named because the single conserved mitochondrial carrier domain is similar to that contained in MTCH1. The MTCH family appears to have one mitochondrial carrier domain and three transmembrane domains with six transmembrane α -helices. Both the N and the C termini of MTCH2 are facing the inner membrane space (IMS), and the three long hydrophilic segments (connecting the two transmembrane regions of each domain) are facing the matrix (Figure 1).

The single conserved mitochondrial carrier domain in the MTCH family tends to have three trans-membrane domains. The unique mitochondrial carrier domain II allows the bind of the outside protein of mitochondria to the OMM but does not allow the transfer to the IMM, which is different from other mitochondrial carrier proteins binding outside proteins on the OMM and translocating them to the IMM.⁹ This is due to the hydrophilic segments of MTCH2 acting as a gatekeeper for the outer membrane, forming a prominent groove accessible to the charged and polar residues, whereas other proteins of the solute carrier 25 family which form a pore, allowing substrates to cross the membrane.¹

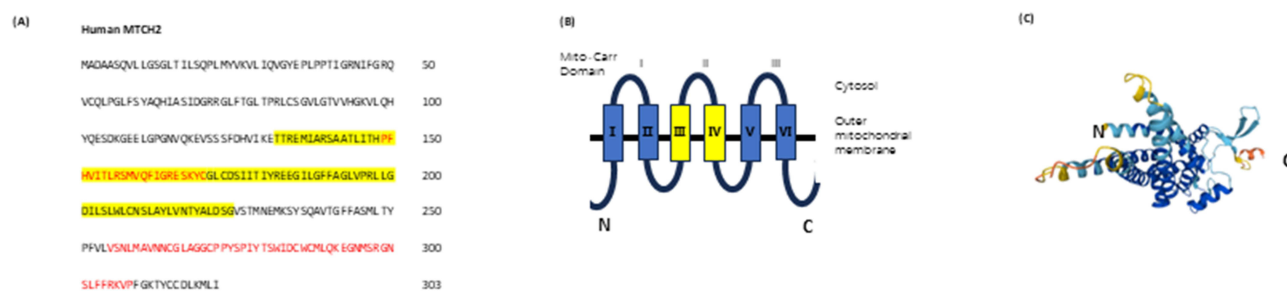


Figure 1 Structure of MTCH2. **(A)** 303 amino acids of human MTCH2, red refers to the position cross-linking to cBID; yellow refers to the amino acids 123 to 206, which construct a mitochondrial carry domain; **(B)** the diagram of human MTCH2, yellow refers to the single middle mitochondrial carry domain from positions 123 to 206 (coloured in yellow); **(C)** 3D structure of human MTCH2.

Note. **(A and B)** are adapted from "Mitochondrial carrier homolog 2 is a target of tBID in cells signaled to die by tumor necrosis factor alpha" by Michal Grinberg, Michal Schwarz, Yehudit Zaltsman, Tzipi Eini, Hagit Niv, Shmuel Pietrokovski & Atan Gross. *Mol Cell Biol.* 2005; 25: 4579–90.⁶

MTCH2 is required for the biogenesis of diverse tail-anchored (TA) mitochondrial outer membrane proteins (ie, FUNDC1, CYB5B and VDAC1) and inserts α -helical proteins into mitochondria outer membrane, of which TA proteins are the largest class.¹ A TA protein features a single C-terminal transmembrane domain. In contrast to other solute carrier 25 family members, MTCH2 has a sequence motif existing in both mitochondria and peroxisomes, and thus results in the mis-localisation of TA proteins to the endoplasmic reticulum.¹ However, recent coarse-grained and atomistic simulations experiments revealed that MTCH2 substantially diminished or even destroyed the free energy barrier for lipid flip-flop, suggesting the high scrambling activity of MTCH2, similar to VDAC dimers.⁴

The error translation of MTCH2 has been found to occur in the manner of a double stop codon read-through whose translation continues beyond the stop codon to a downstream stop codon based on the high translational readthrough efficiency of MTCH2. The double stop codon read-through of MTCH2 can be driven by a cis-acting RNA signal element, resulting in a highly unstable isoform with cytoplasmic localization, different from the canonical stable isoform and mitochondrial localisation.¹⁰

Apoptosis

The most well-known function of MTCH2 is in inducing apoptosis. MTCH2 binds with a pro-apoptotic B-cell lymphoma 2 family member cleaved BH3-interacting domain death agonist (cBID) to regulate the mitochondrial apoptosis. cBID consists of p7 and truncated BID (tBID). MTCH2 initially recruits cBID to mitochondria to unmask the BH3 domain of cBID, and then a complex of cBID, BAX and MTCH2 is built. The complex drives tBID to a highly extended conformation, and then the segments of 59–73 and 111–125 of tBID cross-link to 140–161 and 240–290 of MTCH2, respectively. Meanwhile, helices α 4–7 of tBID insert into the mitochondrial membrane.^{7,11–13} The deeper insertion of tBID is a prerequisite for formatting the complex of tBID and BAX, which forms lipidic pores allowing large macromolecules into mitochondria, leading to the increase in mitochondrial outer membrane permeabilization (MOMP) and release of multiple apoptogenic factors including cytochrome c. Cytochrome c released to cytosol sequentially activates effector caspases.^{6,7,14} Besides, the complex of the modulator of apoptosis-1 (MOAP-1) and MTCH2 has also been shown to be required to insert tBID into mitochondrion.¹⁵

The knockout of *MTCH2* delays instead of eliminates the tBID triggered MOMP and apoptosis accompanied with the decreased sensitivity of the insertion of tBID to mitochondria.^{5,7,16} This could be because of the compensatory role of cardiolipin, which has a similar function to MTCH2 in activating tBID.¹⁷ An impaired recruitment of tBID was found in the depletion of both cardiolipin and *MTCH2*, but not in knockout cardiolipin or *MTCH2* alone.¹⁶ Concordantly, overexpressed MTCH2 is markedly sensitive to apoptosis induced by imatinib treatment in human myelogenous leukemia K562 cells.^{1,16}

Metabolic Diseases

On the basis of the two-fold increased mRNA of *MTCH2* in human skeletal muscle in response to insulin that was first found in 2003¹⁸ and the rapid development of single nucleotide polymorphisms (SNPs) detection technology, studies on the relevance of *MTCH2* SNPs to obesity and diabetes emerged. Also rs10838738 is a cis-expressed quantitative trait locus on the expression of *MTCH2* that has gained great attention. Dozens of studies revealed the association of rs10838738 SNP in *MTCH2* with obesity and diabetes on the basis of the highly expressed *MTCH2* in human white adipose tissue and adipocytes.^{19–22} However, the results of association between SNPs in or near *MTCH2* with obesity and diabetes vary on population and age.²³ Ethnicity has been found to be the most significant moderator affecting the heterogeneity for *MTCH2* with BMI.²⁴ An interaction between sex and *MTCH2* SNPs among Chinese obesity was discovered.²⁵ Moreover, the DNA methylation level of *MTCH2* in human adipose tissue was found to be correlated with increased BMI,²⁶ and played a prominent role with *MTCH2* in adipogenesis in intramuscular fat regulation via regulation of the level of m6A-YTHDF1.²⁷

The investigation in SNPs of *MTCH2* is sequentially extended to other metabolic diseases. The significant associations with lower high density cholesterol levels,²⁸ high blood pressure,²⁹ metabolic syndrome,³⁰ and polycystic ovary syndrome³¹ were observed, and these could be due to the enriched SNPs in or near *MTCH2* in purine, deoxynucleotide, and ribo-deoxynucleotide metabolism³² and associated with total carbohydrate, mono- and disaccharide, and polysaccharide intakes.³³ There is a non-referent allele, *MTCH2*p.Pro290Ala, which is also found to be associated with increased BMI, and the referent allele of p.Prp 290 (rs1064608) in *MTCH2* induces the lower expression of *MTCH2*.³⁴

The relation between SNPs of *MTCH2* and metabolism has been found in child growth and development, i.e., lower birth weight³⁵ and childhood BMI trajectories.³⁶ However, the association with paediatric BMI is controversial,^{37,38} and no association with BMI across adulthood is observed.³⁹ The genetic risk score built by summing risk alleles including *MTCH2* SNPs is found to be related to BMI, obesity, faster weight gain in childhood⁴⁰ and early menarche.⁴¹

The relation between *MTCH2* and metabolism could be attributable to the involvement of *MTCH2* in lipid homeostasis/storage and glucose metabolism. Homozygous mutants of *Mtch1* in *C. elegans* significantly reduce fat storage, and overexpression of *Mtch1* triggers lipid accumulation.⁴² The knockdown of *Mtch2* in *Drosophila* results in cardiomyopathy, less adiposity and a shortened life span.⁴³ Consistently, *Mtch2*-GFP transgenic mice and *MTCH2* overexpressed HEK29 cells show the dysfunction of lipid metabolism, resulting in fatty and lactate accumulation and impaired oxygen consumption, and this might be regulated by the increased pyruvate dehydrogenase kinase, genes of medium chain acyl-CoA dehydrogenase, acetyl-CoA acyltransferase 2 and fatty acid synthase (FASN).^{43,44} However, *MTCH2* is favourable in the situation where glucose oxidation and tricarboxylic acid cycle are predominant, such as heart failure.⁴³ Moreover, *MTCH2* is helpful in stimulating mitochondrial hyperfusion to elongate mitochondria in a bioactive lipogenesis intermediated lysophosphatidic acid way to boost energy production under starving conditions.⁴⁵ The direct binding between estrogen receptor alpha (ERα) and *MTCH2* has been identified by a yeast-two-hybrid screen,⁴⁶ and a further finding revealed that *MTCH2* has an inhibitive impact on the transcriptional potential of ERα, a known regulator of metabolic homeostasis.⁴²

The effect of *MTCH2* targeted clinical assessment and potential intervention have been assessed. The genetic risk scores composed of seven SNPs including *MTCH2* that is negatively associated with excess BMI loss after roux-en-Y gastric bypass surgery.⁴⁷ However, weight loss among obese women does not alter the expression of *MTCH2*,¹⁹ and alleles of *MTCH2* are not associated with weight regain in the course of one year after a lifestyle intervention in overweight children.⁴⁸ *Mtch2* deletion mice eat more compared to control mice when fed a high-fat diet but are less susceptible to weight gain with less fat per body weight and lower levels of circulating insulin.⁴⁹ This could be due to the raised muscle metabolic capacity, energy demand and expenditure resulting from the increased mitochondrial metabolism and mass.⁴⁹ Superparamagnetic iron oxide nanoparticles induce the upregulation of *MTCH2* in human adipocytes among diabetics,⁵⁰ which might be helpful for the apoptosis of adipocytes. The *MTCH2*–treatment interactions are observed for short-term weight loss among diabetics.⁵¹ Moreover, a lower expression of *MTCH2* has been found in eclampsia patients, but the underlying mechanism was not investigated.⁵²

Neurodegenerative Diseases

The highest MTCH2 expression level is in the hippocampal formation and cerebellum in the mouse brain.⁵³ Decreased gene expression of MTCH2 has been identified as a risk factor of Alzheimer's disease (AD).^{54,55} SNPs in MTCH2 have been shown to be related to AD,^{32,56} schizophrenia⁵⁷ and emotional eating in humans.⁵⁸ Functional variants at 11p11.2 of MTCH2 is involved in AD development via altering cellular amyloid- β and phosphorylated tau.⁵⁹ MTCH2 is a conjoined gene, in which SNPs are related to both cardiovascular and AD,⁶⁰ both obesity and AD,⁵⁶ and both AD and glaucoma.⁶¹

The underlying mechanism of the relation between MTCH2 and AD seems to be related to the mitochondrial apoptosis and the interaction with other AD genes. Mitochondria apoptosis that regulated by cooperation between MTCH2 with BID promotes Ca^{2+} -induced neuronal injury.⁶² *Mtch2* knockout in the mouse forebrain triggers the deficiency of mitochondria calcium handling and mitochondrial motility in the hippocampus, resulting in the reduction of synaptic connectivity, motor coordination and impaired hippocampal long-term potentiation and rotarod test.⁶³ Meanwhile, activated microglia was increased, and neuron density was reduced.⁶⁴ However, the specific influence of MTCH2 on neurodegenerative disorders varies with age.⁶⁴ *Mtch2* deficient 3-month-old mice have an increased swimming speed compared with controls, but *Mtch2* forebrain conditional knockout mice at the ages of 9 and 14 months have a deterioration of spatial navigation and lower short- and long-term potentiation accompanied with plastic properties and neurodegeneration in the hippocampus.⁶⁴ There is a shorter stay in the rotarod test in MTCH2 conditional knockout mice at age 3 months than at ages 9 and 14 months. The electrophysiological response to the tetanic stimulation is significantly different between *Mtch2* forebrain conditional knockout mice at the ages of 9 and 14 months. There is a contrast result in *Caenorhabditis elegans*, in which age-related proteostasis collapse is suppressed by the loss of MTCH1/MTCH2 via activating CED-4/3 and heat shock proteins and suppressing the activity of HSF-1.⁶⁵

MTCH2 has been found to be associated with AD related genes or mental diseases related genes, including CELF1,⁵⁵ SPI1³² and FMR1.⁶⁶ CELF1 is an AD risk gene, and there is expression of MTCH2 within CELF1 locus in AD brains.⁵⁵ MTCH2 is associated with SPI1, a well-known microglial transcription factor. SPI1 also interacts with CELF1, and the knockdown of *SPI1* reduces AD pathology.³² FMR1 encodes fragile X mental retardation proteins, loss of which is the leading cause of inherited forms of mental retardation and autism, and MTCH2 is negatively correlated to the level of FMR1.⁶⁶ SNPs of MTCH2 are related to emotional eating in humans⁶⁴ but not in zebrafish.⁶⁷

Cancers

MTCH2 has been identified as a "Poised Gene Cassette" to balance the complex interplay of pro- and anti-oncogenic genes,⁶⁸ and the role of MTCH2 is different in different cancers. Inhibition of MTCH2 tends to have therapeutic effects on acute myeloid leukemia (AML), glioblastomas, hepatocellular carcinoma and osteosarcoma, but seems to deteriorate colorectal cancer, cervical cancer and gastric cancer. In AML, inhibition of MTCH2 shows the loss of engraftment potential effect in vitro and in vivo.⁶⁹ The knockout of *MTCH2* depresses growth, viability and clonogenic growth in AML cells.⁶⁹ Moreover, *MTCH2* knockdown promotes differentiation from hematopoietic stem cells to differentiated myeloid population and from primitive/stem-like AML fractions to differentiated AML cells.⁶⁹ *Mtch2* knockout in a murine model of leukemia transduced with *Mll-af9* oncogene decreases the leukemogenic potential of MLL-AF9 oncogene,⁶⁹ and this might be because of the increased histone acetylation that resulted from the increased mitochondrial/nuclear pyruvate content and pyruvate dehydrogenase instead of the pro-apoptotic effect of BID combination.⁶⁹

A *MTCH2* (Chr11: 47,647,265 A>G) gene sequence change is found in rapidly growing glioblastoma, indicating that the change of variant prioritization after annotation may be involved in the aggression of glioblastomas.⁷⁰ The high expression of MTCH2 in malignant glioma has been shown to be related to a metabolic shift from OXPHO to aerobic glycolysis and mitochondrial dysfunctions, and AKT signaling seems to be involved in this relationship.⁷¹ Mitochondrial dysfunction and apoptosis in hepatocellular carcinoma have been shown to be related to aberrantly enriched nuclear-encoded long noncoding RNA (lncRNA) metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), and the transportation of MALAT1 to mitochondria is mediated by MTCH2.⁷² Upregulated MTCH2 has also been found in clinical osteosarcoma samples.⁷³ In osteosarcoma, overexpression of *MTCH2* rescues the attenuated cell viability,

inhibited proliferation, promoted cell apoptosis, elevated OXPHOS and suppressed the Warburg effect triggered by *APOC1* silencing,⁷⁴ and the regulation of oncogene FASN on MTCH2 is detected by iTRAQ-based proteomic analysis.⁷⁵

On the contrary, upregulation of MTCH2 tends to have a therapeutic effect on thymic squamous cell carcinomas, cervical cancer, colorectal cancer and gastric cancer. The therapeutic effect of MTCH2 in thymic squamous cell carcinomas is through inducing apoptosis.⁷⁶ MTCH2 has been found to be a therapeutic target of dihydroartemisin and alisertib. Upregulated MTCH2 and caveolin 1, after dihydroartemisin treatment, inhibit cell viability and prompt the apoptosis of cervical cancer cells and increases the sensitivity to treatment.⁷⁷ A network pharmacology analysis reveals that MTCH2 is a potential therapeutic target of alisertib to treat colorectal cancer,⁷⁸ and SNPs of MTCH2 have been found to be related with colorectal cancer.⁷⁹ Further depletion of both cardiolipin and *MTCH2* results in an impaired recruitment of tBID in the human colorectal cancer cell line HCT116.¹⁶ Similarly, silence of MTCH2 increases the invasion of gastric cancer cells.⁶⁸ MTCH2 cooperates with the mitochondrial ubiquitin E3 ligase MARCH5 and the ubiquitin E2 conjugating enzyme UBE2K to degrade myeloid cell leukemia-1 protein (MCL1) by the proteasome.⁸⁰ This facilitates the clearance of unfit cells following DNA damage and cell cycle arrest in many types of cancer cells.⁸⁰ Moreover, treatment with aminoethyl dihydrogen phosphate upregulates the protein expression of MTCH2, BAD and BAX and downregulates antiapoptotic protein B-cell lymphoma 2.⁸¹ Bioinformatics analysis reveals the association between MTCH2 and tumor-promoting factors and the alteration of the DNA methylation pattern of MTCH2 in different cancer tissues, moreover, the combined effect of clustered genes, including MTCH2, could predict the survival probability of patients with 14 types of cancer.⁸²

The findings of the effect of MTCH2 on breast cancer are controversial, and this might be due to the fact that breast cancer has diverse sub-types and different stages. Most coding sequences of MTCH2 are conjoint with exons 7 to 17 of FNBP4 to construct a fusion gene, which has been found to be associated with breast cancer⁸³ and myofibroma.⁸⁴ The decreased mRNA expression of MTCH2 is reverse regulated by abundant miR-135b in basal and normal-like human breast cancers.⁸⁵ Similarly, the involvement of MTCH2 in normal human breast gland development might result in the association of MTCH2 with the epithelial–mesenchymal transition in breast cancer.⁸⁶ However, the protein level of MTCH2 is increased 2.3 times in breast tumor MDA-MB-231 cell line after treatment with sub-toxic dose of snake venom compared with untreated cells.⁸⁷ MTCH2 expression reduces Met-HGF/SF-induced proliferation and scattering by attenuating and altering the downstream signaling of Met in breast cancer cell lines.⁷³ SNPs of MTCH2 have also been found to be related with endometrial cancer.⁸⁸

Embryonic Development

MTCH2 is necessary for embryogenesis and plays a crucial role in fertility, formation of liver and intestine and differentiation of haematopoietic stem cells. Although heterozygote *Mtch2*[±] mice are viable, fertile and show no phenotypic abnormalities, homozygous *Mtch2*^{-/-} mice die at embryonic day 7.5 due to multiple defects, suggesting that MTCH2 is a prerequisite for embryogenesis.⁵ Knockdown of *Mtch2* progressively affects postembryonic growth of zebrafish larvae with significantly smaller embryo than control zebrafish at 8dpf and the impaired development of liver and intestine, and this could be resulted from metabolic impairment and an energy deficient state.⁶⁷

MTCH2 helps to maintain the self-renewal and quiescence of haematopoietic stem cells (HSCs) in bone marrow niches⁸⁹ and in embryonic stem cells (ESCs).⁹⁰ Non-motile HSCs enter into peripheral cycle replenishment with the blood with mature leukocytes and red blood cells on demand, leading to exhaustion of quiescent HSCs. Loss of MTCH2 facilitates the transition of non-motile HSC into cycles via enhancing the proliferation of HSCs, and this relates to the metabolic shift from glycolysis to OXPHOS in HSCs, where glycolysis is preferred and the enlarged mitochondria.^{89,91} Loss of MTCH2 and elevation in OXPHOS have been shown to protect HSCs and haematopoietic progenitor cells from irradiation-induced death in vivo and *in vitro*.⁸⁹ MTCH2 prompts mitochondrial fusion and depresses mitochondrial fission in the naïve-to-primed interconversion during embryo development, resulting in mitochondria elongation and an increase in mitochondrial mass, mtRNA and mitochondria respiration.^{91,92} The elongated mitochondria facilitate partial exit from naive pluripotency without entering differentiation via modulating nuclear gene reprogramming to drive reprogramming of mitochondria metabolism including glucose and glutamine metabolism and histone deacetylation.⁹¹ In ESCs, overexpression *MTCH2* rescues the *COP55* knockout induced growth defect, reduced glycolysis, enhanced

OXPHOS, elevated reactive oxygen species (ROS) and subsequent DNA damage accumulation,⁹⁰ suggesting that MTCH2 facilitates ESC maintaining genome integrity and self-renewal capacity. The translation of the MTCH2 gene or MTCH2-regulated mitochondria from bone marrow mesenchymal stem cells to RAW264.7 cells, which suppresses the upregulated apoptosis and ROS stimulated by lipopolysaccharide,⁹³ suggesting the potential for MTCH2 treatment.

Reproduction

The testis is an organ in a high level of apoptosis with the expression of MTCH2, which is initially detected during the first spermatogenic wave and fluctuates depending on the different developmental stages and testicular cells.⁹⁴ MTCH2 level increases with mild hyperthermia-induced testicular apoptosis.⁹⁴ Similarly, the *Mtch2* overexpression mouse line shows a low fertility rate and no progeny for the last generation.⁴⁴ On the contrary, the reduction of *Mtch1* in worms results in fertility defects, homozygous mutants of *Mtch1* in *C. elegans*. and MTCH2 in mice cause sterile adults,⁴² and loss of MTCH2 is detected in cattle-yak.⁹⁵ These findings suggest that an appropriate level of MTCH2 is required for male fertility. A recent study reveals that the level of MTCH2 expression and subsequent pro-apoptotic proteins including BID, BAX, cytochrome C, caspase-9, and caspase-3 are decreased after the stimulation of silica nanoparticles, resulting in the apoptosis of spermatogenic cells.⁹⁶

Discussion

The first well-known role of MTCH2 was regulating apoptosis, and this affected the following studies. The vast quantities of SNP studies investigate the associations of MTCH2 with metabolic diseases including obesity, diabetes, cardiovascular diseases and neurodegenerative diseases including AD, leading to the further exploration of the underlying mechanism of the association. Due to the high metabolic demand and suppressed apoptosis of cancer cells, upregulation of MTCH2 tends to have a therapeutic effect on colorectal cancer, cervical cancer and gastric cancer. However, inhibition of MTCH2 shows the therapeutic prospect on several cancers, i.e., the myeloid leukemia, glioblastomas and hepatocellular carcinoma. With the application of technology of gene knockout in mouse, the fatality of homozygous *Mtch2*^{-/-} mice attracts attentions on the role of MTCH2 in embryonic development. MTCH2 is found to be a prerequisite of embryogenesis and organ development (i.e., liver and intestine), a protector of self-renewal and quiescence of stem cells and a promotor of spermatogenesis.

Studies on the function of MTCH2 in health and diseases have been increasingly emerging, however, the current findings generally are still in the early stages. There are many research fields that MTCH2 has not been considered for, such as follicular development, pregnancy complications, immunological diseases and respiration system diseases, etc. A sign of the therapeutic potential of MTCH2 has emerged based on the fact that superparamagnetic iron oxide nanoparticles, dihydroartemisin, alisertib, aminoethyl dihydrogen phosphate and snake venom could regulate the expression of MTCH2, and moreover MTCH2 seems to be the downstream factor of FASN, COPS5 and miR-150. However, none of the above studies is initially designed to investigate that MTCH2 acts as a treatment target through excluding the interference with other molecules.

In conclusion, the emerging studies demonstrate the physiological role of MTCH2 in metabolic diseases, neurodegenerative diseases, cancers, embryonic development and reproduction, although further investigations for deeper elucidation are required. This review fills the gap in the summary of the current findings with MTCH2, from disease-oriented aspects, to highlighting the therapeutic prospect of MTCH2 and encouraging future studies to discover more comprehensive functions of MTCH2 in health and diseases.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

All the authors declare that they do not have any financial and personal relationships with other people or organizations that could influence the design, supervision or reporting of their work. The authors declare that they have no competing interests.

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