Am J Transl Res 2025;17(4):2411-2421
www.ajtr.org /ISSN:1943-8141/AJTR0162592

Review Article

Research progress on the role of Claudin family proteins in mediating blood-brain barrier selective permeability in tumor metastasis

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Received December 11, 2024; Accepted March 17, 2025; Epub April 15, 2025; Published April 30, 2025

Abstract: The blood-brain barrier (BBB) serves as a critical protective mechanism for the central nervous system (CNS), controlling the selective passage of molecules between the brain and the bloodstream. Claudin proteins, key components of tight junctions, play a central role in maintaining BBB integrity and regulating its permeability. Recent research has increasingly focused on how Claudins contribute to brain metastasis, where tumor cells alter Claudin expression to breach the BBB and invade brain tissue. While Claudin family such as Claudin-1 and Claudin-5 are essential for maintaining BBB function, their dysregulation in tumor cells facilitates BBB disruption, promoting metastasis. This review explores the dual role of Claudins in tumor progression, detailing how they regulate BBB permeability and enable tumor cells to cross the barrier. Additionally, we discuss the potential of Claudin proteins as therapeutic targets in cancer treatment, offering new insights into mechanisms of brain metastasis.

Keywords: Claudin, BBB, tumor metastasis, selective permeability, cancer treatment

Introduction

The blood-brain barrier (BBB) is a selective permeability barrier between the brain and the bloodstream, primarily composed of endothelial cells, the basement membrane, pericytes, and glial cells [1]. Its primary function is to protect the brain from harmful substances, pathogens, and toxins, while allowing essential nutrients such as oxygen and glucose to reach neural tissue (**Figure 1**). The BBB is mainly formed by brain microvascular endothelial cells, tight junctions, the basement membrane, and pericytes [2]. Among the key components of the tight junctions, the Claudin proteins play a crucial role in maintaining BBB integrity by regulating the permeability of substances across endothelial cell layers. Claudin proteins, in interaction with other tight junction components like occludin and ZO proteins, form tight junctions between endothelial cells, controlling the passage of ions, water-soluble substances, and small molecules between the blood and the brain [3, 4]. These proteins are essential not only for maintaining the structural integrity of the BBB but also for regulating the selective exchange of substances, which is fundamental to the homeostasis of the brain's microenvironment [5].

In addition to its protective function, the BBB plays a dual role in tumor metastasis. On one hand, it acts as a physical barrier to limit the entry of tumor cells into the central nervous system (CNS), preventing brain metastasis. On the other hand, tumor cells can breach the BBB through a series of molecular mechanisms that involve alterations in tight junction protein expression, allowing them to invade brain tissue and form metastatic lesions [6]. Many cancers, such as breast cancer, lung cancer, and melanoma, commonly spread to the brain via the bloodstream, resulting in brain metastases [7-9]. During BBB disruption, tumor cells typically alter the expression of tight junction proteins, including Claudins, which increases BBB permeability. A study by Abuelrub et al. [10] demonstrated that tumor cells regulate BBB

https://doi.org/10.62347/GGGX3909

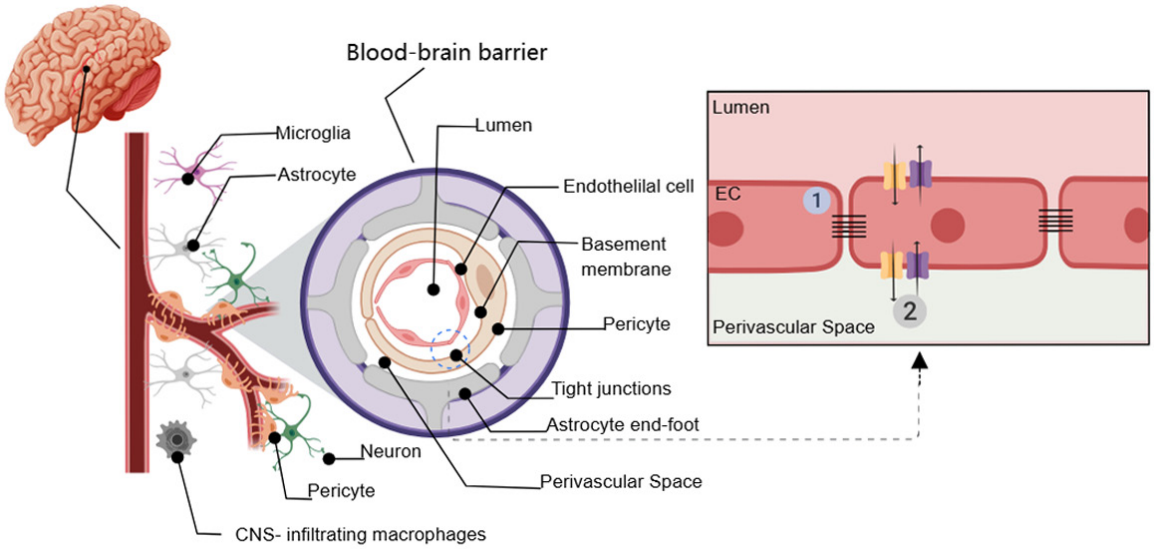

Figure 1. Structure of blood-brain barrier. CNS: central nervous system; EC: endothelial cells.

permeability by modulating the expression of Claudin proteins (e.g., Claudin-1, Claudin-5), thus facilitating their penetration through the BBB. These findings indicate that both the upregulation and downregulation of Claudins can significantly influence tumor cell penetration of the BBB, promoting metastasis.

Therefore, while Claudin proteins are essential for the normal function of the BBB, their alteration during pathological conditions, such as tumor metastasis, highlights their potential as critical molecular targets. Targeting Claudins may offer novel therapeutic approaches to managing brain metastasis by restoring BBB integrity and inhibiting tumor cell invasion.

Blood-brain barrier structure and function

Basic structure of the blood-brain barrier and its components

The BBB is a highly specialized and selective barrier that separates the brain from the bloodstream, ensuring that the brain's microenvironment is tightly regulated [11]. It is primarily composed of brain microvascular endothelial cells, the basement membrane, pericytes, and glial cells [12]. Unlike other vascular tissues, these endothelial cells of the brain's microvasculature are tightly joined by tight junctions, which form a nearly impermeable barrier between cells, effectively restricting the passage of large molecules and potentially harmful substances from the blood into the brain [13]. This unique structural feature of the BBB ensures that essential nutrients and water-soluble substances can pass through, while harmful substances are kept out. Key to the function of the BBB are the tight junction proteins, including Claudin, Occludin, and ZO proteins, which coordinate the regulation of intercellular connections [14]. These proteins play a central role in maintaining the selective permeability of the BBB, regulating the passage of ions, small molecules, and water-soluble substances between the endothelial cells. Claudin proteins, in particular, are central to BBB function due to their unique structural features and their ability to regulate tight junctions. Through their interactions with other junctional proteins, Claudins help maintain both the integrity of the barrier and its selective permeability, ensuring that only necessary substances can cross from the blood into neural tissue [5].

In addition to tight junctions, the basement membrane and pericytes provide structural and functional support to the BBB. The basement membrane serves as a scaffold for the endothelial cells, contributing to the overall stability of the BBB. Pericytes, embedded within the basement membrane and interacting closely with endothelial cells, play a dynamic role in regulating BBB function. They contribute to the modulation of the barrier's permeability and help maintain its integrity under varying

Table 1. Functions of Claudin family members in BBB

Claudin Family Member	Tissue Expression	Role in BBB	Impact on BBB Permeability	Relevance to Tumor Metastasis
Claudin-1	Widely distributed in tight junctions	Maintains tight junction integrity	Low expression increases permeability	Impaired function facilitates tumor cell invasion [29, 30]
Claudin-5	BBB (endothelial cells)	Regulates BBB permeability and structural integrity	High expression stabilizes the BBB; low expression increases permeability	Changes in expression enhance tumor cell migration [25, 26]
Claudin-3	Epithelial and endothelial cells	Contributes to tight junction formation	-	-
Claudin-2	Kidney, intestine, BBB	Involved in paracellular permeability	Increased expression enhances permeability	-

Note: BBB: blood-brain barrier.

physiological conditions [2, 15, 16]. Moreover, glial cells, particularly astrocytes, provide additional support by maintaining close contact with the endothelial cells, ensuring the structural and functional stability of the BBB. Astrocytes are crucial for regulating the blood-brain interface and contribute to the adaptability of the barrier in response to changes in the brain's microenvironment [17] (**Figure 1**).

Function, classification, and role of Claudin proteins in blood-brain barrier permeability and tumor metastasis

The Claudin family comprises 27 members, playing a crucial role in the formation and regulation of tight junctions [18]. These junctions are essential for controlling the selective permeability of cellular barriers, such as the BBB. Claudins are expressed across various tissues and organs, with Claudin-1, Claudin-3, and Claudin-5 being particularly critical for the integrity of the BBB [19]. Through their interaction with other tight junction-associated proteins, such as occludin and ZO proteins, Claudins stabilize intercellular junctions and regulate the permeability of the BBB [20]. A summary of the functions of major Claudin family members is shown in **Table 1**.

Among the Claudin family members, Claudin-1 and Claudin-5 have been extensively studied due to their key roles in BBB function. Claudin-5 is responsible for regulating the permeability of brain microvascular endothelial cells and maintaining the structural integrity of the barrier [21, 22]. High expression of Claudin-5 enhances the stability of tight junctions, thus reducing permeability, whereas its downregulation or loss of function facilitates BBB disruption, making it easier for tumor cells and other harmful substances to cross the barrier [23, 24]. Studies by Sun et al. and Zhang et al. have shown that low expression of Claudin-5 correlates with increased BBB permeability, promoting tumor cell invasion [25, 26].

Similarly, Claudin-1, although less studied in the context of the BBB, also contributes to its function [27]. The loss or downregulation of Claudin-1 impairs tight junction integrity, compromising the BBB and increasing its susceptibility to invasion by harmful substances [28]. Research by Liebner et al. and Roche et al. highlights how changes in the expression of Claudin-1 and Claudin-5 can modify BBB permeability, which is further influenced by environmental factors such as intermittent hypoxia, emphasizing the role of Claudins in BBB regulation [29, 30].

Beyond their structural roles, Claudin proteins also regulate cellular signaling and intercellular interactions, helping to maintain BBB integrity. Their involvement extends to tumor metastasis, as alterations in their expression are critical for tumor cells to invade the brain.

Regulation of BBB selective permeability: the role of Claudin proteins and the impact of internal and external factors in tumor metastasis

Selective permeability is one of the characteristics of the BBB, essential for maintaining the brain's microenvironment by controlling the passage of substances. This selective permeability is tightly regulated not only by the properties of tight junction proteins, such as Claudins, but also by a range of internal and external factors [31].

Internal regulation: Neural activity plays a significant role in modulating BBB permeability.

According to Hang et al., neural activity activates specific receptors in the brain that influence tight junction dynamics between endothelial cells, thereby regulating BBB permeability. This modulation is essential for maintaining homeostasis within the brain's microenvironment [32].

External regulation: Inflammation is another key factor that can alter BBB permeability. TNF-α, an inflammatory cytokine, has been shown to increase BBB permeability by promoting the degradation of tight junction proteins, including Claudin-5. Studies, such as those by Munoz Pinto et al., demonstrate that TNF-α selectively enhances BBB permeability at brain metastatic sites, facilitating tumor cell invasion [33]. Moreover, tumor cells can directly interact with the endothelial cells of the BBB, disrupting tight junctions and creating conditions conducive to metastasis [34].

The complex interplay between internal factors (neural activity) and external factors (inflammation, tumor cells) is central to understanding how tumor cells breach the BBB. The expression levels of Claudin proteins, which regulate BBB permeability, are critical to the stability of tight junctions. A deeper understanding of these dynamic regulatory mechanisms is essential for developing therapeutic strategies aimed at limiting tumor metastasis to the brain.

Role of Claudin proteins in tumor metastasis and BBB permeability

Recent studies have demonstrated that Claudin proteins not only regulate the selective permeability of the BBB but also play significant roles in tumor initiation, progression, and metastasis [35, 36]. The expression and functional alterations of Claudin proteins are closely linked to the invasive behavior and metastatic potential of tumor cells. For example, Claudin-1 and Claudin-4 are frequently overexpressed in various cancers, including breast, liver, and pancreatic cancers, where they disrupt the tight junctions between cells. This disruption enhances tumor cell migration and invasiveness, thereby promoting tumor metastasis [36]. In contrast, Claudin-5, a key protein in maintaining BBB integrity, plays a critical role in tumor metastasis to the brain. Downregulation of Claudin-5 expression has been shown to increase BBB permeability, allowing tumor cells to cross the barrier and invade brain tissue, facilitating brain metastasis [37].

Other members of the Claudin family also contribute to tumor progression. Claudin-7, for instance, is aberrantly expressed in colorectal cancer, where it destabilizes tight junctions, promoting tumor cell migration and increasing invasiveness [38]. Claudin-3 overexpression is particularly notable in ovarian and breast cancers, where it correlates with enhanced tumor cell invasiveness and metastasis. This may be due to the regulation of the tumor microenvironment and alterations in BBB function, creating favorable conditions for tumor cell dissemination [39, 40]. Claudin proteins influence both the interactions between tumor cells and the extracellular matrix (ECM) and promote tumor cell migration by modulating the ECM's composition and stiffness. Targeting Claudin proteins holds potential as a therapeutic strategy to inhibit tumor metastasis. Investigating their role in regulating BBB permeability will provide valuable insights into the development of novel therapies for managing brain metastasis and other forms of cancer dissemination.

Alterations in Claudin family members and their impact on tumor metastasis

The Claudin family consists of 27 distinct proteins, and their expression varies significantly across different tumor types. Alterations in the expression of Claudin proteins are often correlated with the invasiveness and metastatic potential of various cancers [35]. During tumor metastasis, changes in the expression of Claudin proteins can influence BBB permeability and facilitate tumor cell migration and invasion. For instance, Claudin-1 is frequently overexpressed in highly invasive tumors, including breast cancer, liver cancer, and pancreatic cancer, where it plays a role in enhancing tumor cell motility and invasiveness [41]. This overexpression of Claudin-1 promotes the degradation and remodeling of the ECM, which is crucial for facilitating the colonization and spread of tumor cells to distant organs. Furthermore, tumor cells can activate certain Claudin proteins, leading to local tissue disruption and providing an opportunity for tumor cells to migrate through the bloodstream or lymphatic system, ultimately forming metastatic lesions [42].

In addition to their role in altering the tumor microenvironment, Claudin proteins also modulate the response to treatment. The expression levels of these proteins can influence how tumor cells respond to chemotherapy, radiation, or targeted therapies. By regulating Claudin protein expression, it may be possible to control tumor invasiveness, improve treatment outcomes, and develop more effective therapies for metastatic cancers.

Overall, Claudin proteins play an essential role in modulating tumor invasiveness and metastasis. Their regulation during tumor progression offers important insights into the molecular mechanisms underlying cancer spread and may provide potential targets for therapeutic intervention.

Mechanisms of tumor cell invasion and metastasis to the brain

The process of tumor cells metastasizing from a primary site to the brain is complex and involves multiple stages: tumor cells have to cross the BBB, invade brain tissue, and establish a proliferative environment in the brain [43]. Initially, tumor cells proliferate at the primary site, invade surrounding tissues, and enter the bloodstream or lymphatic system, forming circulating tumor cells (CTCs). These CTCs then travel through the bloodstream and reach the microvasculature of the brain [44]. However, the BBB, with its highly selective permeability, typically prevents most substances, including tumor cells, from entering the brain. To overcome this challenge, tumor cells employ a range of mechanisms to breach the BBB [45].

To cross the BBB, tumor cells must first adapt their morphology and functionality to enhance adhesion within the blood vessels. Tumor cells often upregulate specific adhesion molecules, such as integrins and glycoproteins, allowing them to adhere more strongly to endothelial cells in the blood vessel wall [46]. Additionally, tumor cells can secrete proteases like metalloproteinases, which degrade the basement membrane and tight junction proteins between endothelial cells, thereby disrupting the tight junctions and increasing the permeability of the BBB. As a result, tumor cells can breach the BBB and invade brain tissue [47].

Once tumor cells cross the BBB, they encounter the unique microenvironment of brain, including hypoxia, acidic conditions, and specific immune responses, which help tumor cells adapt and establish metastatic colonies [48]. Some tumor cells also induce local immune suppression, evading immune system surveillance and further promoting their survival and growth in the brain. Moreover, interactions with glial cells, astrocytes, and endothelial cells in the brain's microenvironment further support tumor expansion [45]. Certain Claudin proteins, particularly Claudin-5, play a critical role in tumor cell invasiveness and metastatic ability. Studies have shown that the downregulation of Claudin-5 and other BBB-associated tight junction proteins enhances BBB permeability, providing a pathway for tumor cells to cross the barrier and invade brain tissue [37]. Once tumor cells enter the brain, they proliferate and form metastatic lesions, further expanding through mechanisms like angiogenesis and local proliferation. Tumor cells in the brain may also develop resistance to conventional therapies, making brain metastasis a clinically challenging and difficult-to-treat condition.

The mechanisms of Claudin proteins regulating BBB permeability

The Claudin protein family plays a crucial role in the formation and regulation of tight junctions, which are essential for maintaining the integrity and selective permeability of the BBB [36]. The BBB functions as a highly selective barrier between the brain and the bloodstream, primarily formed by tight junctions between endothelial cells. Claudin proteins, such as Claudin-1, Claudin-5, and Claudin-3, are key components of these junctions, regulating the passage of molecules between the blood and brain tissue. Claudins regulate BBB permeability by forming tight junctions between endothelial cells, thereby restricting the free passage of water-soluble substances and large molecules. By controlling the expression and function of specific Claudin proteins, the BBB is able to precisely regulate the entry and exit of various substances, such as ions, nutrients, and waste products, maintaining the stability of the brain's microenvironment [49].

For instance, Claudin-5 is considered the most critical tight junction protein in BBB endothelial cells, as it plays a significant role in regulating the permeability of the BBB. Munoz et al. demonstrated that the downregulation of Claudin-5

leads to increased permeability of the BBB, while its upregulation helps stabilize tight junctions and maintain the integrity of the barrier [33]. Conversely, in pathological conditions such as tumor metastasis, Claudin proteins expression can be altered. These changes often result in the disruption of the BBB, allowing cells to breach the barrier and invade brain tissue [50]. Tumor may downregulate Claudin-5 expression, which directly enhances BBB permeability and facilitates tumor cell migration across the barrier, thus promoting brain metastasis [37].

Furthermore, Claudin proteins are not only essential for the normal functioning of the BBB under physiological conditions but also play a key role in regulating its permeability during disease processes. For example, inflammatory cytokines, such as TNF-α, can modulate Claudin expression, further disrupting BBB integrity. This regulation underscores the potential of Claudin proteins as therapeutic targets, as manipulating their expression could help restore BBB function or prevent tumor cell invasion, particularly in conditions like brain metastasis. These findings suggest that Claudin proteins are integral to both the physiological regulation of the BBB and the pathological changes observed during disease states. As such, targeting Claudin proteins may provide a promising strategy for modulating BBB permeability and developing treatments for brain-related diseases, including metastatic brain cancers.

Mechanisms and pathways of tumor metastasis across the BBB

Spreading of cancer cells from a primary site to the brain is a complex, multi-step process, with breaching the BBB being a critical event in this journey. Initially, tumor cells proliferate at the primary site, invade the surrounding tissue, and enter the bloodstream or lymphatic system, forming CTCs. These CTCs travel through the bloodstream to reach the brain's microvasculature, where they face the formidable challenge of overcoming the BBB [44]. To breach this barrier, tumor cells employ several strategies to regulate BBB permeability and facilitate their entry into the brain. One of the primary strategies is to secrete enzymes, such as MMPs, which degrade the ECM surrounding endothelial cells. This degradation compromises the physical integrity of the BBB, increasing its permeability and creating a passage for tumor cells to invade brain tissue [47]. In addition to ECM degradation, tumor cells also regulate the expression of tight junction proteins, particularly Claudin-5. The downregulation of Claudin-5 disrupts the tight junctions between endothelial cells, directly increasing BBB permeability. This alteration facilitates the migration of tumor cell cross the BBB and into the brain [37]. Tumor cells can also modulate other tight junction proteins to further destabilize the barrier, enhancing their ability to invade brain tissue. To further promote tumor invasion, tumor cells increase the expression of adhesion molecules such as integrins and E-cadherin. These molecules facilitate the adhesion of tumor cells to endothelial cells of the brain vasculature, driving their migration and enabling them to cross the BBB [51]. Once tumor cells successfully enter the brain vasculature, they face the challenge of immune surveillance. To overcome this, tumor cells employ immune evasion mechanisms by secreting immune-suppressive factors that prevent recognition and attack by the host immune system. This creates a favorable environment for tumor cells to grow and establish metastatic lesions within the brain [52-54]. Through these finely regulated processes, tumor cells are able to breach the BBB and establish metastatic growth within brain tissue. This process not only represents a critical step in brain metastasis but also serves as an important target for the development of novel therapeutic strategies, including targeted therapies and immunotherapies, aimed at inhibiting tumor cell invasion and metastasis.

Therapeutic potential of Claudin proteins in brain metastasis and targeting strategies

As research into the role of Claudin proteins in the function of the BBB advances, their therapeutic potential in tumor metastasis, particularly brain metastasis, has become increasingly apparent [55-57]. Claudin proteins, as integral components of tight junctions between endothelial cells, play a crucial role in maintaining the structure and selective permeability of the BBB [35]. Research has shown that tumor cells can modulate the expression of Claudin proteins, particularly through downregulation of

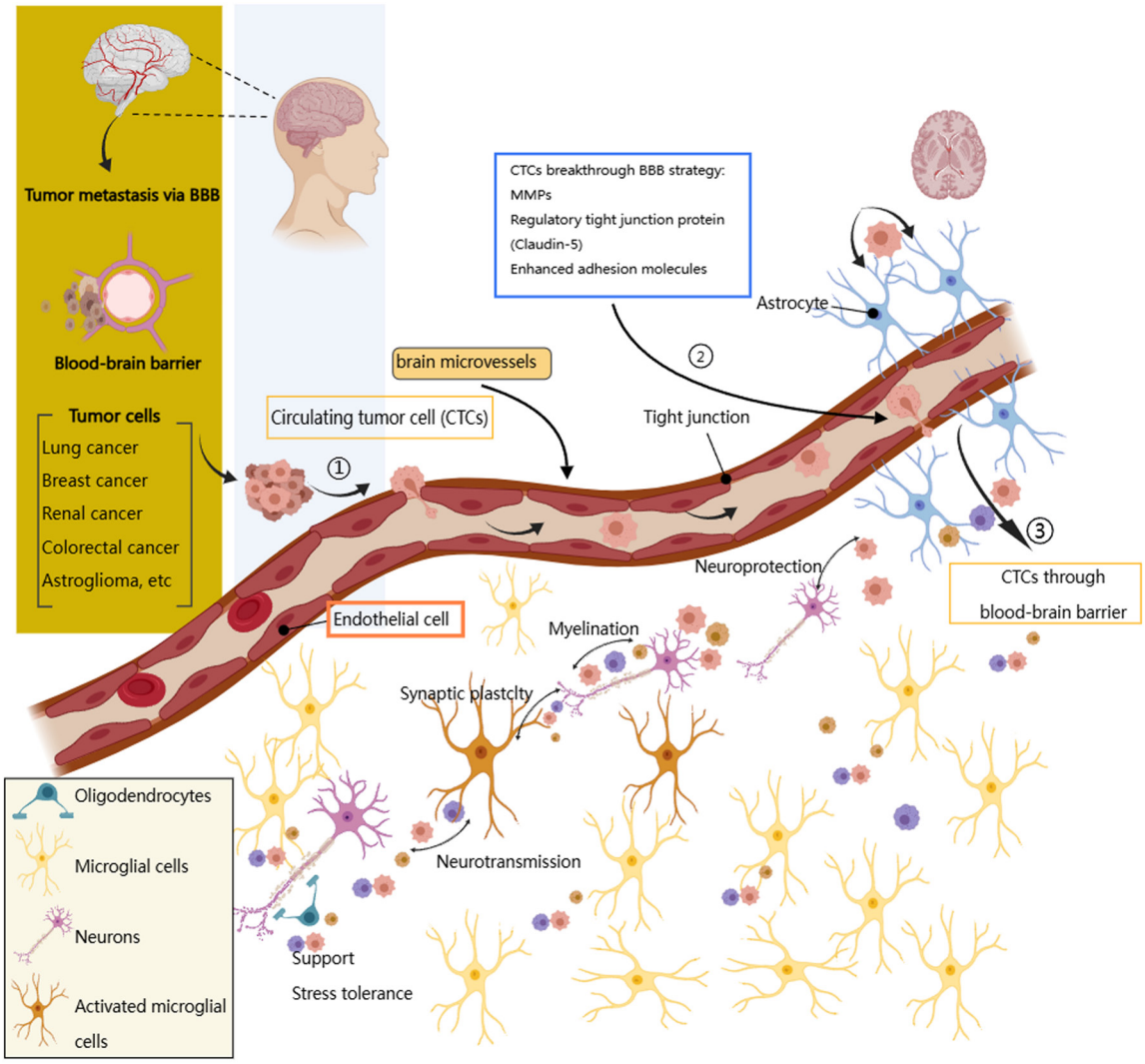

Figure 2. Mechanisms of tumor cell transmigration across the BBB. CTCs: circulating tumor cells; BBB: blood-brain barrier; MMPs: matrix metalloproteinases.

Claudin-5 and upregulation of Claudin-1, which compromises the integrity of the BBB and facilitates tumor cells crossing the barrier, leading to brain metastasis [41] (**Figure 2**). Given this pivotal role, Claudin proteins not only serve as critical factors in enabling tumor cells to breach the BBB but also present as promising targets for targeted therapies.

Two primary therapeutic strategies have emerged: First, inhibiting the abnormal expression or function of Claudin proteins to restore the BBB's barrier function, thus preventing tumor cells from crossing the BBB [7, 58]. Second, utilizing immunotherapies or small-molecule drugs that specifically target Claudin subtypes (e.g., Claudin-1, Claudin-5) to block interactions between tumor cells and the endothelial cells of the BBB, thereby reduces tumor cell invasiveness and metastatic potential [21]. For example, studies have explored the use of anti-Claudin-5 antibodies to enhance the selective permeability of the BBB and reduce the ability of tumor cells to cross the barrier, potentially decreasing brain metastasis incidence [59]. Additionally, Claudin proteins may serve as valuable diagnostic markers for early detection and monitoring tumor brain metastasis progression. Changes in the expression patterns of Claudin proteins could provide information for clinical practice, helping assess tumor invasiveness, metastatic potential, and therapeutic

responses [60, 61]. Overall, Claudin proteins, as central regulators in tumor brain metastasis, offer significant therapeutic potential. Targeting Claudin proteins could not only effectively block the brain metastasis process but also improve patient prognosis, paving the way for more personalized cancer treatments.

Clinical research on Claudin proteins in tumor metastasis: current status and emerging therapies

Currently, clinical research has largely focused on other therapeutic targets, such as angiogenesis, immune evasion, and tumor microenvironment regulation [62, 63]. In contrast, clinical studies targeting Claudin proteins remain in their early stages, particularly in the context of tumor brain metastasis, where relevant trials are yet to reach widespread clinical application. However, as our understanding of the BBB and tumor metastasis mechanisms deepens, increasing attention is being directed toward the role of Claudin proteins in tumor metastasis, especially their potential in treating brain metastasis. Current clinical studies primarily explore the combination of Claudin-targeted therapies with conventional treatments. For instance, anti-Claudin-5 antibodies and small molecule inhibitors targeting Claudin proteins have been explored in combination with chemotherapy agents like paclitaxel and carboplatin [64]. These therapeutic agents aim to modulate Claudin protein expression or function, thereby increasing BBB permeability, enhancing drug delivery to the brain, and improving the effectiveness of treatments for tumor brain metastasis [65]. Another promising approach is gene therapy, which is gradually gaining attention as a method to regulate Claudin protein expression. By utilizing viral vectors or liposomes to deliver genes that control Claudin expression directly into tumor cells or the brain's microenvironment, it is possible to precisely modulate the levels of Claudin proteins, thereby intervening in the metastatic process [66, 67]. This targeted gene therapy holds great promise for advancing treatment strategies for tumor brain metastasis by offering precise control over Claudin protein regulation. It is important to note that, although clinical trials exploring Claudin-targeted therapies are beginning to emerge, they remain in the early stages. As clinical research progresses and new Claudin-targeted treatment strategies are developed, Claudin proteins are expected to become an essential therapeutic target in cancer treatment, particularly in addressing brain metastasis.

Conclusion

This review highlights the dual role of the Claudin protein family in tumor metastasis, particularly its critical function in regulating the selective permeability of the BBB. Claudin proteins not only contribute to maintaining the structural and functional integrity of the normal BBB but also play a pivotal role in enabling tumor cells to breach the BBB and establish brain metastases. Alterations in the expression of Claudin proteins are strongly associated with the invasiveness and metastatic potential of tumor cells, as well as the disruption of the BBB integrity. Dysfunction or dysregulation of Claudin family members is, therefore, a key factor in facilitating the metastasis of tumors to the central nervous system. Future research should delve deeper into the specific mechanisms by which Claudin proteins contribute to tumor metastasis, assess their feasibility as potential therapeutic targets, and explore novel strategies for treating brain metastasis. Targeting Claudin proteins offers promising therapeutic avenues that could improve patient outcomes and provide new directions for personalized cancer treatment.

Acknowledgements

This work was supported by Development Program in Shandong Province (grant numbers 202301040472; JCYXKFPY202407) and the Medical and health research projects of Zibo (grant number 20230100001).

Disclosure of conflict of interest

None.

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