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# New insight into DAVF pathology—Clues from meningeal immunity

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In recent years, with the current access in techniques, studies have significantly advanced the knowledge on meningeal immunity, revealing that the central nervous system (CNS) border acts as an immune landscape. The latest concept of meningeal immune system is a tertiary structure, which is a comprehensive overview of the meningeal immune system from macro to micro. We comprehensively reviewed recent advances in meningeal immunity, particularly the new understanding of the dural sinus and meningeal lymphatics. Moreover, based on the clues from the meningeal immunity, new insights were proposed into the dural arteriovenous fistula (DAVF) pathology, aiming to provide novel ideas for DAVF understanding.

KEYWORDS

**meningeal immunity, meningeal lymphatic vessels, meninge barrier, dural sinus, dural arteriovenous fistula (DAVF)**

## 1. Brain and its immune protection

The central nervous system (CNS) of humans has evolved in an extremely complex way, which enables it to become an intelligent organ to receive multiple input sensory and then integrate these signals and feedback appropriate outputs, achieving precise control of the overall behavior activities (1, 2). For decades, the understanding from "The brain is an immune-privileged organ" to "The meningeal immune system plays critical roles in maintaining brain function" continues to be refined (3, 4). It is not surprising that the most complex organ of the human body is constantly exposed in the antigen contexts. Due to the extraordinary strength of the protection of the meningeal immune system (MIS), which maintains the physical cushion and immune protection against injurious impacts, various physiological activities of the CNS can proceed normally without interference (5). Meanwhile, accumulating evidence reminds us that meningeal immunity may represent origins for numerous neurological disorders (3, 6, 7).

## 2. Meningeal immune system

For centuries, the only functional significance of the elaborate barrier system was considered to physically protect the CNS, and the brain was once thought to be an immunity-privileged organ (8, 9). In recent decades, researchers in this field have made great contributions to reveal that the roles of immune surveillance and response could also be performed by the meningeal barrier system (4). On the macro level, the MIS consisted of meninges (a multiple-layer membrane including the dura, arachnoid, and pia mater), meningeal vasculature (meningeal arteries, venous sinuses, and lymphatic vessels), and meningeal nerve branches (10–13). From the micro space, the neuro-immune cell unit is the basis of the system, running the interaction between the CNS and the immune system (14–17). Cytokines and related immune molecules are the major executives to steer and generate immunoregulatory responses (18, 19). The following descriptions will highlight the important functions of each component.

### 2.1 The meningeal barrier

Diverse innate and adaptive immune mechanisms in CNS borders have been described recently (13, 20, 21). Interestingly, the meninges are ideal options to explore the CNS immune surveillance. Collectively known as the meninges, the membranous structures on the surface of the brain are made up of three layers of cellular-layered membranes.

The outermost layer adjacent to the skull is the dura mater, which could be distinguished into the periosteal layer and the meningeal layer (8). The dura mater could perform efficient immune surveillance by driving immune cell circulation and maintaining infiltration homeostasis (22, 23). The dural sinus is the characteristic structure of the dural vascular architecture. Notably, potent evidence revealed it could be a neuroimmune interface, which enables CNS immune surveillance. In the presence of neuroinflammatory infiltration, the immune niche will be altered, leading to the appearance of related pathological features.

The innermost layer adhered tightly to the surface of the cerebral and spinal parenchyma is the transparent pia mater. This layer is semipermeable to the cerebrospinal fluid (CSF) that flows into perivascular spaces. Previous evidence demonstrated that the pial meninges might be the entry point for peripherally immune cells entering into the CNS (4, 8). The middle layer is the peculiar spiderweb-like membrane, which is a tight arachnoid barrier, regulating the transportation of molecules by tight junction-like structures. Anatomically, it separates the dura layer from the CNS parenchyma. Collectively, the pial membrane and arachnoid are called leptomeninges (8).

Housed between pial and arachnoid meninges, the CSF flows smoothly, ensuring the normal circulation of necessary substances and the metabolism of various accumulation. Meanwhile, the buoyancy provided by the fluid is an artful force to respond to impact or squeeze from its own mass or movement. The three meninges are separated but cooperate together, participating in the CNS immune surveillance (Figure 1).

### 2.2 The meningeal vasculature

The meninges are highly vascularized, and the structure and function of the vascular architecture are complex. In this part,

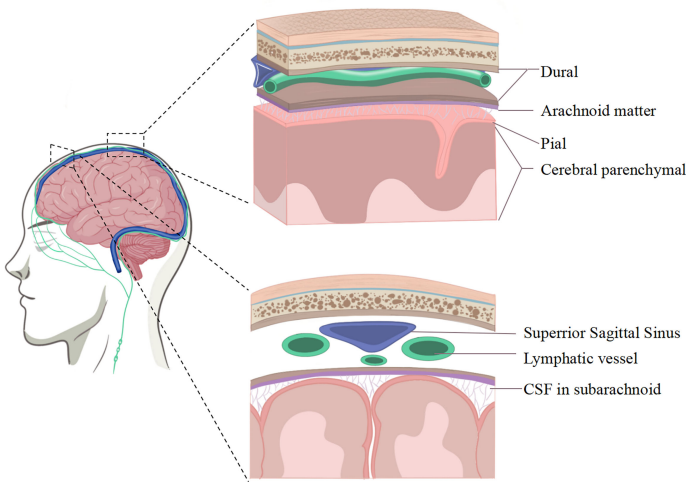


FIGURE 1
Illustration of the meningeal immune system.

the emphasis is placed on the description of meningeal lymphatics and dural vessels and sinuses to fully understand their structure and newly recognized functions.

### 2.2.1 Meningeal lymphatic vessels: From the past to the updated view

Centuries ago, the Italian anatomist Paolo Mascagni described the anatomical discoveries of meningeal lymphatic vessels (MLVs) exactly. However, controversies about the lack of lymphatic circulation in the cerebra ensued (24). After nearly 200 years of debate, the advanced imaging techniques provide definitive structural and functional characterization of MLVs (12, 25–29). More importantly, since CNS interaction with peripheral immunity has been firmly established due to MLV linkage, the concept of immune privilege in the CNS is completely broken (3–5).

In most species, such as fish, rodents (rats and mice), nonhuman primates, and even humans, meningeal lymphatics are found to be evolutionarily conserved (29–32). Previous findings reported that MLVs were paralleled to the dural venous structures. Recent publications refreshed the findings: the meningeal lymphatics at the lateral and basal skull creep with the cranial nerves' track and then pass through the skull and drain to cervical lymph nodes (CLNs) (30, 33). Although the exact transportation line of materials from the parenchyma and CSF is still in debate, some results suggested that these vessels could directly connect the CNS to the peripheral immune system *via* draining immune molecules and cells into the deep CLNs (26).

The existence of the meningeal lymphatics is a landmark discovery that opened the way to current research of meningeal immunity. Recent works supplied comprehensive insights about the meningeal lymphatics' function during homeostasis, aging, and even in CNS disorders (26, 28, 34–36). The CSF, the interstitial fluid (ISF), and the lymphatic fluid are important media for the circulation of immune cells and molecules. The application of tracers allows us to visualize the immune trajectories, which is a complex process related to numerous impact factors including arterial pulsation and the fluid pressure of each part (33, 37). The currently accepted path is as follows: endogenous antigens (metabolites and proteins) from the cerebral parenchyma are presented into the ISF, subsequently entering the subarachnoid space, then drained by lymphatic vessels to the CLNs. Future observations will present convincing arguments that meningeal lymphatics are important outflows of CSF molecules.

Recent works of Chen et al. (38–40) are groundbreaking. In 2019, they showed that after cerebrovascular injury, the meningeal lymphatics could grow into the damaged brain. As a response of repair, the ISF would be drained by ingrown lymphatics to relieve cerebral edema (38). Meanwhile, as "growth tracks," neovascularization can be "guided" by the lymphatic vessels to complete reconstruction, and then the ingrown lymphatic vessels will disappear in the form of apoptosis (38). Two years later (in 2021), a further study added brilliance to the present splendor. The results showed that by direct transdifferentiation of ingrown lymphatic vessels, acute cerebrovascular regeneration could also be achieved (39). Furthermore, according to their latest study (in 2022), the molecular mechanism about how the vessel directionality of cerebrovascular regeneration was revealed, which was closely related to the Cxcl12b/Cxcr4a signal pathway (40). These findings highlighted the involvement of meningeal lymphatics in the regeneration or neovascularization after vascular injury, which undoubtedly opened up a new world for the research of cerebrovascular diseases. In line with the above evidence, it is reasonable to reconsider whether the pathogenesis of the dural arteriovenous fistula (DAVF) formation is related to MLVs.

### 2.2.2 Dural sinus "newly discovered": More than just a drainage channel

Normally, the main blood supply to the dura comes from the external carotid artery (ECA) system, and venous blood is collected through the sinus and enters the venous system. The fenestrated vasculature is a characteristic of the dural vascular architecture (8, 11, 22). Recent findings challenged the traditional concept: dural sinus is more than just a drainage channel but may serve as a neuroimmune interface (23). Briefly, these breakthroughs could be described as follows: 1) The CNS-derived antigens in the CSF are found to accumulate at dural sinuses. 2) Captured by dural sinus-associated antigen-presenting cells (APCs), these antigens would be presented to patrolling T cells. 3) T cell trafficking could be orchestrated by the dural sinus stroma. In turn, by recognizing antigens from the CSF, T cells could also enhance the phenotype and effector function of tissues in the dura mater.

Similarly, accumulative works revealed that immune cells such as T cells and APCs are present in these immune synapses to perform immune surveillance (41–43). More importantly, although disease outcomes vary, the initial process of triggering an immune response may be consistent, taking the activation of APC–T cell interaction as an example (23, 41–43). Fitzpatrick et al. (20) added to the knowledge of dural sinus from meningeal humoral immunity. Adjacent to dural venous sinuses, the IgA-secreting plasma cells were observed on the meninges during homeostasis. In the condition of aging and neuroinflammation, it is also proven that this vulnerable venous barrier surface is essential for defending the CNS. Thus, exploring the relationship between the dural sinus immune function and the (patho) physiological process of neurological diseases is promising.

### 2.2.3 The vasculature-associated barriers: Special shield for CNS parenchyma

The vasculature-associated barriers are of significance to the traditional concept of CNS immunity. In addition to the physical

protection of meninges, the vasculature-associated barriers, involving the blood–brain barrier (BBB) and blood–meninge barrier (BMB), also provide special protection for the CNS parenchyma. BBB is a specialized vasculature barrier with selective impermeability, which allows for partially blood-derived products to enter the parenchyma (44–46). Similarly, the BMB is also a specialized selective impermeability barrier, preventing the entrance of blood components from the leptomeningeal vasculature into the CNS (4, 47). Under pathological conditions, the previously impermeable blood-derived factors may enter the brain parenchyma, causing a cascade of reactions including immune responses (45, 46).

Notably, nonselective leakage of blood components from the CNS vasculature, which is the main result of the BBB damage, is frequently observed in diverse acute or chronic neurological disorders (48, 49). The primary and/or secondary immune responses and associated inflammation are increasingly recognized mediators of diverse cerebral anomalies. Immune and inflammation responses precipitate in the BBB breakdown, dysregulated transport, and immune trafficking, aggravating endothelial dysfunction. Importantly, these events also happen to link immune interactions with cerebrovascular dysfunction. In addition, the localized vascular anomalies, such as the DAVF, exactly occurred in meningeal vasculature. Consequently, it is reasonable to believe that the pathological processes including the formation and development of DAVF are closely related to meningeal immunity.

## 2.3 The meningeal innervation

The meninges are highly innervated by various nerve fibers, involving sympathetic and parasympathetic nerves, as well as sensory fibers (50–53). Many pioneers have contributed to the description of the meningeal innervation, revealing that there are significant differences in innervation between the pachymeninx and the leptomeninx of the cranial cavity and spine (4, 54).

The leptomeninx innervation is mainly focused on the cerebral arteries. Fricke et al. (55) researched the localization of nerve fibers in the ventral leptomeningeal connective tissue compartment and described the nerve fibers within the pia that appear to be the primary termination. It must be noted that differentiated innervation patterns of the leptomeninx were also presented in their work in 1997 (55).

Andres et al. (56) reported that the innervation of the dura mater is also extensive, and the vascular and nonvascular regulation targets are both related to the dural fibers. Various segments of the meningeal vessels and venous sinuses are the main location (56).

In addition, the vasoconstrictor and the associated blood flow could be regulated by neuropeptides (50, 57–60). Peripheral nerve fibers could also project to the meninges (60, 61). For providing important sensory feedback, sensory fibers that control changes in temperature, pH, and mechanical pressure extend within the meninges (62, 63). Most importantly, like the skin barrier and gastrointestinal mucosa, numerous immune hotspots and messages could also be found around dural sinuses (4, 64, 65). The above evidence feasibly intrigued our interests to investigate the roles of meningeal innervation in maintaining meningeal immunity homeostasis.

## 2.4 The meningeal cells, molecules, and immunity function

Immune cells and related characteristic cytokines are the primary guardians of immune homeostasis, which actually execute all immune regulation instructions. Cellular immunity and humoral immunity are essential for the protection of the CNS parenchyma. For decades, the spectrum of these microscopic molecules' roles in physiological and pathological conditions gradually becomes clear.

### 2.4.1 The meningeal cellular immunity

So far, accumulated evidence built the intact framework of the meningeal cellular immune system, and main studies were focused on T cells and macrophages (26, 64, 66–69). The meningeal T cell always acts as the immune surveillance guard and immunohomeostasis maintainer (12, 26, 43, 68–72). As the latest findings we mentioned above, the CNS-derived antigens accumulated around the dural sinuses could be captured by APCs and then be presented to patrolling T cells through the CSF pathway (23). Activated T cells would promote meninges to initiate antigen processing. In the research field of multiple sclerosis (MS), studies on meningeal T cells provided a new consideration of neuroimmunology and the MS pathology. As MS is believed to be mediated by myelin-specific T cells, the potential mechanisms of how T cells acquire their encephalitogenic phenotype and initiate inflammation have been demonstrated (26, 43, 68, 69). In addition, when searching for the pathway of how the T cells reach the CSF and get into and out of the meninges, the functional lymphatic vessels lining the dural sinuses were discovered (12, 71). The T cells were also shown to have the potential to support memory and learning, which may shed light on immune-based therapy exploration for cognitive decline (72). In the experimental models of autism and aggregation behavior, meningeal γδ17 T cells were suggested to promote behavioral changes (70). These findings suggested that meningeal T cells are potent executors of meningeal immune function.

Specialized macrophage populations at the CNS borders perform critical roles in health and disease conditions (64). As the most abundant cell population in healthy meninges, macrophages were reported to form the origin to the phenotype turnover (73, 74). The meninge-associated

macrophages could be divided into three populations: leptomeningeal macrophages, perivascular macrophages, and choroid plexus macrophages (64, 73). To date, all of these categories are thought to guard the meningeal barriers and to control the antigens and metabolite drainage (64, 73, 74). In the MS research field, activated macrophages are found abundantly accumulated before clinical symptoms caused by inflammatory infiltration (75, 76). In neurodegenerative diseases, meningeal macrophages are reported to have dual roles (31, 35, 77, 78). By removing insoluble amyloid-β, macrophages could help in delaying or salvaging cerebral amyloid angiopathy (79). However, once overburdened, dysfunctional macrophages would act as internal hostile molecules to exacerbate Alzheimer's disease (AD) pathology processes (79, 80).

Notably, the brain borders are inundated with highly populated immune cells, and multiple immune cell subsets coordinate with each other to maintain normal immune function (81).

### 2.4.2 The meningeal humoral immunity

In recent years, one of the major breakthroughs in the research field of the MIS is undoubtedly the supplementation of meningeal humoral immunity knowledge (16, 17, 20). Given that studies in recent decades are mainly focused on meningeal cellular immunity, a detailed generalization of meningeal humoral immunity is not available. In this part, we summarized the contents of meningeal humoral immunity comprehensively, providing a new perspective for further research.

B cells have previously been shown to be located near the dural sinus regions with slow blood flow. Once there is fenestration, these blood-borne pathogens could be permitted to access the CNS parenchyma (82). Traditionally, circulating antibodies were not thought to be present in the CNS of healthy individuals. However, in the disease state, antibodies involving IgA and IgG can be found in the CSF (83–85). These pieces of evidence are the location basis for the occurrence of humoral immune events.

In the work of Fitzpatrick et al. (20), they showed that the IgA-secreting plasma cells infiltrated the meninges of humans and mice during homeostasis. With age and disruption of the intestinal barrier, peri-sinus IgA plasma cells increase (20). In addition, meningeal IgA was shown to be essential for defending the vulnerable barrier surface of the CNS in their work (20). Several other outstanding works have clearly described the origin and migration of meningeal B cells (16, 17). The latest findings revealed the following: 1) The meninges host a substantial myeloid cell pool in the brain border, which would mediate immune surveillance. Meanwhile, meninges also harbor a specific lymphopoietic niche for the CNS borders. 2) Under homeostasis, the meningeal immune cells could be supplied by the bone marrow niches adjacent to the brain and spinal cord. 3) Migration of meningeal myeloid cells through the meningeal barrier to parenchyma is the next step in the microenvironment of CNS injury and inflammation (16, 17, 20). Interestingly, through B-cell receptor sequencing, it was also confirmed that the gastrointestinal barrier is an important source of meningeal B cells (20, 86). To understand the origin and the physiological and pathological function of humoral immune cells at the brain border is an essential step in revisiting meningeal immunity, which also encourages the rethinking of therapeutic approaches.

## 2.5 The meninge vessels/innervation cells/molecular units and immunity function

From what has been reviewed above, we propose the concept of a complete MIS for the first time. The MIS is a tertiary structure. The primary structure is a barrier structure composed of three layers of tangible membrane, involving the dura mater, arachnoid, and pia mater (from outside to inside). The secondary structure is the vasculature and meningeal innervation. The meningeal lymphatics often run parallel to blood vessels, and the dural sinuses are important immunosurveillance sites. The meningeal nerve covers a wide range of areas and plays an important role in regulating vascular function. The third structure is the direct executor of meningeal immune function, including immune cells, and related immune molecules and cytokines, which play ultimate roles both in humoral and cellular immunity. For the function of the MIS, we also clearly summarize it into three aspects: 1) immune surveillance, 2) drainage and clearance, 3) and repair and regeneration (Figure 2).

# 3. Meningeal immune system response to central neural system diseases' pathogenesis

The meninges are strategically located in the CNS. In the case of infectious and non-infectious stress, the MIS perceives unbalanced homeostasis earlier and then actively forms an inflammatory response and activates clearance mechanisms before pathogens reach the parenchyma. Abundant pioneering works have repeatedly highlighted the powerful immune function of the meninges (87). In this part, we will briefly summarize the MIS with these diseases characterized by neuroinflammation, then restrict ourselves to discuss the potential possibility of the pathogenesis of DAVF with the meningeal immunity.

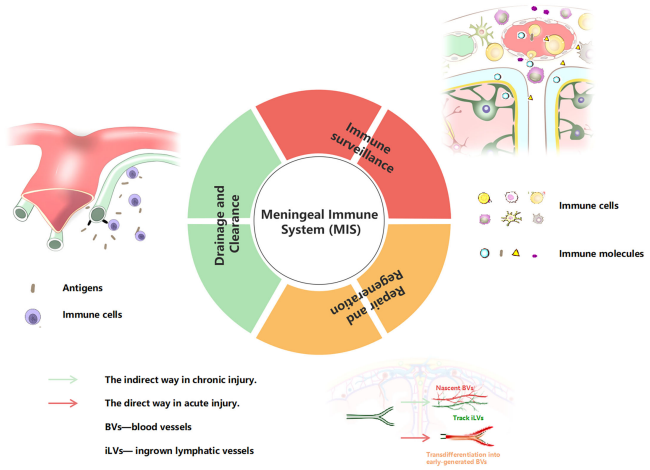


FIGURE 2
Summary of the MIS functions. BVs, blood vessels; iLVs , ingrown lymphatic vessels.

## 3.1 General description of the MIS and CNS diseases

In recent years, a vast body of studies has found that the MIS is related to the occurrence, progression, or prognosis of more CNS diseases to varying degrees. For example, the MIS is believed to play important roles in the pathogenesis of multiple sclerosis (26, 88–90), Alzheimer's disease (35, 91–93), and Parkinson's disease (78, 94, 95). Meanwhile, the regulation of the MIS about the immune surveillance and lymphatic vessel drainage to the brain tumor is also demonstrated (96–98). Stroke associated with hemorrhage or ischemia is one of the recent research hotspots. Much meaningful work has described the importance of the MIS in cerebral stroke, including subarachnoid hemorrhage (99, 100), intracerebral hemorrhage (101), or ischemic stroke (102, 103). In the brain injury studies, meningeal lymphatic drainage is reported to be associated with prognosis (104, 105). Recently, researchers also found that the MIS has a cross-era function, which is directly or indirectly involved in the repair of cerebrovascular injury (38–40). Naturally, the MIS is linked to the immune responses of infectious diseases, including bacterial meningitis (73) or parasitic infections (69, 106, 107), as well as viral infections (108, 109). In other diseases, such as migraines (110–113), glaucoma (114, 115), and even in the aging process (20, 23, 35), evidence of active immunomodulation and surveillance of the MIS can also be found. Given that this is not the focus of this work, here we summarize these studies related to the MIS in a graph (Figure 3).

Of particular note is that the neuroinflammatory condition is an overlapping pathologic process during these disorders, and this happens to be a trigger point for the meningeal immune response (4, 87). These works contributed to prove that the MIS supports normal CNS development and function and governs the pathological process dominated by neuroinflammation (87). It seems that during both noninfectious and infectious microenvironments, neurological dysfunction is often a consequence of meningeal inflammation. Thus, from the view of CNS immune regulation, therapeutic strategies to alleviate these debilitating neurological conditions could be attractive.

## 3.2 New insights into the DAVF pathology

Over the years, researchers have tried to figure out the formation process of vascular abnormalities (116–119). However, it is impossible to know the dynamic formation process because the entity of the lesion is already formed when the patient is presented and diagnosed. Current views tend to define DAVF as an acquired disease, which is closely related to the inflammatory microenvironment after venous hypertension and hypoxia (120–123). Cytokines related to neovascularization are the main pathologic findings. In a 1996 report, researchers examined the angiogenic stimulants in human DAVF sinuses and revealed that the basic fibroblast growth factor (bFGF) levels in the sinus of patients with DAVF were higher when compared with those in the normal group, even in normal dural sinuses (124). Notably, none of the enrolled patients had a history of sinus thrombosis or head injury. Another study confirmed the same results and added that vascular endothelial growth factor

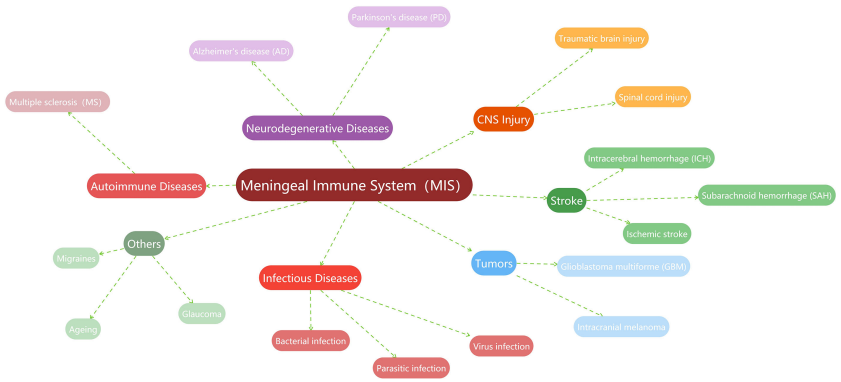


FIGURE 3
Summary of studies related to the MIS.

(VEGF) was not expressed in normal specimens but was observed in the DAVF group (125).

Certainly, some possible causes as traumatic brain injury (TBI) and sinus thrombosis are thought to be the culprits. It would be reasonable because these injuries could lead to a common pathologic condition—neuroinflammation (122, 126–129). The work of Hamada et al. (130) targeted to discuss this problem. In their research, a comparison was made among five control cases and nine DAVF cases, six of which angiographically showed sinus occlusion. At least in some cases, the venous sinus occlusion might be the cause of hypertension to force the abnormal connections between arteries and veins to open, leading to the formation of DAVFs. At this point, we have reason to postulate that in the inflammatory microenvironment caused by sinus hypertension, the MIS is also responding positively, and the formation of DAVF might be a result of the repair process.

Conclusions drawn in animal models also echoed this (131–140), and one of the outstanding contributions would be attributed to the work of Yang et al. (141). In the context of venous hypertension, the hypoxia and inflammation cascaded, then the infiltration of various angiogenic factors leads to the tendency of abnormal vascular anastomosis. The benign result of venous pressure regress might be related to the formation of compensatory draining veins. Otherwise, development of DAVF and venous hypertension would be the ultimate possible vicious circle. Some of these animal model studies are progressive, while we noticed that the current models do not perfectly reflect the pathophysiology of the disease. Thus, the establishment of stable animal models is urgently needed as well as conducting a series of basic studies to test these hypotheses.

Taken together, either as a starting agent or as a result of a vicious cycle, the inflammatory microenvironment is always the background for the occurrence and development of DAVF. The meninges are unlikely to ignore the lesions that occur within themselves. Surely, how this immune reaction works is something fascinating that deserves further study (Figure 4).

## 4. Evidence-based assumptions and perspectives

Based on the abundant evidence above, we propose several scientific hypotheses that may open up new directions for future research. Firstly, in the case that the state of the epidural *in situ* or remote site in the CNS is unsteady for a long time, the abnormal vascular anastomoses might be compensatory products of immune surveillance and regulation by the MIS. There are many reasons for this steady-state imbalance, such as trauma, surgery, or infection that can be recorded and observed clearly, while other meningeal immune activation pathways that may have been overlooked, such as a peripheral infection that may communicate with the CNS, are also important mining sites. Secondly, as MLVs have been shown to be involved in the repair and reconstruction of cerebrovascular injury (38, 39), the assumption that the formation of DAVF might be closely related to meningeal lymphatics is quite reasonable. It is not ruled out, and even very likely, that a fistula is one of the imperfect products of the repair process. Thirdly, given the fact that DAVF already exists, the immune monitoring and maintenance functions of the MIS have apparently been activated. A recent work has also discussed cerebrovascular diseases including DAVF from the perspective of CNS immunity, which is undoubtedly a strong support for our assumptions (119). Thus, though it can be challenging, promising alternative therapeutic targets could be explored from the viewpoint of the MIS immune modulation. Excitingly, with the current access as imaging techniques (with tracer agents), gene-edited mice, and high-throughput sequencing, we would be allowed to achieve an unprecedented description of the MIS.

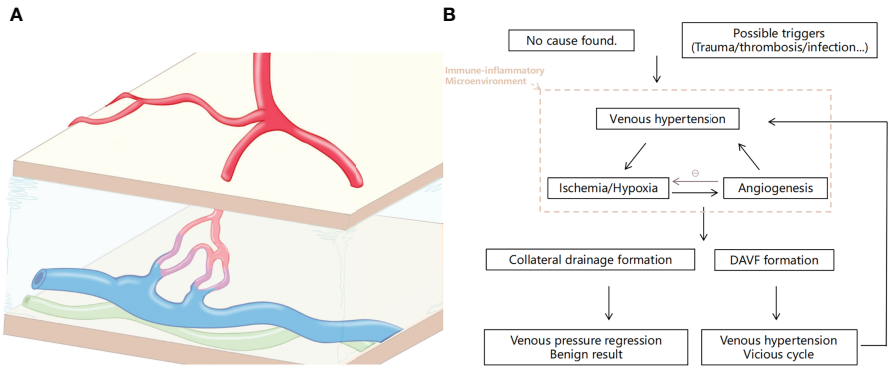


FIGURE 4
Illustration of the dural arteriovenous fistula (DAVF) and the pathological process of the disease. **(A)** Schematic of DAVF that displayed the abnormal vascular architecture of the dura involving arterial feeders, draining veins, and accompanying lymphatic vessels. **(B)** Brief diagram of the pathophysiological process of DAVF occurrence and development.

Some of the other insights for treatment strategies are also interesting, although there are still some limitations because there is no direct evidence to support immunotherapy. At present, interventional embolization and surgery are the main treatments for DAVF, and some studies on stereotactic radiotherapy are also being carried out (142). However, there are still some lesions that cannot be obliterated due to anatomical reasons and material limitations. Meanwhile, the occurrence of *de novo* DAVF after treatment is also common (143–145). Furthermore, in addition to the elimination of lesions on imaging, the long-term prognosis of patients is also worthy of our attention. Therefore, innovative treatments are urgently needed. It is clear that the venous pressure, hypoxia, and inflammatory microenvironment do exist in the context of the lesion. As studies have shown, immunosuppressive therapy has potential in the treatment of CNS diseases (146). Factors of immunity may also be related to the prognosis of patients with this type of cerebrospinal vascular disease. As we found in our recent work, Complement component 4 binding protein alpha (C4BPA) and Complement Component 1, Q Subcomponent, A Chain (C1QA) are potential biomarkers for the diagnosis of spinal dural arteriovenous fistulas (SDAVFs), revealing that complement pathway activation might be one of the molecular mechanisms for venous hypertension myelopathy (147). Some clinical clues are worth pondering. There are many reports of confusion between SDAVF cases and myelitis cases (148). It is well known that steroids have good anti-inflammatory effects. However, hormonal shock therapy can lead to rapid deterioration of the patients' symptoms. Notably, the use of hormones after surgery may be worth trying, which may improve patients' prognosis. Importantly, given that immune factors play important roles in the overall disease process, it is really worth exploring whether boosting the beneficial immune factors or suppressing the detrimental immune factors can improve the problem.

## 5. Conclusion

In this review, we defined the MIS as a tertiary structure. Recent advances in meningeal immunity of healthy and diseased brains were reviewed. Moreover, by gaining clues from the immunity, we proposed new insights into the DAVF pathology, which may provide new ideas for understanding DAVF and looking for novel therapeutic targets. In conclusion, great breakthroughs have been made in the exploration of the potential functions of meninges, while there is still so much to be explored in this area that motivates our curiosity.

## Authors contributions

TT and ZP contributed equally to this work and should be considered to be co-first authors. TT reviewed related literatures and drafted the paper. ZP reviewed related literatures and drew the illustration figures. ZS checked for the literatures and contributed to the outline. YM discussed important points and made important revisions to the paper. HZ designed the concept and approved paper for publication. All authors contributed to the article and approved the submitted version.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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