Chapter

Astrocytic S100B, Blood-Brain Barrier and Neurodegenerative Diseases

Anuradha Krishnan, Hao Wu and Venkat Venkataraman

Abstract

Increased life span and expectations of a better quality of life have resulted in a spotlight on neurodegenerative and cardiovascular diseases generally associated with aging. The drive toward evidence-based medicine has necessitated a constant search for objective biomarkers to assay disease onset, progress, and outcomes to make the best clinical decisions. Enhancement of their use depends on the mechanistic understanding of the biomarker's role in the disease process itself. This chapter focuses on S100B. It is a calcium sensor protein that is primarily astrocytic. While it plays a complex, interlinked role in signaling, serum levels of S100B as a biomarker for clinical decisions is also an area of intense investigation. Both aspects are presented, with an emphasis on the role of S100B in in maintaining a blood-brain barrier, especially in the context of suggesting a unified mechanism for the onset and progression of neurodegenerative diseases.

Keywords: S100B, calcium, blood-brain barrier, biomarker, neurodegeneration, tight junctions

1. Introduction

Rudolph Virchow first proposed the concept of neuroglia as a component of the connective tissue of the brain "nervekitt" [1]. The term "astrocyte" is attributed to Michael von Lenhosseck, coined to denote the stellate (star-like) morphology, with independent contributions also by Kolliker and Anderiezen (reviewed in [2]). The diversity of this group of cells was brought into clear focus by the excellent drawings by Cajal [3]. Glial cells, including astrocytes, were once believed to be limited to passive support in the functioning of the brain. Work over the last few decades has ushered in the understanding that they actively participate in normal metabolism and physiology of the brain, even more so during injury response and repair. They alter the microenvironment through secretion of a variety of signals including cytokines as a result of intracellular process collectively termed "activation," which operates at both ends of time scale—acute and short-term (trauma) as well as chronic and long-term (neurodegenerative diseases). While meant to be adaptive and reparative, they could also lead to exacerbation of injury or disease (for some reviews, please see [4–12]). Understanding the process of activation and its effect on the microenvironment is fundamental to devising positive interventions. One of the important signaling molecules involved in this process is S100B, a calcium sensor protein, which is secreted to act at the extracellular level but also

functions intracellularly (reviewed in [13–15]). While primarily astrocytic, it is expressed in other glial cells, non-neuronal cells, and is also detected in the serum. In this chapter, the role for S100B in the neurovascular unit (NVU)—important for the blood-brain barrier (BBB)—is discussed. A summary of conditions in which the serum S100B levels are proposed to be of values as a biomarker provides the backdrop. Based on the findings, a mechanism that places the NVU, with a central role of S100B, at the heart of neurodegenerative diseases is suggested.

2. S100B: the protein

S100B, an astrocytic protein, was originally obtained from the bovine brain [16], as a mixture with S100A1—the fraction was termed "S100" due to partial solubility in 100% saturated ammonium sulfate solution [16], reviewed in [15]. Over 50 years after the identification of S100B, the S100 family now includes more than 20 genes paralogous to S100B, with functions in healthy as well as diseased states [17]. The S100 proteins exist mostly as dimers—homodimers or heterodimers—and share common structural motifs such as the Ca-binding EF hand.

S100B is a homodimer of a 92-amino acid protein, termed S100b, with a molecular mass of 10,713 Da, but migrates between 9 and 14 kDa on SDS-polyacrylamide gels. Crystal structures and refined NMR structures [18, 19] reveal that the monomer contains two EF-hands—one non-canonical and one conventional—that bind calcium; the dimer is in antiparallel orientation. Upon binding calcium, the molecule switches to a more open conformation with hydrophobic patches exposed to facilitate interaction with other molecules. However, these conformational changes are unlike other more conventional EF-containing proteins and are unique for S100B protein—experimentally supported through calcium-induced mobility shift assays [20]. Thus, the S100B protein is specialized to sense changes in calcium levels and mediate appropriate responses, especially in the nervous system.

Expression of S100B in the nervous system is primarily in the glial cells—astrocytes in the central nervous system and Schwann cells in the peripheral nervous system, where they carry out intracellular as well as extracellular functions [reviewed in [14, 15]]. Since these functions are relevant to both healthy and diseased states and S100B is detectable in serum, specifically humans, a focused effort has been underway to determine if S100B could serve as a biomarker.

3. S100B: the biomarker

Biological marker (biomarker) is defined as "a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathological processes or pharmacological responses to a therapeutic intervention" (Biomarker Definitions Working Group). An optimal biomarker is ideally measurable easily, quantitatively related to the extent of the condition, yields reproducible results, and provides guidance regarding outcomes/clinical decisions [21]. The quest for a biomarker may pass through several avenues that include imaging, functional imaging, microRNAs, and microarrays. Even as these journeys have increased the knowledge base, they have also highlighted the complexity of the process. Typically, however, biomarker levels in body fluids—blood, cerebrospinal fluid, saliva, or urine—are more common.

A summary of current information on the correlation of serum S100B levels to different conditions is provided in **Table 1**.

Condition		Citation	Comments
Brain-related			
Traumatic brain injury			
	Mild	[22]	
	Moderate	[23–26]	Not a reliable predictor of good vs. bad outcome
	Severe	[24]	Useful to predict if the patient will regain consciousness 3–6 min after injury, in addition to predicting the outcome
	Children	[27, 28]	Normal serum levels are higher than in adults. Cannot be used as a predictor of injury, but is a predictor of outcome
	Sub-concussive head impacts	[29]	
Non-traumatic intracerebral hemorrhage		[30, 31]	
Stroke (ischemic and hemorrhagic)		[32, 33]	
Heart-related			
Cardiopulmonary bypass surgery		[34]	Meta-analyses
Congestive heart failure		[35]	Further increase if accompanied by renal insufficiency
Dilated cardiomyopathy		[36]	
Skeleton-related			
Orthopedic trauma		[37]	
Hip arthroplasty		[38]	
Cancer-related			
Brain metastases of lung cancer		[39]	
Estrogen receptor-positive breast cancer		[40]	Elevated levels indicate poor disease-free survival
Malignant melanoma		[41–44]	Elevated levels indicate poor disease outcome
Neonates-related			
Congenital heart disease		[45]	Levels dropped to normal 7 days post-operative
Intraventricular hemorrhage, intrauterine growth restrictions, perinatal asphyxia		[21]	
Hypoxic ischemic encephalopathy		[46]	
Other diseases			
Epilepsy		[47, 48]	
Delirium		[49, 50]	
Neuromyelitis optica (AQP4+ve)		[51]	

Condition	Citation	Comments
Neurosarcodiosis	[52]	
Obstructive sleep apnea	[53]	
Proliferative diabetic retinopathy	[54]	
Schizophrenia	[55, 56]	
Systemic lupus erythematous	[57]	

Table 1.
Conditions with elevated serum S100B levels.

In all of the conditions above, serum S100B levels are elevated. It is noted that there are some sporadic reports of decreased levels, particularly in the case of diabetes and anorexia nervosa [58, 59].

The diverse nature of the pathologies with which elevated serum S100B levels are associated, coupled with the lack of functional correlation, has made mechanistic explanations difficult to say the least. While S100B is currently known to be expressed in multiple tissues, the primary source of serum S100B is believed to be of astrocytic origin [60, 61]. Therefore, for S100B levels in serum to be elevated, astrocytic S100B must be able to reach the blood, which would not normally happen due to the presence of the blood-brain barrier (BBB).

The BBB comprises the physiological and functional barrier that separates the nervous system from the circulatory system [62, 63] and its breakdown allows for the leakage of damaging humoral elements into the brain parenchyma [63–67].

4. S100B and blood-brain barrier (BBB)

4.1 BBB and neurodegenerative diseases

The BBB is mainly formed by a monolayer of brain vascular endothelial cells (BVECs) that are sealed by tight junctions (TJs) [reviewed in [68–70]]. It actively regulates transportation of metabolic wastes and nutrients, such as ions, glucose, and amino acids, between blood and brain interstitial fluid (ISF) [reviewed in [69]]. On the other hand, other plasma components such as immunoglobulins and cells such as leukocytes are restricted. Thus, the BBB enables neurons and supporting cells to receive nutrients and remove wastes. In addition, they provide protection from the immune system. The concept of the neurovascular unit (NVU), to maintain the function of the BBB in health and underlie its response during disease, has been proposed [71–74].

Impaired function of the BBB has been linked to a variety of pathological conditions that affect the brain [reviewed in [62, 63, 67, 75]]. These include epilepsy [reviewed in [76]], psychiatric diseases such as neuropsychiatric lupus [77], dementias such as Parkinson's disease [78–80], Alzheimer's disease (AD) [81–86], other neurodegenerative diseases such as Huntington's disease [87], amyotrophic lateral sclerosis [88, 89], multiple sclerosis [90, 91], and those caused by viral infections [92–94]. The compromise of the BBB has been tightly linked causally or as a diagnostic marker to chronic neurodegenerative diseases such as AD [95–97] and acute conditions such as delirium [98]. Yet, the causes and consequences of the BBB breach in those diseases remain elusive. Work carried out in this laboratory has established a role for S100B in maintaining an intact BBB using a mouse (S100BKO) model [66].

4.2 S100B is essential to maintain BBB

The detection of leaked serum components, such as IgG, has been widely used to assess impairment of BBB function [64]. In a study from this laboratory by Wu and coworkers [66], vascular leaks in the brain were evaluated by immunostaining brain sections from S100BKO mice to detect extravascular IgG. Previous studies have shown that intravenous injection of pertussis toxin [PT] generates leaks in the BBB [64, 99]. Therefore, wild type and S100BKO mice were injected with PT and the effect on BBB permeability was investigated.

Extravasated IgG from the blood vessels was detected as perivascular leakage clouds marking sites of BBB breach. In wild-type mice, leak clouds were detected only upon injection of PT; in the S100BKO mice, however, they were detected even without PT injection by 6 months of age and were exacerbated by PT injection. Thus, there is an endogenous BBB deficiency in S100BKO mice, which is increased by treatment with PT. The BBB breach was chronic and age-dependent, increasing with age [66]. Thus, the system mimics the chronic, age-associated compromise of BBB in humans. In addition, selective binding of neurons by IgG was also temporally and spatially associated with these leak clouds, suggesting that neuron-binding autoantibodies are present and BBB compromise allows their access to neurons in the brain; an increase in the brain-reactive autoantibodies was also associated with increased BBB breach [66].

Interestingly, despite detectable pathology, there was very little glial response as measured by increased expression of glial fibrillary acidic protein (GFAP) [66]. Is it possible that S100B is necessary to trigger the astroglial response to neuronal injury/insult? The question remains to be answered.

The potential reason for the BBB breach, however, could be identified: Based on electron microscopic analyses, disorganization of endothelial tight junctions is proposed to cause the observed BBB breach [66].

4.3 S100B is essential to maintain blood-retinal barrier (BRB)

Tight junctions are also important for the maintenance of the blood-retinal barrier (BRB). The existence of blood-retinal barrier (BRB) is well established [100–104], although its similarity to the BBB remains to be completely elucidated [105, 106] and its establishment, less understood [107]. If S100B was essential for the maintenance of tight junctions in vascular endothelial cells and lack of it caused BBB breach, would similar breaches be observed BRB also? The results presented below show that this is, indeed, the case.

In untreated wild-type mice (**Figure 1A**), staining for IgG was restricted to within blood vessels, which indicates an intact barrier. In PT-injected wild-type mice, IgG extravasated from the blood vessels. However, the perivascular leakage clouds were not obvious while the IgG-bound ganglion cells were detected (indicated by arrows in **Figure 1B**). The results suggest that neuron-binding autoantibodies are present and BRB compromise allows their access to neurons in the retina. Leak clouds outside the blood vessels were observed in S100BKO mice in the absence of PT (**Figure 1C**). Upon PT injection of S100BKO mice, the perivascular leak clouds persist (**Figure 1D**). Thus, an endogenous BRB deficiency in S100BKO mice was observed. The presence of retina-specific autoantibodies was confirmed independently by Western blot analyses (**Figure 1E**). The result shows that their appearance is age-dependent, as in the BBB.

Thus, the effect of S100B deprivation leads to chronic barrier disruption in both brain and retina through disruption of the endothelial tight junctions, most likely. The details of the mechanistic aspects of the action of S100B on tight junction maintenance remain to be established: both intracellular and extracellular routes are possible [14]. An intracellular mechanism is supported by observations that S100B is

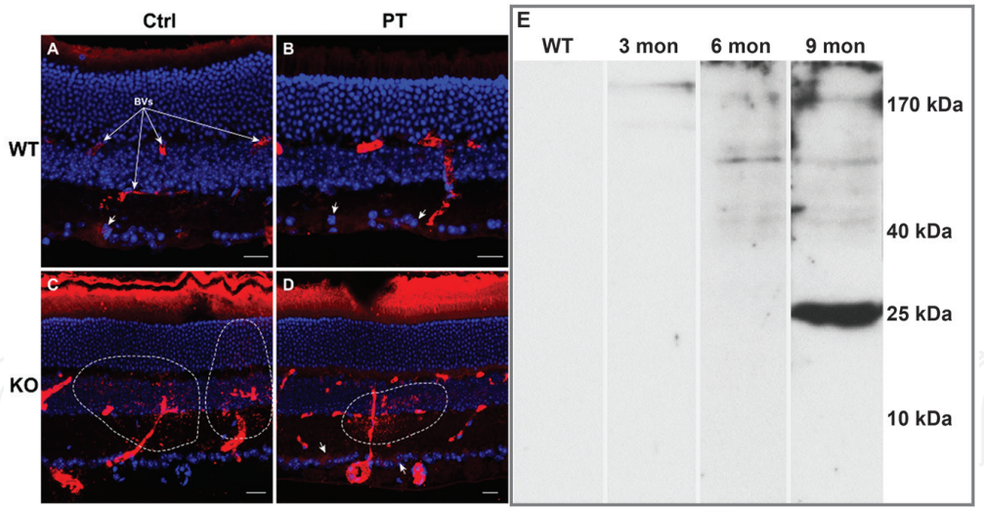

Figure 1.
S100BKO mice demonstrate significant BRB compromise in the retina and express retina-specific autoantibodies. Overlay of IgG immunostaining (red) with DAPI (blue) is presented from the retinal sections of untreated wild-type mice (A), PT-treated WT mice (B), S100BKO mice (C), and S100BKO mice treated with PT (D). Scale bar, 20 μm. Western blots (E) of the swine retinal protein extract were probed with pooled sera from wild-type mice (WT) or from S100BKO mice at 3 (3 Mon), 6 (6 Mon), or 9 (9 Mon) months of age. A representative result is shown. Molecular size markers are indicated alongside.

expressed in endothelial cells [108, 109]; furthermore, assembling and maintaining functional tight junctions is dependent upon several signaling pathways [reviewed in [110–112]], all of which are known to be influenced by S100B: calcium homeostasis [13, 14, 113], guanylate cyclase activation [114, 115], modulation of rhoGTPases such as Rac1 [116] and protein kinase C activity [108]. Extracellularly, S100B, most likely, acts through the receptor for advanced glycation end products (RAGE) expressed on endothelial cells [117] and results in the activation of the Ras-ERK1/2-NF-κB pathway [reviewed in [14]]. This pathway regulates endothelial hyperpermeability [reviewed in [111]], particularly the assembly of TJ proteins [118]. Moreover, the expression of NF-κB itself is regulated by S100B [119, 120]. Additional receptors for S100B, such as CD166/ALCAM and Toll-Like Receptors (TLR), are also known. Therefore, extracellular S100B may also be critical for endothelial function in maintaining the BBB.

5. Blood-brain barrier (BBB) and neurodegenerative diseases

5.1 Autoantibodies and neurodegenerative diseases

The BBB breach allows autoantibodies in the blood vessels to gain access to neurons and other cell types, causing compromise in function and, in extreme cases, cell death. The breach itself could be generated over time through age or disorders or acutely through traumatic injuries. Debris released from sick or dead cells would now be encountered by the immune system, which would mount an antibody response, generating autoantibodies. This results in a potentially devastating feedback loop: the autoantibodies cause compromise of cells, releasing debris, which, in turn, augments the response. The only way to halt this cycle will be through the loss of the targeted antigens: either through endocytosis or receptor stripping. Typically, that would also lead to dysfunctions in neurons and other cells [121, 122].

This "positive feedback loop" hypothesis is suggested by a decreased expression of MAP2, shown to be indicative of neuronal stress [123, 124], in both *in vivo* [66] and *in vitro* model systems of BBB [125] or BRB [126] breach. Previous studies have also shown a widespread presence of brain-reactive autoantibodies in human serum [127] and changing autoantibody profiles upon disease [96, 122, 128–130]. Much evidence now

suggests that BBB breakdown also contributes to acute dysfunctions such as post-operative delirium and recovery from anesthesia [131, 132]. An increase in BBB permeability, like in S100BKO mice reported here, has been observed previously in humans with age [82] and with many chronic dysfunctions **Table 1**. Therefore, the S100BKO mouse may serve as a useful model to mimic the status of the aged BBB. It is well documented that the elderly population is highly susceptible to neurodegenerative diseases and delirium.

Increased levels of autoimmune antibodies (generally associated with increased BBB permeability) have been reported in several diseases (reviewed in [129–134]). A positive correlation between autoantibody prevalence and age/diseased state has propelled the idea that they are potential diagnostic tools in AD and Parkinson's disease [122, 129–136].

5.2 Toward a unified mechanism

A clear understanding of the structural components and functions of the BBB may be the key to delineating pathologies of the brain. Here, we propose the idea that neurodegeneration is a multi-step process (**Figure 2**) involving BBB breach,

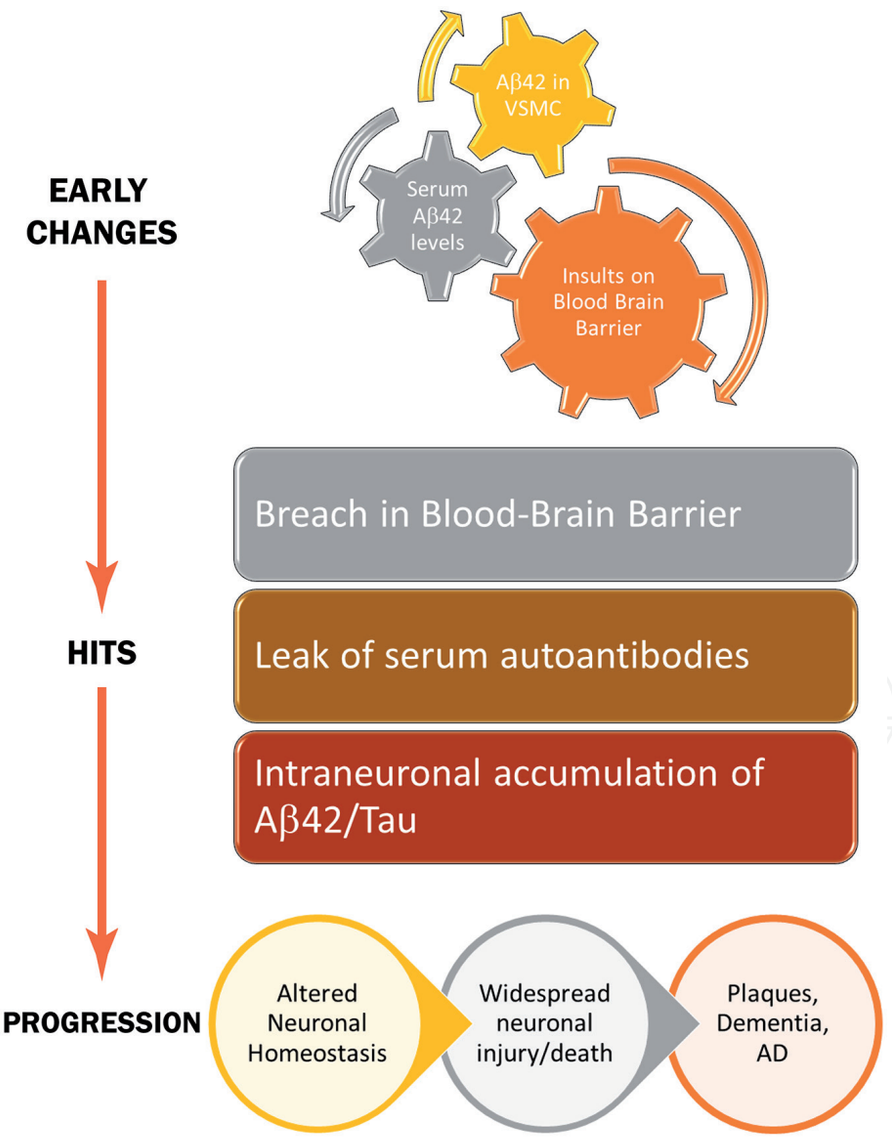

Figure 2.
Blood-brain barrier breach, autoantibodies and neurodegeneration. A unified mechanism is proposed for neurodegenerative diseases. Early changes include changes in the NVU, serum, and other insults on the BBB. Once the BBB is breached, it leads to the extravasation of serum components and access/production of brain-reactive auto antibodies. This results in a positive feedback loop, altering homeostasis and eventually resulting in the disease phenotype through neuronal injury/death.

infiltration of auto antibodies and other damaging plasma components into the brain parenchyma with death of the neurons as the long-term sequelae. Multiple studies indicate that the BBB is very important to the brain health, neuronal integrity, and homeostasis; when BBB breach occurs, it allows for the extravasation of blood-borne molecules (such as Aβ42 in AD), brain-reactive antibodies, and inflammatory factors into the normally immune-privileged brain parenchyma [127, 137–139]. Access of the previously excluded and potentially damaging blood-borne plasma elements to the brain interstitium results in disruption of brain homeostasis, impaired neuronal function, and eventually, neuronal loss [64, 134, 140, 141]. Furthermore, injury or disease of the central nervous system (CNS), such as AD, causes gliosis, which is characterized by the activation of astrocytes, microglia, and other cell types.

Insults to the BBB can be brought about by several pathological conditions and result in the compromise of this protective layer. Studies from our lab show that the inner blood-retinal barrier (BRB) is very similar to the BBB and can be used as a model system to study BBB [126]. The use of brain-reactive autoantibodies to diagnose neurodegenerative diseases with a high degree of confidence has also been reported [122, 135, 136, 142–145].

Taken together, investigations into the BBB maintenance will yield rich dividends toward the mechanistic understanding that may underlie multiple neurodegenerative diseases, increased diagnostic tools in terms of model systems and biomarkers and, perhaps, also drug delivery options. Delineation of S100B signaling pathways is likely to contribute significantly toward this end.

6. Conclusions

S100B, primarily astrocytic in origin, is a unique signaling molecule that impacts multiple signaling pathways—sometimes negatively, sometimes positively [15, 146]. The dual nature of action—intra- and extracellular—poses a significant challenge in delineating the precise mechanism of action in many instances. Yet, S100B is emerging as a central molecule (**Figure 3**) in regulating normal and

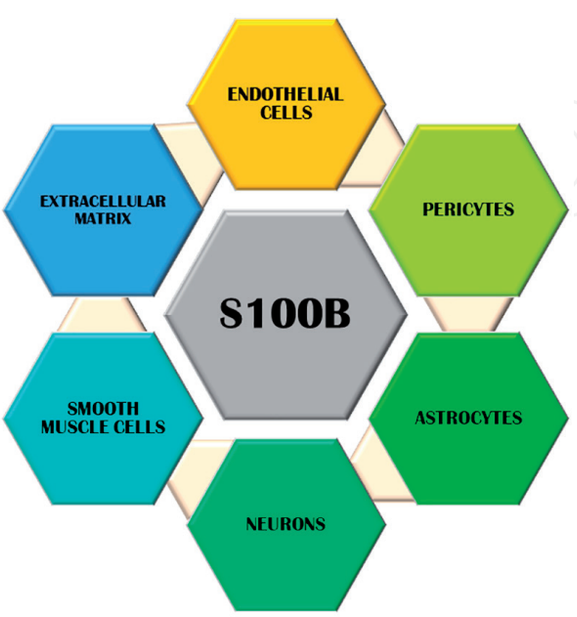

Figure 3.
A central role for S100B, an astrocytic protein. The figure depicts the multiple cell-types contributing to an intact BBB that form the NVU. By virtue of being an extracellular signal as well as being expressed intracellularly, S100B is proposed to play a central role in maintaining BBB and serve as a marker for neurodegeneration.

disease processes—especially where astrocytes/glial cells are involved—the enteric glial cells being a recent and exciting example [147]. It is hoped that a fundamental mechanistic understanding would enable decipher the process, refine the clinical relevance biomarker, and carry the laboratory bench knowledge to the patient bedside to improve quality of life and clinical interventions.

Acknowledgements

The authors are extremely grateful to excellent discussions with Professor Robert Nagele. The support for research through grants from Osteopathic Heritage Foundation and American Osteopathic Association is gratefully acknowledged.

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