Meninges' lymphoid structures, not so good, so bad, or so ugly

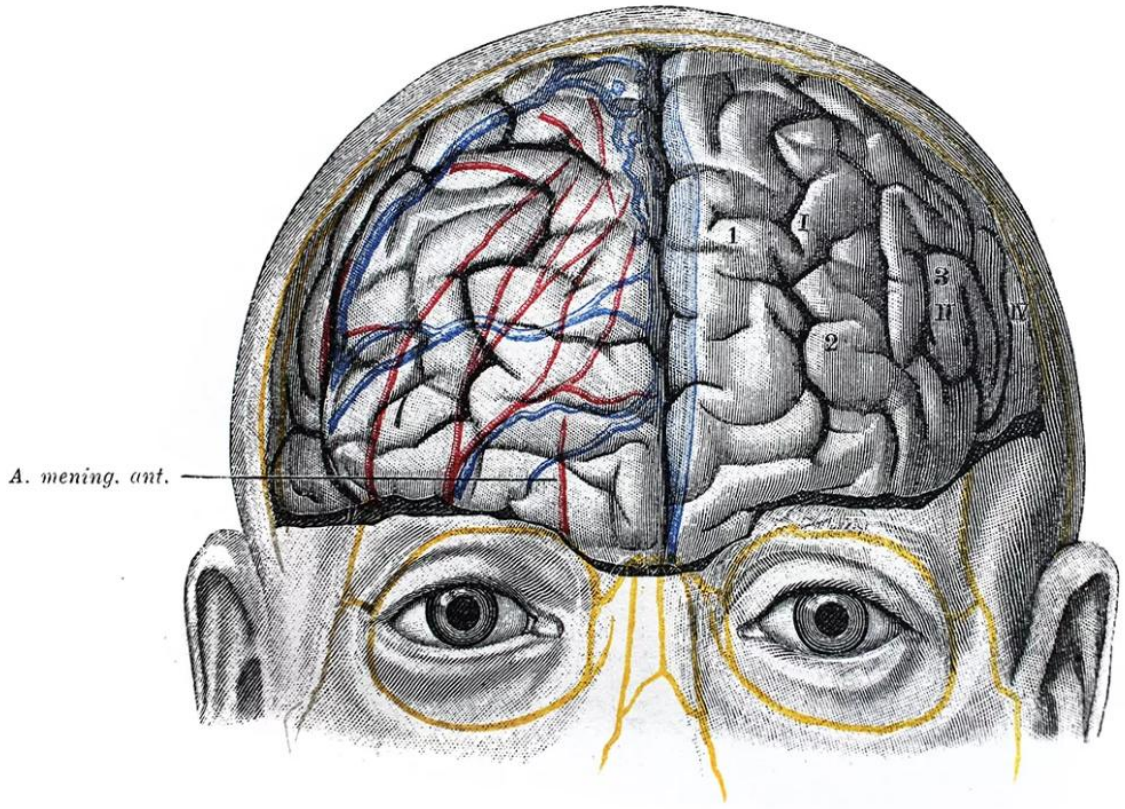

Illustration from the book "Die Anatomie" by Merkel, 1885.

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By Mar de Miguel

A little-known tissue composed of a cluster of immune cells could offer novel insights into the development of neurological disorders. Meninges' immune system changes with age and neurodegeneration. Are they protecting the brain or fueling disease?

Mapping and analyzing the so-called ectopic lymphoid structures (ELSs) in the meninges at different ages in preclinical models of neurodegenerative diseases such as Alzheimer's may help clarify whether they are good, bad, or ugly, as in the iconic film by

Sergio Leone. Each condition reveals a distinct pattern that could help identify new biomarkers or key targets for immunotherapy.

The meninges surround and shield the brain and spinal cord. They consist of a membranous tissue with different layers. Dura mater, arachnoid mater, and pia mater allow the circulation of cerebrospinal fluid and act as an immunological barrier, preventing infections and the passage of certain substances.

This function is shared with the blood-brain barrier (BBB), which protects the brain through capillaries that oxygenate and nourish the central nervous system. However, while the BBB relies on endothelial cells, astrocytes, and pericytes to establish this selective filter, the meninges interact with the peripheral immune system.

“Once dismissed under the concept of the brain being immune privileged, the meninges and peripheral immunity are now recognized as key players in brain health and disease,” said first author Amit Fruitman Davidi, who is a PhD researcher in the laboratory of senior author Eitan Okun.

“Our findings highlight the potential of adaptive immune responses to influence disease course, much as they do in autoimmune disorders like multiple sclerosis or in cancer immunology, where antibodies, cytokines, and immune cell subsets can profoundly reshape a tissue’s environment,” Fruitman Davidi added.

“Ectopic lymphoid structures are found in sites of pathology in our body. It can be, for example, around a solid tumor. Over there, ELSs play a protective role. They will boost the immune response towards the tumor. … The more ELSs you have, the better the prognosis,” Okun told *BioWorld*.

“In multiple sclerosis. You find ectopic lymphoid structures in the brain in sites of inflamed tissue. Over there, they play an adverse role. The more ectopic lymphoid structures you see in this autoimmune disease, the more exacerbated the pathology is,” he added. Okun is a professor and head of the Paul Feder laboratory for Alzheimer's disease research at Bar Ilan University.

ELSs resemble lymph nodes but are formed in peripheral tissues from aggregates of T and B lymphocytes, macrophages, follicular dendritic cells (FDCs), plasma cells and stromal cells. ELSs form in cancer and inflammatory conditions, including autoimmune diseases, such as multiple sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and Sjögren’s syndrome, among others.

In respiratory infections, ELSs contribute positively to the immune response. However, in persistent infections, the structures can cause chronic inflammation, tissue damage, and an autoimmune reaction.

In general, whether their role is beneficial or harmful depends on the context. In the case of neurodegenerative diseases, the question has long remained open until now. Are they the good, the bad, or perhaps... the ugly?

The research described in the *Proceedings of the National Academy of Sciences* (*PNAS*), Aug. 11, 2025, the immune alterations in the meninges based on age, sex, or neurodegenerative diseases such as Alzheimer's and Down syndrome or trisomy-21, which is also associated with amyloid plaque formation.

Neither the good, the bad, nor the ugly

Okun, Fruitman Davidi and their colleagues analyzed the formation, size, and number of ELSs in the meningeal dural sinuses during aging. They used transgenic mouse models of both sexes with different neurodegenerative pathologies, including AD models that overexpress the amyloid precursor proteins (APP) and presenilin 1 (PSN1) proteins, mice with a tau mutation related to frontotemporal dementia, and a murine model of Down syndrome that overexpresses amyloid precursor proteins (APP) and also exhibits hyperphosphorylated tau.

Italian pioneer of the spaghetti Western Sergio Leone and actor Clint Eastwood had no trouble creating the most iconic roles in Western film history. However, when it comes to the role of ELS in neurodegenerative disease through the meninges, it’s not about heroes or villains. The results show that ELS accumulate in the dura mater with age, but their impact depends on brain pathology and sex.

In male mice, the number and size of ELSs increased at 18 months. In females, this increase occurred before, at 12 months. The number of ELSs also rose in mice overexpressing APP.

“Women are more susceptible to Alzheimer's compared to men. And therefore, we found it interesting that, in females, there is an increase in the number of structures, and then it decreases. Maybe it has to do with the hormones, which are themselves a risk factor for women for Alzheimer's,” Okun said.

In males, the number of ELSs continued to rise. However, ELS accumulation decreased in APP/PS1 mice and in Down syndrome models with APP overexpression and hyperphosphorylated tau.

“It is very likely that the immune system differs between all these different models. The Down syndrome model also reliably recapitulates the widespread immune dysregulation that people with Down syndrome exhibit. So, it is possible that their entire immune system wouldn't allow for the structures to form,” Okun remarked.

Understanding the mechanisms that explain these results is part of his future direction. The scientists explained that meningeal myeloid cells may contribute to the formation of ELS through the lymphotoxin-β receptor, which activates the clustering of other cells. ELSs show dynamic behavior that reflects the brain's health status and could be used as biomarkers or therapeutic targets to slow neurodegeneration, especially in age-related diseases such as Alzheimer's.

“This study raises fundamental questions about the role of adaptive immunity in AD, whether it is protective, harmful, or both, which remains a topic of debate. Our next steps include identifying the specific B cell subsets that form these structures, as aging is known to shift B and T cells toward more autoimmune phenotypes,” Fruitman Davidi commented.

“We also aim to trace the origin of these cells, which could reveal the purpose of their presence in the meninges under this pathological context. Another key goal is to define the relationship between meningeal ELSs and the brain parenchyma, are cytotoxic T cells primed in the meninges before entering the brain? Are antibodies or cytokines secreted into the cerebrospinal fluid to influence brain inflammation?” she said (Fruitman Davidi, A. et al. Proc Natl Acad Sci U S A 2025, August 11. doi: 10.1073/pnas.2425081122).

KEYWORDS Alzheimer’s disease amyloid beta Bar Ilan University Down syndrome dura mater meninges tau