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Wallerian Degeneration: Morphological and Molecular Changes

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Review Article

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Abstract

Wallerian degeneration is a process that follows damage to the nerve fiber. Instantly after the initial injury, Wallerian degeneration begins at the distal stump. The axon breaks down, retraction of the myelin sheath happens and the axoplasm is surrounded within ellipsoids of myelin. In respond to loss of axons by disruption of their myelin sheaths, myelin genes are down regulated and Schwann cells dedifferentiated. Schwann cells start multiplying, and macrophages continue to digest debris. By the end of the first week, Schwann cells form a chain within the endoneurium. After about 2 weeks, macrophages disappear, leaving behind endoneurial tubes filled with Schwann cells. Here, we discussed morphological changes and sub cellular events during Wallerian degeneration.

Keywords: Hypoglossal Nerve; Lysosomal Enzymes; Medulla; Catabolic; Chromatolysis; Phenotype; Depolymerization; Schwann Cells; Neurotrophin-3

Abbreviations: MAPK: Mitogen-Activated Protein Kinase; AAD: Acute Axonal Degeneration; PNS: Peripheral Nervous System; CNS: Central Nervous System; mRNA: Messenger RNA; BDNF: Brain-Derived Neurotrophic Factor.

Introduction

Augustus Waller

Dr. Augustus Waller (1816-1870), British physiologist, defined morphological alterations together with the study of axons insulated from their cellular bodies; therefore its description as wallerian degeneration [1]. Waller conducts experiment on frogs in 1850, by cutting their glossopharyngeal and hypoglossal nerves. He then detected the distal nerves from the site of injury, which were disconnected from their cell bodies which is located in the brain stem. Waller nominated the fragmentation of myelin, which he mentioned to as "medulla", into discreteunits of different sizes. The disintegrated axons shaped droplets that could be stained, consequently allowing studies of the development of individual nerve fibers [2].

Morphological Changes during Wallerian Degeneration

Wallerian degeneration is the trophic process of disintegration of a neuron or axon that happens in the neuron at the site of the injury and moves in a distal course from the cell body as follows [3]. The axon breaks down through a process of inflammation and following granulation that lasts about 3 to 4 days. In this process, extrusion of the myelin sheath happens and leads to surround the axoplasm within ellipsoids of myelin and hydrolysis happens by lysosomal enzymes within these ellipsoids. Ellipsoids or digested chambersare defined as secondary demyelination process and described as follows. Myelin fragmented into droplets. This swellingwhich forms beside the internodes contains axonal granules. Degeneration ofaxons and myelin happens together. In fact, because of a close collaboration between the axon and its myelin, and myelin dies if the axon disappears [4]. Consequently, the motor end-plate degenerates. Proliferation of the Schwann cells which contain nuclei and cytoplasmic organelles occur and subsequently, a column of Schwann cells form and recognize as a Büngner band. Simultaneously, proliferation of the adjacent endoneurial cells also happens. These Bungner's band or columns of Schwann cells provide corridors for regenerating axons to reach to their targets that were denervated. Also, growth factors which are secreted by Schwann cellsenforce the outgrowth of axonal sproutsfrom the proximal cut ends of neuron [5]. Concomitantly, in the injured distal cut end, Schwann cells release growth factors that entice new axonal buds recruiting from the proximal stump after complete cut. Therefore, possible reinnervation of the target cell or organ happens. Of course, the regeneration is not complete, as possible confusing happens during reinnervation of the proximal axons to designate cells [6]. This regeneration initiates in about 7 days. Each axon emits a number of processes called axonal sprouts that grow into the Bungner bands. The speed of growth is about 1 to 4 mm per day. This process is dependent on close immediacy of the axonal sprouts and the Büngner bands [7]. With this regard, the estimation of healing period by measuring the distance from the site of the injury to the middle of the denervated muscles. With regard to the slowest speed (1 mm/day), the healing period can be estimated as the distance in millimeters. When a nerve has been completely cut, it is important to suture the cut ends to provide the least inhibition to the axonal sprouts to regenerate. If an inhibition such as fibrosis stops the axonal sprouts to reach the close Bungner band, the axonal sprouts will regenerate in a random manner and form swellings called as a neuroma. These neuromas can be a source of significantdistress. The resultant neuroma may then be an additional source of irritation to the patient [8]. Similar changes that happen in the neuron distal to the injury, other changes take place proximal to the injury. Following an injury, the injury will lead to degenerate of a few internodes proximal to the injury in a same ratecomparable to the catabolic degeneration that happens distal to the injury [9]. A reaction happens in the cell body which is located in the spinal cord, named the axonal reaction as follows. An insignificant enlargement of the cell body, a dislocation of the nucleus to one side of the cytoplasm (an eccentric nucleus), and a distribution of the granular endoplasmic reticulum of the Nissle substance within the cytoplasm. The mentioned even it is termed as central chromatolysis and signifies the efforts of the cell body to create more products for the axoplasmic flow necessary to promote regeneration [10].

Distal End Changes

After damage, morphological changes occur not only at the damage site, but also in the proximal and distal regions. Above-mentioned, this process refers to events that occur after nerve injuries, during which a conductive micro-environment is re-created for axonal growth and neuronal regeneration. This process occurs during the first week after injury and when axonal damage markers

such as the lack of cell membrane integrity and the breakdown of the axonal skeletal system occur. Axonal changes at the distal nerve cut end result in the breakdown of the nerve endings to create a way to repair the axon. The marked sign of this phase is the granulation of the cellular skeleton. This occurs after the flow of extracellular ions such as calcium and sodium, causing a cascade of events such as apoptosis. Calcium influx signaling promotes resealing of cut ends. Axonal injuries initially lead to acute axonal degeneration (AAD), which is due to rapid separation of the proximal cut end (the part nearer the cell body) and distal cut end (the part farther the cell body) within 30 minutes of injury [11]. Granular disintegration of the axonal cytoskeleton and inner organelles occurs after axolemma degradation. Early changes include accumulation of mitochondria in the paranodal regions at the site of injury. Endoplasmic reticulum degrades and mitochondria swell up and eventually disintegrate. The depolymerization of microtubules occurs and is soon followed by degradation of the neurofilaments and other cytoskeleton components [12]. The disintegration is dependent on Ubiquitin and Calpain proteases (caused by influx of calcium ion), suggesting that axonal degeneration is an active process and not a passive one as previously misunderstood [13]. Thus the axon undergoes complete fragmentation. The rate of degradation is dependent on the type of injury and in the PNS is also slowerthan in the CNS. Another factor that affects degradation speed is the diameter of the axon: larger axons require a longer time for degradation ofthe cytoskeleton and thus takes a longer time to degenerate and macrophages are recruited by a signal from the Schwann cell. It has been shown that the distal cut end is capable of transmitting the potential of action hours after interruption. Recently, it has been seen that there is an increase in the BDNF [14] and GDNF [15] mRNA expression [16]. Also, mRNA expression of neurotrophin-3 and ciliary neurotrophic factor decrease [14,17].

Proximal End Changes

Changes occur in proximal cut end vary according to the location of damage with regard to the nerve trunk and severity of injury. Apoptosis occurs if the injury is near the trunk.In severe injuries; the nerve trunk is affected by chromatolysis and is restored by changing the genetic program of the cell body to the regenerative phenotype [18]. During this process, associated-growth factors such as GAP-43, tubulin, and actin will increase, and neurofilaments which are involved in the formation of axon diameter, will decrease [15,19,20]. Nerve protectors, such as heat shock proteins will be up-regulated to increase the survival of injured neurons [21,22]. When axon ultimately reaches their target organ [23], neuronal maturation is required, and the gene expression in the neurons switches from regenerative to supportive state. Schwann cells are the primary mediators and initiators of many events inWallerian degeneration at the site of injury [24]. Schwann cells play as the key to restoring axons. When axons and Schwann cells loose connection, Schwann cells find a non-myelinating behavior, and several proteins such as PMP22, Krox-20 [25], P0 and Connexin-32 [26] are decreased [27]. Synthetic process stops, and differentiation process begins with production of C-jun [28] and neurotrophic factors such as NGF [29] and ciliary neurotrophic cell cycle factor [27]. These factors are involved in the formation of Schwann cells reservoir by aid of intrinsic compounds such as erythropoietin. These changes are regulated by the release of mitogens such as ATP and Neuregulin from the proximal cut end of the neuron. Neuregulins are believed to be responsible for the rapid activation [30,31]. They activate ErbB2 receptors in the Schwann cell microvilli, which results in the activation of the mitogen-activated protein kinase (MAPK) [24]. Although MAPK activity is detected, the injury *sensing* mechanism of Schwann cells is yet to be fully understood. The *sensing* is followed by decreased synthesis of myelin lipids and eventually stops within 48 hrs. The myelin sheaths separate from the axons at the Schmidt-Lanterman incisures first and then rapidly deteriorate and shorten to form bead-like structures. Above-mentioned factors together with acetylcholine help to maturation of Schwann cells in the development of myelin [32]. Schwann cells continue to clear up the myelin debris by degrading their own myelin, phagocyte extracellular myelin and attract macrophages to myelin debris for further phagocytosis [33].

Schwann Cells and Macrophages

However, the macrophages are not attracted to the region for the first few days; hence the Schwann cells have the major role in myelin cleaning. Schwann cells purify cell residues with the process of phagocytosis and macrophages. Schwann cells have been observed to recruit macrophages by release of cytokines and chemokines after *sensing* of axonal injury. This effect goes back to the MAC-2 protein that supports the Schwann cell phagocytosis [34]. Schwann cells are the source of monocyte-1 adsorbent protein that interferes with the recruitment of macrophages [35]. The macrophages are absorbed by the Schwann cells in the area of the damage, a process that is dependent upon the breakdown of the blood-brain barrier [35]. In peripheral nervous system, macrophages attach their receptor called CCR2 which is necessary for Wallerian degeneration [36]. The

recruitment of macrophages helps to improve the clearing rate of myelin debris. The resident macrophages present in the nerves release further chemokines and cytokines to attract further macrophages. Another source of macrophage recruitment factors is serum. Delayed macrophage recruitment was observed in B-cell deficient mice lacking serum antibodies[33].While Schwann cells mediate the initial stage of myelin debris clean up, macrophages come in to finish the process. Debries clean up done by macrophages are mediated by opsonins, which label debris for removal. The 3 major groups found in serum include complement, pentraxins, and antibodies. However, only complement has shown tohelp phagocytosis of myelin debris [27]. Macrophages are involved in the use of damaged nerve cholesterol and the production of apolipoprotein E from other lipoproteins [37,38]. After cleaning the myelin residues, dedifferentiated Schwann cells proliferate in the endoneurial tube of the in the extracellular matrix. Possible sources of proliferation signal are attributed to the ErbB2 receptors and the ErbB3 receptors [39]. Cellular candidates such as dedifferentiated Schwann cells, neutrophils, dendritic cells, fibroblasts, and endothelial cellshave the capability to perform phagocytosis and clearance of debris whichhave shown that neutrophils play an impressive role in myelin removal during Wallerian degeneration [40]. It is reported that neutrophils phagocytosis is done byusing lytic enzymesproduced from their granule proteins to digest and remove foreign debris. Also, neutrophil granules are important for macrophage differentiation and cytokine production [41].

Conclusion

Wallerian degeneration or also called as Wallerian degeneration of the pyramidal tract is a process that results when a nerve fiber is cut or crushed and the part of the axon distal to the injury (i.e. farther from then neuron's cell body) degenerates. A related process known as 'Wallerian-like degeneration' occurs in many neurodegenerative diseases, especially those where axonal transport is impaired. In peripheral neuropathies such as Guillain-Barré syndrome and Charcot-Marie-Tooth, Wallerian degeneration is also studied. In addition, C57BL/*Wlds* mice which has delayed Wallerian degeneration opens new windows to better and precise study of cellular and molecular processes in accompany with Wallerian degeneration. Decreasing the onset of Wallerian degeneration increases the quality of nerve regeneration. Also, two main aims in managing peripheral nerve injuries include modulation of inflammatory responses and upgrading of axonal regeneration. Understanding the mechanisms and differences of Wallerian degeneration between central nervous system and peripheral nervous system is a promising way to treat related disease and disorders.

References

1. Candido KD, England B (2017) Neurolytic Injections for the Treatment of Pain in the Rehabilitation Patient. In: Comprehensive Pain Management in the Rehabilitation Patient, Springer, pp: 511-527.

2. Guo AH, Hao FL, Liu LF, Wang BJ, Jiang XF (2017) An assessment of the correlation between early postinfarction pyramidal tract Wallerian degeneration and nerve function recovery using diffusion tensor imaging. Genet Mol Res 16(1).

3. Snyder-Warwick AK, Yee A, Mackinnon SE (2017) New Insights and Applications in the Treatment of Nerve Injuries. In: Esophageal and Gastric Disorders in Infancy and Childhood, Springer, pp: 549-570.

4. Gamage KK, Cheng I, Park RE, Karim MS, Edamura K (2017) Death receptor 6 promotes Wallerian degeneration in peripheral axons. Curr Biol 27(6): 890-896.

5. Yates D (2017) Axon degeneration: A receptor for injury. Nat Rev Neuroscience 18(5): 266.

6. Anand S (2017) Guidance of Regenerating Peripheral Axon Subtypes Using Molecular Cues.

7. Stark A, Mc Carter S, Kesmann J, Rea W (2017) A Potential Role of Chronic Exposure to Extremely Low-Frequency Electromagnetic Fields in Triggering Persistent Pain Post Breast Cancer Surgery: A Review. Surgery 3(4): 244-250.

8. Gomez-Sanchez JA, Pilch KS, van der Lans M, Fazal SV, Benito C, et al. (2017) After nerve injury, lineage tracing shows that myelin and Remak Schwann cells elongate extensively and branch to form repair Schwann cells, which shorten radically on re-myelination. J Neurosci 37(37): 9086-9099.

9. Deng J, Weng J, Kou Y, Zhang P, Wang Y, et al. (2018) Territory maximization hypothesis during peripheral nerve regeneration. Neural Regen Res 13(2): 230-231.

10. Sánchez M, Anitua E, Delgado D, Garate A, Bilbao AM, et al. (2018) A Novel and Versatile Adjuvant Biologic Therapy in the Management of Neuropathies. In:

Platelet Rich Plasma in Orthopaedics and Sports Medicine, Springer, pp: 225-239.

11. Akassoglou K, Merlini M, Rafalski VA, Real R, Liang L, et al. (2017) In vivo imaging of CNS injury and disease. J Neurosci 37(45): 10808-10816.

12. George R, Griffin JW (1994) The proximo-distal spread of axonal degeneration in the dorsal columns of the rat. J Neurocytol 23(11): 657-667.

13. Hassen GW, Kesner L, Stracher A, Shulman A (2017) Calpain Inhibition: A Potential Therapeutic Target for Neurodegenerative and Neuromuscular Disorders. Front CNS Drug Discov 3: 33-71.

14. Sheldrick A, Camara S, Ilieva M, Riederer P, Michel TM, et al. (2017) Brain-derived neurotrophic factor (BDNF) and neurotrophin 3 (NT3) levels in post-mortem brain tissue from patients with depression compared to healthy individuals–a proof of concept study. Eur Psychiatry 46: 65-71.

15. Michalski B, Bain JR, Fahnestock M (2008) Long-term changes in neurotrophic factor expression in distal nerve stump following denervation and reinnervation with motor or sensory nerve. J Neurochem 105(4): 1244-1252.

16. Koskela M, Bäck S, Võikar V, Richie CT, Domanskyi A, et al. (2017) Update of neurotrophic factors in neurobiology of addiction and future directions. Neurobiol Dis 97: 189-200.

17. Keefe KM, Sheikh IS, Smith GM (2017) Targeting neurotrophins to specific populations of neurons: NGF, BDNF, and NT-3 and their relevance for treatment of spinal cord injury Int J Mol Sci 18(3): 548.

18. Menorca RMG, Fussell TS, Elfar JC (2013) Peripheral nerve trauma: Mechanisms of injury and recovery. Hand Clin 29(3): 317-330.

19. Tetzlaff W, Bisby MA (1989) Neurofilament elongation into regenerating facial nerve axons. Neuroscience 29(3): 659-666.

20. Fu SY, Gordon T (1997) The cellular and molecular basis of peripheral nerve regeneration. Mol Neurobiol 14(1-2): 67-116.

21. Lewis SE, Mannion RJ, White FA, Coggeshall RE, Beggs S, et al. (1999) A role for HSP27 in sensory neuron survival. J Neurosci 19(20): 8945-8953.

22. Costigan M, Mannion RJ, Kendall G, Lewis SE, Campagna JA, et al. (1998) Heat shock protein 27: developmental regulation and expression after peripheral nerve injury. J Neurosci 18(15): 5891-5900.

23. Antoniadis G (2017) The Peripheral Nerve: Neuroanatomical Principles Before and After Injury. In: Modern Concepts of Peripheral Nerve Repair, Springer, pp: 1-10.

24. Wong KM, Babetto E, Beirowski B (2017) Axon degeneration: make the Schwann cell great again. Neural Regen Res 12(4): 518-524.

25. Topilko P, Schneider-Maunoury S, Levi G, Evercooren ABV, Chennoufi AB, et al. (1994) Krox-20 controls myelination in the peripheral nervous system. Nature 371(6500): 796-799.

26. Simunovic N, Sprague S, Bhandari M (2009) Methodological issues in systematic reviews and meta-analyses of observational studies in orthopaedic research. J Bone Joint Surg Am 91(3): 87-94.

27. Zhang X, Li C, Fowler SC, Zhang Z, Blagg BSJ, et al. (2017) Targeting Heat Shock Protein 70 to Ameliorate c-Jun Expression and Improve Demyelinating Neuropathy. ACS Chem Neurosci 9(2): 381-390.

28. Parkinson DB, Bhaskaran A, Arthur-Farraj P, Noon LA, Woodhoo A, et al. (2008) c-Jun is a negative regulator of myelination. J Cell Biol 181(4): 625-637.

29. Funakoshi H, Frisén J, Barbany G, Timmusk T, Zachrisson O, et al. (1993) Differential expression of mRNAs for neurotrophins and their receptors after axotomy of the sciatic nerve. J Cell Biol 123(2): 455-465.

30. Birchmeier C, Nave K (2008) Neuregulin-1, a key axonal signal that drives Schwann cell growth and differentiation. Glia 56(14): 1491-1497.

31. Pellegrino RG, Spencer PS (1985) Schwann cell mitosis in response to regenerating peripheral axons in vivo. Brain Res 341(1): 16-25.

32. Vrbova G, Mehra N, Shanmuganathan H, Tyreman N, Schachner M, et al. (2009) Chemical communication between regenerating motor axons and Schwann cells in the growth pathway. Eur J Neurosci 30(3): 366-375.

33. Cheng Q, Wang Y, Yu J, Yi S (2017) Critical signaling pathways during Wallerian degeneration of peripheral nerve. Neural Regen Res 12(6): 995.

34. Reichert F, Saada A, Rotshenker S (1994) Peripheral nerve injury induces Schwann cells to express two macrophage phenotypes: phagocytosis and the galactose-specific lectin MAC-2. J Neurosci 14(5): 3231-3245.

35. Toews AD, Barrett C, Morell P (1998) Monocyte chemoattractant protein 1 is responsible for macrophage recruitment following injury to sciatic nerve. J Neurosci Res 53(2): 260-267.

36. Lindborg JA, Mack M, Zigmond RE (2017) Neutrophils Are critical for myelin removal in a peripheral nerve injury model of Wallerian degeneration. J Neurosci 37(43): 10258-10277.

37. Rotshenker S (2003) Microglia and macrophage activation and the regulation of complement-receptor-3 (CR3/MAC-1)-mediated myelin phagocytosis in injury and disease. J Mol Neurosci 21(1): 65-72.

38. Brück W (1997) The role of macrophages in Wallerian degeneration. Brain Pathol 7(2): 741-752.

39. del Pilar Camacho-Leal M, Sciortino M, Cabodi S (2017) ErbB2 Receptor in Breast Cancer: Implications in Cancer Cell Migration, Invasion and Resistance to Targeted Therapy. In: Breast Cancer-From Biology to Medicine. In Tech, pp: 164-179.

40. Mantovani A, Cassatella MA, Costantini C, Jaillon S (2011) Neutrophils in the activation and regulation of innate and adaptive immunity. Nat Rev Immunol 11(8): 519-531.

41. Soehnlein O, Lindbom L (2010) Phagocyte partnership during the onset and resolution of inflammation. Nat Rev Immunol 10(6): 427-439.