DOI: https://doi.org/10.17650/1683-3295-2024-26-4-110-115

THE ROLE OF INNATE AND ADAPTIVE IMMUNITY IN WALLERIAN DEGENERATION IN PERIPHERAL NERVE CRUSH INJURY

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Some trauma patients develop peripheral nerve injury due to crush injuries resulting from severe trauma and blunt force. Recovery from peripheral nerve injuries is frequently inadequate and requires months or even years. This recovery process is associated with both the innate immune system, comprised of Schwann cells, neutrophils, and macrophages and the adaptive immune system. Prior to the regeneration process, the two immune systems work collaboratively to eliminate myelin and axon protein debris in Wallerian degeneration.

Keywords: immune systems, myelin debris, axon protein, elimination

For citation: Besin V., Naesilla N. The role of unnate and adaptive immunity in Wallerian degeneration in peripheral nerve crush injury. Neyrokhirurgiya = Russian Journal of Neurosurgery 2024;26(4):110–5. (In Engl.).
DOI: https://doi.org/10.17650/1683-3295-2024-26-4-110-115

Роль врожденного и приобретенного иммунитета в валлеровой дегенерации при размозжении периферических нервов

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У некоторых пациентов развивается повреждение периферических нервов в результате травм, сопровождающихся сдавливанием тканей. Восстановление после травм периферических нервов часто бывает неудовлетворительным и требует месяцев или даже лет. Процесс восстановления связан как с врожденным иммунитетом, в частности шванновскими клетками, нейтрофилами и макрофагами, так и с приобретенным иммунитетом. Перед началом процесса регенерации два аспекта иммунной системы работают вместе, чтобы устранить миелин и разрушенные аксональные белки в ходе процесса валлеровой дегенерации.

Ключевые слова: иммунная система, разрушенный миелин, аксональные белки, элиминация

Для цитирования: Besin V., Naesilla N. The role of unnate and adaptive immunity in Wallerian degeneration in peripheral nerve crush injury. Нейрохирургия 2024;26(4):110–5. (На англ.).
DOI: https://doi.org/10.17650/1683-3295-2024-26-4-110-115

INTRODUCTION

Peripheral nerve crush injury is an injury to the peripheral nerves produced by acute trauma compression from a blunt object [1, 2]. Crush injuries have the most incidence among peripheral nerve injuries, with 1.91 % in extremity trauma. A nerve crush injury can result in impulse conduction abnormalities, nerve dysfunction, and long-term damage [1]. When peripheral nervous system axons are damaged, a complex multicellular reaction follows. These nerves should undergo three major repair mechanisms: Wallerian degeneration, axonal regeneration, and reinnervation of end organs [2].

Abnormalities in any stage can contribute to the poor functional outcome commonly observed in peripheral

nerves injury patients. The process of axonal degeneration and regeneration involve non-neural cells, including immune cells and Schwann cells, in addition to injured neurons. This study was aimed to summarize current findings regarding immune system's role during the repair process following crush injury.

PERIPHERAL NERVE CRUSH INJURY

As mentioned briefly, acute trauma compression is the cause of peripheral nerve crush injury. Crush injuries occur in various degrees; however, the hallmark is that the injury does not cause total nerve transection [2]. Numerous conditions, including fracture, dislocation of the joint, hemorrhage, and severe pressure, can result in peripheral nerve crush injuries [3]. When an injury involves the lower extremities, the sciatic nerve is often affected. This may be the result of compression of the nerve roots, femoral column fracture, hip dysplasia, or contusion. For the upper extremities, one of the most classic examples is carpal tunnel syndrome, which causes compression and crush injury to the median nerve [2]. Crush injury, also known as axonotmesis, is a second-degree peripheral nerve injury. Axonotmesis is identified by the presence of axonal and myelin sheath lesions, with intact perineurium and epineurium still preserve the nerve's anatomical structure [3]. Additionally, the Schwann cell basal membrane that borders fascicles and nerve fibers is also structurally intact, allowing Schwann cells to function as a guide in axonal regeneration [4].

Nerve damage following a crush injury results from direct external pressure on the nerve, mechanical deformation due to the redistribution of tissue from the zone of compression, and ischemia as a result of pressure exceeding the capillary perfusion pressure. Local ischemia caused by vascular lesions in crush injuries initiates biochemical responses that culminate in an inflammatory response to the crush injury, as well as increased local vascular permeability and intraneural edema [3]. This intraneural edema, in turn, will alter the microenvironment by increasing local pressure, leading to a further reduction of blood flow and alterations in electrolyte contents of the endoneurium. It results in axonal hypoxia, compression, and disruption. If the condition persists, it causes neuropraxia or axonotmesis. This ischemia phenomenon is the beginning of axonal Wallerian degenerations [3, 5].

WALLERIAN DEGENERATION

As an injury between two axonal (proximal and distal) segments occurs, the distal component of the lesion begins a degenerative process [6, 7]. Wallerian degeneration must occur prior to the initiation of axonal regeneration. The effectiveness of the degenerative process is affected by the rapid and efficient inflammatory process. Hence, the primary objective of Wallerian degeneration is the elimination of myelin and axon protein debris and promoting regeneration and reinnervation. The clearance phase of myelin in Wallerian degeneration is complete within two to three weeks following the injury [4].

Wallerian degeneration is composed of cellular and molecular processes which is identified as the intrinsic degeneration. The rapid degradation of the injured distal axon and the infiltration of immune cells at the injury site are the key characteristics [4, 8, 9]. This phenomenon is rooted from a lack of communication to the cell body and metabolic events. As the proximal segment displays reactive edema with typically mild retrograde deterioration, edematous, proteolytic, and autolytic granulation persists in the distal segment for three to four days [3].

Wallerian degeneration begins with calcium involvement following trauma [10, 11]. Due to the abrupt lack of oxygen supply, calcium ions may enter Schwann cells and axon axoplasm. This causes a disruption in the axonal energy homeostasis and leads to a rapid depletion of nicotinamide adenine dinucleotide (NAD) and adenosine triphosphate (ATP) [12–14]. In turn, mitochondria lose their membrane potential and start swelling, leading to an increase in reactive oxygen species production. In addition to calcium influx, the release of internal calcium reserves causes further calcium waves. The calcium influx in axons subsequently activates calpain protease whose proteolytic activity facilitates axon disintegration [3, 4, 14].

The cells involved in Wallerian degeneration depend on the location of the injured nerve; for peripheral nerve, the cells involved are Schwann cells, neutrophils, and macrophages. Notably, immune cell overactivation in injured peripheral nerves may also result in excessive Wallerian degeneration, inhibit normal repair, and impede peripheral nerve regeneration [3].

INNATE IMMUNITY

A brief summary of innate immunity and its concordant cytokines in Wallerian degeneration is presented in Table 1. Immediately after the injury, Schwann cells separate from axons which is preceded by Schwann cell dedifferentiation [15]. Schwann cell dedifferentiation is the transformation of myelinated Schwann cells into non-myelinated or immature Schwann cells. This transformation supports the involvement of Schwann cells in mediating the early phases of debris clearance by autophagy and phagocytosis of myelin debris and cytokine production in Wallerian degeneration [4, 7, 16]. Demyelination and dedifferentiation of Schwann cells are essentially triggered by two mechanisms: upregulation of the *JUN* gene and rapid activation of receptor tyrosine kinase erbB2 and enhanced intracellular Notch domain expression (within 10 minutes) [4].

Many danger-associated molecular patterns (DAMPs) are produced at injury site. DAMP, the early byproduct of axonal degeneration, include necrotic cells, heat shock proteins, and extracellular matrix components. DAMPs activate Schwann cells by attaching to Toll like receptors (TLRs). In a culture study, Schwann cells was reported to activate and produce proinflammatory genes *via* the

TLR2 and TLR3 pathways. The breakdown of the extracellular matrix by proteolytic enzymes not only abolished the inhibition of TLR4, but also produces soluble endogenous agonist that activates this receptor, such as heparan sulfate [17].

Table 1. *Cytokines and chemokines produced by innate immunity cells during Wallerian degeneration*

Innate immunity	Adaptive immunity
Schwann cells	Tumor necrosis factor alpha (TNF-α) Interleukin-1α (IL-1α) Interleukin-1β (IL-1β) Macrophage chemoattractant protein-1 (MCP-1) Galectin-3 (Gal-3) Macrophage inflammatory protein 1-α (MIP1-α) Leukemia inhibitory factor (LIF)
Macrophage	
Macrophage M1	Interleukin-1 (IL-1) Interleukin-6 (IL-6) Tumor necrosis factor alpha (TNF-α)
Macrophage M2	Interleukin-6 (IL-6) Interleukin-10 (IL-10) Interleukin-13 (IL-13)

In response to DAMPs binding to TLRs, Schwann cells express inflammatory cytokines. Signals from TLRs trigger proinflammatory cytokines via nuclear factor-kappa B (NF-κB) transcription [4, 18]. As the DAMP binds to TLRs, myeloid differentiation primary response gene 88 (MyD88) is activated in the cytosol. MyD88 will activate tumor necrosis factor (TNF) receptor associated factor-6 (TRAF-6). TRAF-6 then activate interleukin (IL) – 1 receptor associated kinase-1 (IRAK-1) and IL-1 receptor associated kinase-4 (IRAK-4). The formation of IRAK1/2/4 and MyD88 complexes triggers molecular interactions among TRAF6, TABs, and TAK1 which lead to the activation of the IKK/IκBα pathway and MAPK pathway. These pathways are involved in NF-κB translocation and AP-1 translocation, respectively [19].

IRAK1 overexpression enhances the phosphorylation of p65 and c-Fos, hence activating NF-κB [19]. Translocation of NF-κB from the cytoplasm to the nucleus initiates gene transcription and its subsequent binding to DNA upon activation [20]. This gene is responsible for the production of inflammatory cytokines and chemokines, as well as adhesion molecules, such as TNF-α, IL-1α, IL-1β, macrophage chemoattractant protein-1 (MCP-1), Galectin-3, macrophage inflammatory protein (MIP) 1-α, leukemia inhibitor factor (LIF), a nerve growth factor that regulates leukocyte proliferation and recruitment [15].

Schwann cell-produced cytokines and chemokines induce myelin breakdown by stimulating PLA2 (phospholipase A) expression. PLA2 activation is responsible for the hydrolysis of phosphatidylcholine on the membrane. This will enhance formation of lysophosphatidylcholine, which has a rapid and potent myelinolytic effect. Through binding to C-reactive protein, lysophosphatidylcholine activates the traditional complement pathway, resulting in C5 activation to C5a [21, 22]. Activation of C5 to C5a via the classical complement activation pathway by lysophosphatidylcholine triggers the initial influx of neutrophils to the site of damage. Within eight hours of an injury, neutrophils are the first immune cells to infiltrate and aggregate distal to the lesion. As the first line of defense against damage, neutrophils phagocytose and utilize lytic enzymes derived from their granule proteins to breakdown and eliminate debris. However, the lifetime of neutrophil is short. Thus, the bond between lysophosphatidylcholine and degenerated myelin will also signal macrophage phagocytosis, resulting in more removal of myelin protein and axon debris [4, 23].

Increased production of TNF-α dan IL-1α is identified within five to six hours after injury by Schwann cells, while IL-1β expression began five to ten hours after injury. The highest levels of TNF-α dan IL-1β were recorded on the first day following damage, prior to the entry of macrophages [4, 15]. TNF-α cytokines and Schwann cell-derived LIF stimulate Schwann cells' expression MCP-1, promoting macrophages recruitment to Wallerian degeneration area, together with IL-1β secretion [24]. Schwann cells are also a source of the protein monocyte-1 adsorbent, which regulates macrophage recruitment to nerve lesions [25]. Two to three days after an injury, monocytes begin to migrate toward the nerve tissue. In the injured area, monocytes will transform into macrophages. Within days, macrophages predominate the completion of Wallerian degeneration [15].

Macrophages bind to the CCR2 receptor in the peripheral nervous system. It was discovered that macrophage infiltration at the damaged nerve location was considerably reduced in CCR2-deficient mice. A multitude of chemokines and cytokines are secreted by macrophages to recruit other macrophages [18, 24]. On the third day after axotomy, a study on injured sciatic nerve reported more macrophages from the circulation are recruited to injured area and the level of macrophages peaked between day-14 and –21 [9]. Activated macrophages could differentiate into different types, such as M1 and M2 types. M1 phenotypes are induced by interferon gamma and lipopolysaccharide and produce proinflammatory cytokines such as IL-1, IL-6, TNF-α, and other chemokines [7]. As will be discussed in the next section, M1 macrophages promote the development of T-cells, such as Th1 and Th17, which mediate inflammation. Meanwhile, M2 macrophages has anti-inflammatory effects, necessary for tissue repair and inflammation resolution, characterized by the production of IL-10 and IL-13 [18]. Schwann cell proliferation and migration can be influenced by both macrophage phenotypes, albeit at different speeds; M2 was able to accelerate Schwann cell migration by twice the rate as M1. *In vitro* studies have shown that M2 macrophages possess a neuroprotective component and the potential to release neurotrophic substances that promote regeneration [7, 26, 27].

IL-10 and IL-6 are inflammatory response-regulating cytokines that are primarily released by macrophages, particularly M2 and fibroblasts, and less by Schwann cells. Although IL-6 is thought to play a pro-inflammatory role, multiple studies have demonstrated that it also has an anti-inflammatory property through controlling TNF-expression [4, 18, 28]. IL-10 has an anti-inflammatory effect via inhibiting NF-κB, whereas IL-6 exert anti-inflammatory effect by modulating the expression of TNF-α. A study report on sciatic nerve injury rat model revealed that IL-6 levels increased two hours after injury and persisted for up to 21 days, whereas IL-10 levels increased on the fourth day after injury, peaked on the seventh day, and persisted for 14 days [4, 15, 29]. Additionally, sciatic nerve injury produces overexpression of apolipoprotein E and collagen VI. This results in enhanced polarization of macrophages to M2 phenotype via p38 mitogen-activated protein kinase and tyrosine kinase activations. CCL2/CCR2 signaling is also critical in peripheral nerve injury to induce M2 polarization. G-protein-coupled receptor 84 (GPR84) is a macrophage-produced receptor during inflammation which is found elevated in sciatic nerve damage. It is known that low levels of GPR84 promote macrophage polarization to M2 phenotype and inhibit mechanical or thermal hypersensitivity following sciatic nerve injury [7].

One study demonstrated that IL-1β and TNF-α specifically up-regulated MMP-9 expression in macrophages and Schwann cells after sciatic nerve injury [30]. MMP-9 contributes directly to the extravasation and migration of monocytes and induces Schwann cell myelinolysis. MMP-9 substrates are found in the Schwann cells basal lamina, the endothelium barrier, and perineurial cells of the peripheral nervous system [4]. In response to injury, endothelial and immune cells, among others, create MMP-9 to regulate the disintegration of the blood-nerve barrier, the recruitment of immune cells, the activation of glial cells, and the demyelination and remyelination of nerve fibers. MMP-9 plays a significant function in the myelin protein degradation and the recruitment of macrophages to the damaged sciatic nerve throughout this phase. MMP-9 knockout mice were notably protected against peripheral Wallerian degeneration, according to research studying the role of MMP-9 [31].

ADAPTIVE IMMUNITY

A brief summary of adaptive immunity is presented in Table 2. The adaptive immune response consists both cellular and humoral components. Even during the earliest phases, the cellular and the humoral immune responses play a role and throughout nerve regeneration [32]. T lymphocytes regulate cellular immunity while B cells are responsible for humoral immunity. Activation of naive T-cells begins when T-cell receptors bind to antigens expressed on antigen-presenting cells, the majority of which are dendritic cells. In this case, NF-κB regulates T-cell differentiation and effector function. Post-activation T-cells are capable of differentiating into several T-cell subsets, including Th1, Th2, Th17, and follicular T-cells, which produce various cytokines and drive various immune responses. The NF-κB pathway is also involved in B cell survival, maturation, and homeostasis [18, 33].

Table 2. *The role of adaptive immunity during Wallerian degeneration*

Component	Function
Cluster of Differentiation 8^+ ($CD8^+$) cells T helper 1 (Th1) cells T helper 17 (Th17) cells	Activate proinflammatory Macrophage M1 phenotype
T helper 2 (Th2) cells T regulatory (Treg) cells	Activate anti-inflammatory Macrophage M2 phenotype
Immunoglobulin G (IgG)	Antibody opsonization for myelin debris phagocytosis by macrophages

T-cells were found to infiltrate the injury site three days after injury, they may express several cytokines to alter immune response, and it has been demonstrated that Th1 and Th2 cells promote normal neural regeneration. The most classic role of adaptive immune system is the macrophages polarization shift from proinflammatory M1 phenotype (driven by signals from $CD8^+$, Th1, and Th17 cells) to anti-inflammatory M2 phenotype (mediated by cytokines produced by Th2 and Treg cells) [34].

Regulatory T-cells (Treg cells) are also $CD4^+$ T-lymphocytes and may be distinguished by the surface markers $CD4^+$ and CD25. During inflammatory responses, Treg cells maintain immune homeostasis and regulate immune tolerance by suppressing the activation of other immune cells. $CD4^+$ T-cell activation, proliferation, and differentiation required IL-1β, IL-2, and IL-6. $CD4^+$ $CD25^+$ T-cells will then further stimulate M2 macrophage production of the cytokine IL-10 [35–37].

Trauma events suppress the responsiveness of $CD4^+$ T-cells [38]. The percentage of $CD4^+$ cells and the ratio of $CD4^+$:$CD8^+$ in the peripheral blood of rats seven days after nerve injury were lower in control group. This shows that rats with peripheral nerve injury have a low immunological status, which may result in a diminished immune system's performance. This period of persistently poor immunity is transient. Within 14 days following nerve injury, T-cells return to normal [39].

Myelin debris phagocytosis by macrophages requires antibody opsonization. In this case, innate immunity continues to contribute to adaptive immunity. M2 macrophages are known to be involved in the synthesis, differentiation, and release of IgG and IgM by B cells via the production of the cytokine IL-10 [40, 41]. In addition to IL-10, class II MHC antigens are also expressed by macrophages. An increase in MHC class II antigen stimulates the production of immunoglobulins and the immune cells infiltration [39].

The final phase of myelin degeneration clearance is mediated by hematogenous phagocytes. On the sixth day following crush injury, IgG antibodies are found accumulating in the distal segments of injured nerves. The finding implies the presence of autoantibodies in degenerating nerves, as an attempt to eliminate myelin degradation as quickly as possible [9]. Induction of IgG needs antigen absorption, processing, and presentation; therefore, serum IgG level does not increase until 21 days following the crush injury. Following an injury, the blood-nerve barrier is compromised, resulting in the release of nerve antigens to the circulation. This stimulates immune cells and specific antibodies, which in turn causes the systemic inflammation to begin [39].

CONCLUSION

Peripheral nerve crush injuries are induced by blunt-force trauma without complete nerve transection and intact perineurium and epineurium structures. Wallerian degeneration, an important phase of debris clearance, involves both innate and adaptive immunity and occurs in the distal segment of injured peripheral nerves. Two to three weeks after damage, this phase of myelin clearance of Wallerian degeneration is completed. The most common innate immune cells are neutrophils, Schwann cells, and macrophages and adaptive immune systems include T and B lymphocytes. The two immune systems collaborate to remove myelin and axon protein debris in Wallerian degeneration to prepare for the subsequent axonal regeneration.

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Conflict of interest. The authors declare no conflict of interest.
Конфликт интересов. Авторы заявляют об отсутствии конфликта интересов.

Funding. The study was conducted without sponsorship.
Финансирование. Работа выполнена без спонсорской поддержки.

Ethical clearance. No ethical clearance number/statement and informed consent in this review article.
Этические стандарты. В данной обзорной статье отсутствует заявление об этическом допуске и информированное согласие.

Article submitted: 10.09.2023. **Accepted for publication:** 05.06.2024. **Published online:** 27.12.2024.
Статья поступила: 10.09.2023. **Принята к публикации:** 05.06.2024. **Опубликована онлайн:** 27.12.2024.