COBRE for Skeletal Health and Repair: The Impact of Aging on the Capacity for Peripheral Nerve Regeneration

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ABSTRACT

Peripheral nerves are crucial to the motor and sensory function provided by our upper and lower extremities to our brain and spinal cord. Following trauma or illness, these nerves may be injured, leading to a loss of function that can be significantly debilitating. Fortunately, given the type of injury and under the right conditions, peripheral nerves can regenerate through well-coordinated biochemical processes. However, as individuals age, the ability for nerves to regenerate becomes less efficient, reducing nerve's potential for the nerve to return to its prior level of function. In this article, we review the research that has been conducted to illustrate the reasons for such a decline in regenerative capacity. In doing so, we explore the concept of inflammaging alongside aging-related impairments of the macrophage and Schwann cell during nerve regeneration.

KEYWORDS: COBRE, bone and joint, aging, nerve regeneration

HISTORY OF THE COBRE FOR SKELETAL HEALTH AND REPAIR

The Center of Biomedical Research Excellence (COBRE) for Skeletal Health and Repair was established in 2007 by National Institutes of Health in Rhode Island Hospital, which is affiliated with the Alpert Medical School of Brown University. It consists of three five-year phases (Phase I: 2007–2012; Phase II: 2012–2017; and Phase III: 2017–2022), which is in its 14th year currently. The COBRE goal is to develop a multi-disciplinary translational research center focusing on discovering mechanisms of cartilage joint diseases and developing prevention and treatment strategies. In the first two phases, seven full project junior investigators received R01 or R01-equivalent federal grants, "graduated" from the COBRE training program, and become leaders in their research fields. They published more than 240 peer-reviewed articles, including landmark discoveries in *Nature*, *Molecular Cell,* and *PNAS*. All 20 pilot-project junior investigators received extramural funding as Principal Investigator. New state-of-the-art laboratories and core facilities have been built in bioengineering, imaging, molecular biology and nanomedicine.

The current Phase III COBRE's main objective is to strengthen and transition the COBRE research infrastructure into a competitive, independent, and self-sustaining academic center of excellence. It consists of an Administrative Core, which provides strong leadership in translational research, evaluates the performance of technical Core Resources and Facilities, guides mentoring efforts in the Pilot Projects Program, and implements the COBRE transitioning plan; the Bioengineering Core, which enhances an interactive research environment and provides the unique resources of biomechanical testing at the cell, tissue, and organ levels; the Imaging, Molecular Biology, and Nanomedicine Core, which enhances translational research from bench to bedside, provides critical expertise and equipment in small animal live imaging analysis, and facilitates development of novel nanomaterial delivery vehicles for diagnostics and therapeutics; and the Pilot Projects Program, which mentors a new generation of researchers in multiple disciplines of musculoskeletal research including clinicians, biologists, and engineers, facilitates research collaborations, and sustains the strong research environment.

The COBRE vision that by sustaining and transitioning the established high-caliber research infrastructure will enable clinicians to work side-by-side with basic research scientists, junior investigators with senior investigators, and biologists with bioengineers for the long term into the future. The COBRE for Skeletal Health and Repair has been recognized as one of the country's premier skeletal research centers by the NIH review panels. It carries out cutting-edge research in injury- and aging-associated degenerative bone and joint diseases and develops tissue repair and regeneration strategies. Peripheral nerve injury and regeneration in the extremities is one of the research areas of the COBRE and the review's focus.

INTRODUCTION TO PERIPHERAL NERVE INJURY AND REGENERATION

Peripheral nerve injuries (PNI) may occur following traumatic mechanisms such as laceration, crush, or stretch injuries resulting from medical conditions such as diabetes, medications, or cancer.[1] In America, over 20 million people suffer from peripheral nerve injuries as a result of trauma and illness.[2] Treatment of these injuries has cost upwards of

1.5 billion dollars, and even after treatment, PNIs may still severely affect patients' quality of life.[1]

Studies have shown that, in general, nerve regeneration occurs about 1 mm per day or an inch a month.[3] The process for regeneration stems from Wallerian degeneration, involving the removal and recycling of axonal and myelin debris distal to the injury site to begin creating an environment favorable for regeneration.[4] This process serves as the innate immune response to nerve damage, and in the peripheral nerve system, primarily involves Schwann cells and macrophages as opposed to oligodendrocytes and microglia in the central nervous system.[5] Wallerian degeneration begins with the death of the damaged nerve to the nearest node of Ranvier via a process called chromatolysis followed by clearing the area of regeneration of axonal and myelin debris.[2] The removal of myelin is a crucial step, as myelin debris contain molecules, such as myelin-associated glycoproteins, that can severely affect Schwann cell migration and regeneration of axons.[5] Both macrophages and Schwann cells have been shown to remove myelin from the environment independently (**Figure 1A**).[5]

Soon after a nerve injury, Schwann cells begin to dedifferentiate and proliferate to aid in clearance and longitudinally realign themselves to form bands of Büngner. The bands of Büngner create a direction and environment that promotes axonal regeneration and remyelination.[4,6] Axonal regeneration starts with forming growth cone at the intact nerve from which axonal sprouting occurs. Through contact guiding and neurotrophic factors, the axons extend until reaching the formed bands of Büngner, where the axons and fascicles are then covered by Schwann cells for myelination (**Figure 1A**).[2]

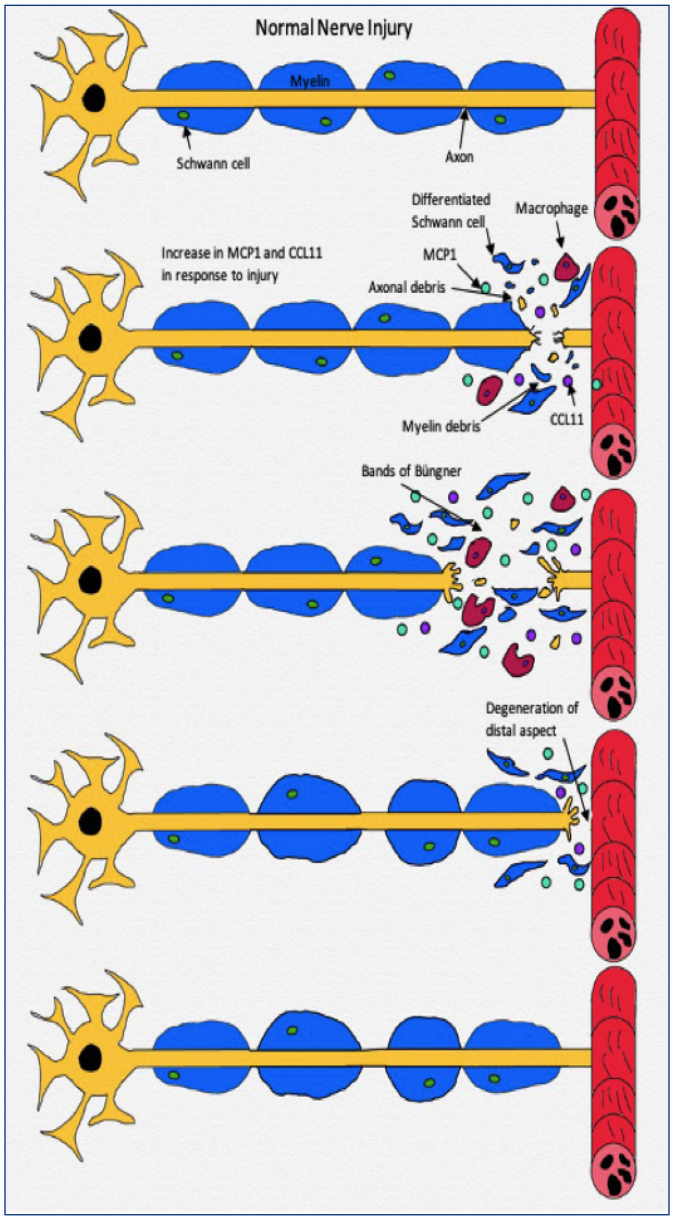
In evaluating this regenerative process's efficiency and effectiveness, studies have found regeneration speeds of peripheral nerves slow with age.[7,8] With age, cells and systemic function become less efficient compared to younger individuals. In addition, with age comes the propensity to develop comorbidities that may affect the health of peripheral nerves due to such conditions as rheumatoid arthritis, Parkinson's diseases, lupus, and Sjogren's syndrome. Peripheral neuropathy may become a symptom of such systemic diseases that may be exacerbated by the decline in the efficiency of nerve regeneration in an aging population.[9,10-12]

The purpose of this review is to evaluate the current understanding of how aging affects peripheral nerve regeneration following injury. In doing so, we explore differences in the microenvironment of nerve regeneration between the young and old by evaluating the inflammatory response to nerve injury alongside the decline macrophages and Schwann cells' function with age.

INFLAMMAGING

As individuals age, their biology becomes less conducive towards nerve regeneration than those who are younger.

Figure 1A. The injury and regenerative process of a nerve in a mature individual. Factors such as MCP1 and CCL11 are upregulated in response to injury. Macrophages are recruited as Schwann cells dedifferentiate to mediate healing. Bands of Büngner formed by Schwann cells then serve to guide regeneration as the distal aspect of the nerve degenerates. Once regeneration is complete, the Schwann cells differentiate to further establish a healthy environment.



One reason this may occur is through inflammaging. Inflammaging is characterized by chronic, low-grade inflammation in the human body that carries risks for poor inflammatory responses when faced with injury or illness.[13] In older individuals, the overall environment is found to be pervasively inflammatory due to an increase in the variety of stressors on the immune system leading to an imbalance between pro- and anti-inflammatory responses.[13]

Inflammatory stimuli that arise from dead cells or debris combined with the declining capacity of the body to clear these materials leads to an autoimmune or autoreactive response that can speed up the aging process in such areas, making them less suitable for regeneration.[13-14] In such inflammatory environments, PNI in aged rats have demonstrated delayed recruitment in macrophages, which subsequently linger at the site of injury longer, producing additional pro-inflammatory cytokines compared to younger rats.[14] While macrophages are typically important for clearing debris, such pro-inflammatory macrophages subsequently suppress Schwann cell function and ultimately axonal regeneration.[15] Rats with crush injuries treated with acetylsalicylic acid (ASA), used as an anti-inflammatory treatment, were found to have accelerated functional recovery, decreased macrophage count, and more advanced remyelination.[14] As a result, the authors suggested that anti-inflammatory treatments may help the progression of nerve regeneration.

Table 1. The role of macrophages and Schwann cells in peripheral nerve injury and regeneration during aging. Intervention targets and treatment options are described.

Components of Regeneration	Intervention Targets	Treatments
Macrophages	• Upregulated CCL1122 29 • Chronically upregulated MCP-1 in a non-injury state8 • Delayed and diminished recruitment to injury site • MCP-1 increase upon injury is downregulated	• ASA has been used as an anti-inflammatory treatment that helps the microenvironment of the regenerating nerve. • Controlled application of cytokines, MCP-1 following injury can improve the progression of regeneration • Inhibition of CCL11 to improve macrophage function
Schwann cells (SC)	• P75, a marker contributing to the differentiation of SCs, is significantly decreased in aged animals, decreasing SC myelination ability • Genetic instability of SCs contributes to the lack of functioning Schwann cell proliferation • c-Jun, a gene responsible for SC proliferation and activity, has its expression impaired in older mice	• Senolytics decrease senescent cell accumulation promoting more effective SC migration to the site of injury 30 • Genetic manipulation to c-Jun and p75 expression could help maintain their function in an aging environment

MACROPHAGE IMPAIRMENT

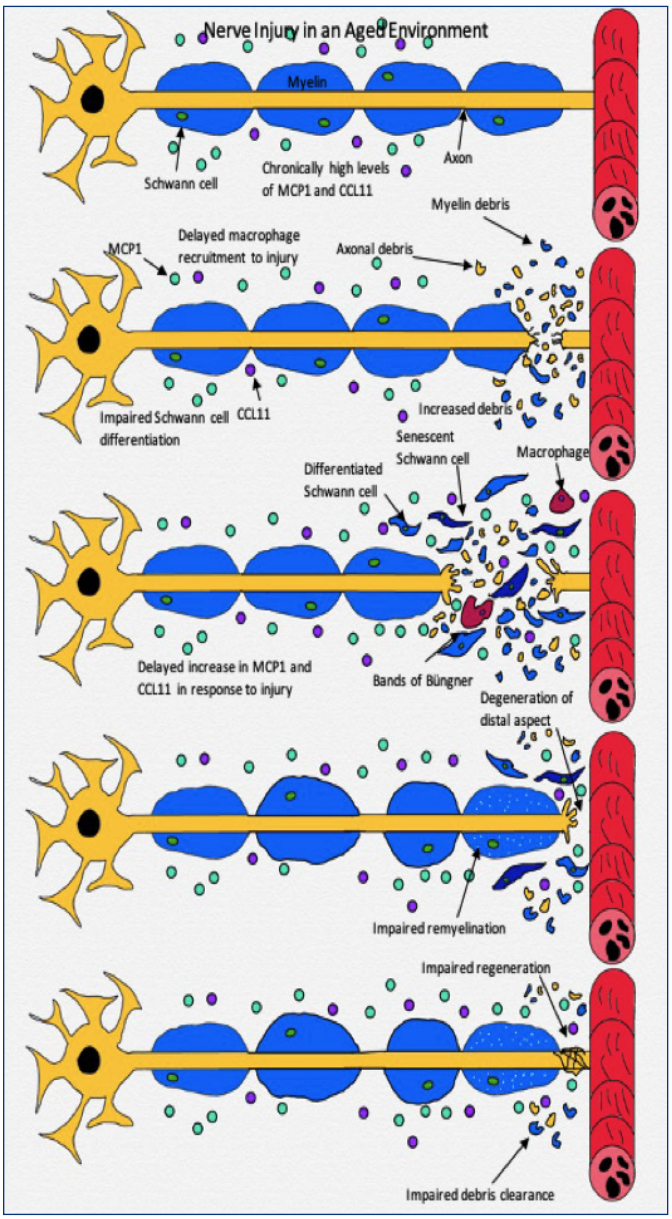
Delayed macrophage recruitment and impairment is a key component behind the slowing of nerve regeneration in aged animals. Following peripheral nerve injury, macrophages help in the clearance of myelin and axonal debris and facilitate angiogenesis and Schwann cell migration to create an environment conducive to regeneration.[8] Given their crucial role, the decline in the recruitment and function of these cells with age has a dire consequence for regenerative ability.

Response to nerve injury is found to be delayed in aged animals due to an accumulation of macrophages later than in young or adult rat models.[14] After about eight days, macrophage count was found to be at comparable levels to younger rats, indicating the magnitude of recruitment may be consistent between ages.[16] Thus, impaired regeneration in aged models could partially be caused by the delay in the recruitment process during the critical early stages of recovery.[16] In addition, studies on age conditioned media (CM) have shown that monocyte migration is significantly less in aged CM than young CM and point towards cytokine signaling of the microenvironment responsible for the delayed recruitment of immune cells.[16] When bone marrow transplants were performed across old and young rats, there was no difference in macrophage counts found across the transplant recipients, indicating that the presence of a young environment or young bone marrow was enough to create a more responsive regenerative environment.[16]

Studies have shown that denervated Schwann cell expression of monocyte chemoattractant protein-1 (MCP-1) plays a significant role in assessing the chemotactic changes of the aged microenvironment.[17] MCP-1 is an important chemokine that regulates the recruitment of macrophages to a site of injury and improves axonal growth.[17] These secretions are a significant component of the chemotactic activity by Schwann cells at the injury site and show the importance of macrophage presence at the site of injury (**Table 1**).[17] With age, studies have shown that MCP-1 released immediately after injury is downregulated in aged nerve injury environments (**Figure 1B**).[16,18] The fewer macrophages initially recruited to the site of injury have been shown to correspond to the decrease in MCP-1 in aged animals contributing to the age impaired regeneration capability of peripheral nerves (**Figure 1B**).

Additional study into MCP-1 has shown that in addition to delayed recruitment of macrophages, its expression persists, producing a chronic inflammatory state shown to hinder continued nerve regeneration.[19] With MCP-1, C-C motif chemokine ligand 11 (CCL11) is another protein produced by macrophages that have been shown to be upregulated in aged peripheral nerve injury environments that interfere with Schwann cell remyelination and axonal regeneration (**Figure 1B**).[14,20-21] While the same macrophage-associated ligands are secreted in peripheral nerve injury environments, the upregulated levels and the persistence they are

Figure 1B. The injury and recovery process of a nerve in an aged individual. With age, MCP1 and CCL11 can become chronically upregulated. In such an environment, macrophage recruitment may be delayed affecting the Wallerian degeneration response to injury. In addition, with age, Schwann cells become impaired in their ability to dedifferentiate causing additional delay in upregulation of regenerative growth factors and an impaired recruitment of macrophages. Some Schwann cells also become senescent and are not active in the regeneration process. Overall, there is reduced clearance of debris following delayed and impaired function of macrophages alongside poor upregulation of a dedifferentiated regenerative phenotype of Schwann cells leading to impaired axonal regeneration and remyelination.



expressed increase with age. These proteins' continued production ultimately leads to macrophage and Schwann cell-related impairment during the nerve regeneration process. Having specifically pinpointed these cytokines, the connection between inflammaging and macrophage impairment in nerve regeneration has become apparent with the potential to act as therapeutic targets.

SCHWANN CELL IMPAIRMENT

Schwann cells (SCs) support peripheral nerves by playing a key role in myelination and axons' remyelination. Upon injury, SCs dedifferentiate into repair cells to secrete regenerative factors, clear debris, recruit macrophages, and lay a path for axonal growth (**Figure 1A**).[8] Like macrophages, SCs also experience negative effects in response to an aging environment They are not as efficient as in younger animals.[8,14,18] As for the cause of a decrease in SC responses, some studies have investigated varying secretion of regenerative factors, genetic changes, and increased damage and fragmentation in the area.

In a study on SCs by Koniyama and Suzuki, the proliferation of SCs throughout Wallerian degeneration in rats of various ages was analyzed.[22] Using thymidine incorporation, the authors were able to measure the proliferation of SCs and fibroblasts. Previous studies have shown that myelin processed by macrophages contribute to SC proliferation during Wallerian degeneration. Koniyama and Suzuki also revealed that axonal components' loss had an inhibitory effect on SCs in actively myelinating nerves.[22] From this data, they were able to determine that the proliferative capacity declined because of both age-related loss of axonal mitogens and a reduction of mitogens from myelin components.

Genetic changes in SCs themselves occur as individuals age, and their functionality also decreases as a result. One example of this is the c-Jun gene (**Table 1**). c-Jun is a critical transcription factor for the presence and proliferation of SCs at injury, and it has been found to vary in levels depending on age.[23] c-Jun is a master regulator in Wallerian degeneration. It controls expression of trophic factors, adhesion molecules, regeneration tracks, and myelin clearance.[24] c-Jun is responsible for the activation of repair mechanisms within SCs by specifying the phenotype of denervated SCs and control over the interactions between axons and SCs.[24] c-Jun presence is induced by injury, as demonstrated by transection of a facial nerve that led to an upregulation of c-Jun during the immune response a few days after injury.[25] In animals without c-Jun, studies discovered the failure of functional recovery, insufficient myelin clearance, failure of axon growth and reinnervation, and death of injured sensory neurons.[25] In a study on aged mice, it was found that aged mice had impaired axonal regeneration while also having a defective cell body response, which lacked both c-Jun expression and phosphorylation.[23] Previous studies have

shown that deletion of the c-Jun gene would cause a delay in recovery and a reduction in innervation, revealing that the regeneration process isn't entirely dependent on the presence of c-Jun.[26] c-Jun has also been known to initiate expression of other regeneration-associated molecules such as CD44, galanin, and α7β1integrin.[25]

As SCs age, there is also the danger of an impairment in the dedifferentiation mechanisms, causing the SCs to remain in a differentiated state. In injury responses, SCs undergo a process of change that alters their structure, molecular profile, and function, creating two distinct differentiation states.[24] p75 is a marker for the repair cell phenotype and has been found to contribute to both dedifferentiation of SCs as well as apoptosis of ineffective and senescent SCs.[27] Studies have shown that animals with a p75 deficiency had significantly impaired motor recovery compared to normal p75 expressing animals through 7–10 weeks.[28] p75 expression is also markedly delayed in SCs in injuries in aged animals when compared to young animals.[8] In aged animals, SCs also exhibit deficiency in myelin clearing ability along with the delayed p75 expression.[8] Inefficient SC differentiation shows a decrease in SC plasticity and SC senescence, which may contribute to the delay in regeneration in the critical stages of injury (**Fig. 1b**). Macrophage recruitment is dependent on factors secreted by dedifferentiated SCs, thus delayed recruitment is one of the downstream effects of inefficient dedifferentiation.[8]

As mentioned previously, macrophage impairment leads to myelin clearance inefficiency. When combined with SCs' impaired ability to clear myelin, the repair response becomes even more inefficient due to age-related changes. It reveals even more downstream effects of the loss of plasticity. Furthermore, because of the plethora of changes SCs undergo with injury responses, they could be especially vulnerable to age-acquired errors in transcription or expression.[8] Studies have shown that older SCs undergo significant karyotype changes when bred in vitro with no anchorage dependency and no increase in telomerase activity: cellular characteristics resembling tumor cells.[29] Overall, genetic instability and genetic changes of aged SCs contributes to the decline of SC function and dedifferentiation capabilities in aged individuals.

DISCUSSION

Nerve regeneration is a coordinated process of cellular dedifferentiation and cellular chemotaxis to generate a microenvironment conducive to healing. In the study of aging as it relates to this regenerative process, a chronic inflammatory state, age-related alterations to the microenvironment, and genetic changes of Schwann cells and macrophages lead to an age-related decline in response to injury and regeneration.

We have reviewed that an aging immune system induces an inflammatory environment called inflammaging, delaying Wallerian degeneration. This inflammatory process also contributes to additional complications associated with delayed macrophage recruitment and impaired macrophage function. Combined with age-related genetic changes leading to poor SC dedifferentiation and SC senescence, nerve injury's response becomes further compromised, negatively affecting the regenerative process.

Potential treatment modalities to improve regeneration in an aged environment involve targeting key cytokines and improving upon cellular function. Chronic elevation of CCL11 with age and its additional expression by macrophages following injury have shown to impair Schwann cell repair activity. Inhibition of this pro-inflammatory target may improve nerve maintenance and repair in the elderly population. In a similar fashion, delayed and subsequent chronic elevation of MCP-1 has been shown to reduce the regenerative support of Schwann cells. Through a timely and controlled application of MCP-1 following injury, axonal regeneration may be improved and better supported.

Genetic impairments of SCs leading to decreased ability of dedifferentiation and increased SC senescence has been demonstrated to be detrimental to nerve regeneration. Potential treatment modalities may involve genetic alterations of aged SCs to increase the expression of c-Jun and the underlying molecular mechanisms for p75 expression to improve the reparative ability of SCs. In addition, to combat against the development of an increasing senescent cell population and its accumulation, senolytics are a potential option. Senolytics are drugs that target and kill senescent cell populations, which present a promising solution to clear senescent cell populations and help restore SC activity and nerve regeneration in aged individuals.

Through a continued understanding of the fundamental aspects of how aging affects regenerative nerve processes, we may be better able to develop therapies to improve upon the response following injury. Suitable interventions will require continued mechanistic studies to improve the localization and targeting of such treatments and further ensure their safety and effectiveness in a vulnerable patient population.

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