

Alpha-2-macroglobulin: The New Weapon for Neuropathic Pains

Jeimylo C. de Castro

Department of Physical Medicine and Rehabilitation, Makati, Philippines.

Corresponding Author: Jeimylo C. de Castro, Department of Physical Medicine and Rehabilitation, Makati, Philippines.

E-mail: jeidec@yahoo.com.ph

Received date: December 26, 2018; **Accepted date:** January 05, 2019; **Published date:** January 17, 2019.

Citation: Jeimylo C. de Castro, Alpha-2-macroglobulin: The New Weapon for Neuropathic Pains, J. International Journal of Mediators of Inflammation. Doi: <http://dx.doi.org/10.31579/ijmi.2019/002>.

Copyright: © 2019 Jeimylo C. de Castro. This is an open-access article distributed under the terms of The Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Introduction

One of the most challenging complaints to treat is neuropathic pains caused by a peripheral nerve injury. The inflammation may cause unnecessary axonal damage and neuropathic pains. Unlike the central nervous system, the peripheral nervous system though has the capability of regenerating. The distal part of the completely torn peripheral nerve undergoes Wallerian degeneration, while that of an incomplete peripheral nerve injury follows a more complicated pattern [1]. Degeneration does not happen immediately. It usually take a few days to complete the degeneration process [2]. There is a subsequent perineurial permeability which is twice the normal permeability of the peripheral nerve which takes about 4-7 days corresponding to the peak of inflammatory response [3, 4]. The increase in permeability will allow the blood borne factors and cells to enter the injured nerve through the blood-nerve barrier. In two weeks, the permeability decreases only to be followed by another sustained permeability that will take place 4 weeks after the nerve injury. These changes reflect the homeostasis that will take place after Wallerian degeneration [4, 5].

Immediately after a nerve injury, the Schwann cells begin to de-differentiate, a process dependent on the ubiquitin-proteasome system [6]. Within 48 hours, the Schwann cells stop producing myelin proteins, up-regulate regeneration associated genes and begin the proliferation process [7-9]. Peak proliferation of the Schwann cells is reached 4 days after injury. These proliferating Schwann cells align to the basal lamina tubes, forming the bands of Bungner, thus providing a support for the substrate for regeneration together with their growth factors [5, 10].

Cytokines are released as a result of nerve injury and inflammation. Axonal damage and neuropathic pains may ensue as a result of this inflammation [11]. In a study reported by Nadeau and colleagues, it showed that sciatic nerve injury produces a rapid production and release of IL-1beta and tumor necrosis factor (TNF) and causes infiltration of neutrophils and proinflammatory M1 monocytes/macrophages into the distal stump [12]. M1 macrophages produce inflammatory cytokines and oxidative metabolites whose role includes indiscriminate killers of microbes and tumor cells while M2 macrophages downregulate inflammation and facilitate wound healing [20, 21]. Interleukin-1 beta and TNF-alpha contribute to neuropathic pain via the activation of non-neuronal cells and infiltration of immune cells [12]. In this nerve injury, the levels of pro-inflammatory cytokines increase which includes TNF-alpha, IL-1beta, IL-6, interferon-gamma (IFN-gamma), and IL-18 [13-16]. These cytokines especially TNF-alpha cause a host of nerve damage characterized by demyelination, macrophage infiltration and pain [17, 18]. Thus, TNF-alpha is used as a biomarker of Wallerian degeneration in the injured peripheral nerve [19]. Further, they have found out that blocking neutrophil entry are more beneficial than just neutralizing pro-inflammatory cytokines such as IL-1 and TNF in the treatment of neuropathic pains [12].

Peripheral nerve injury and the cytokines released is very important in the generation of neuropathic pains, thus the role of these substances provide the key in the understanding of possible intervention for patients suffering in these conditions.

Alpha-2-Macroglobulin (A2M) is a high molecular weight homotetrameric glycoprotein with highly diversified and complex functions but has the ability to inhibit matrix metalloprotease (MMP) and/or any proteinase, regardless of its specificity and catalytic mechanism without the direct blockage of the protease active sites [22]. It is a 718- kDa protein present in plasma and extracellular spaces at a high concentration of 2-4 mg/ml [23] and is synthesized by the liver cells, astroglia and blood cells [33]. It is unique in its functions as it does not inactivate the proteinases, but instead hinders the access of substrates to the active sites of the proteinase [22]. The primary function of A2M is to entrap the proteinases by delivering it to an endocytic proteinase clearance pathway. Only its fast form (F-A2M) however, is recognized and endocytosed by the cells of the clearance pathway and the complexes formed are cleared rapidly in the plasma ([22]. When bound to A2M, the biological activity of some cytokines such as IL-1 beta and basic fibroblast growth factor (bFGF) are inhibited but the other cytokines such as platelet derived growth factor (PDGF), nerve growth factor (NGF) and IL-6 are partially active [22]. Alpha-2-macroglobulin may be the only major regulator of NGF in plasma [24]. Tumor necrosis factor which is mainly produced by monocytes and macrophages bind strongly fast to A2M (F- A2M) forming a TNF-alpha/A2M-proteinase complex which is removed from circulation by the A2M-receptor pathway [25]. The cytokine IL-1 beta binds to F-A2M and retains its activity with the help of zinc ions [26]. Interleukin-6 on the other hand binds to A2M but its activity is not lost and is protected from the proteases while free IL-6 is easily degraded [22].

Since A2M is a protease inhibitor acting against trypsin and chymotrypsin, it thus constitutes as an important mechanism for the regulation and containment of inflammation [22- 27]. In addition, A2M is the first endogenous inhibitor of ADAMTS-7 (a disintegrin and metalloprotease with thrombospondin motifs) and ADAMTS-12 which degrades cartilage oligomeric matric protein among osteoarthritis patients [28-30]. Thus, A2M may function in controlling inflammation and altering the course in nerve injury, stabilize immune functions and the regulation of cell physiology [31]. Arandjelovic and colleagues, have found that A2M and its derivatives emerge as an essential mediator in regulating the progression of nerve injury and therefore is capable of positively influencing its results [32].

Pro-inflammatory cytokines such as IL-1, IL-6 and TNF [34] increased during inflammation not only in the peripheral nerves but also in inflammatory joint problems, cardiovascular events and atherosclerosis event, it is interesting to note how this could be utilized to address inflammation and neuropathic pains and other inflammatory conditions. Montesano and colleagues cited an observation that the A2M of normal and healthy person is about 10-30 ug/ml range while those with painful joints showed a range of about 80-300 ug/ml validating the hypothesis that A2M is a natural defense mechanism against proteolytic activities [35].

In a degenerative disc disease where the cartilage degradation product, the Fibronectin-Aggregan complex (FAC) is identified, intradiscal autologous A2M injection showed clinical improvements, although further studies is needed to see consistent results.

Alpha-2-macroglobulin's ability to generally inhibit proteases both in chronic and neuropathic pains and inflammatory joint problems showed promise from a biological perspective. With the presence of pro-inflammatory cytokines in peripheral nerve injuries, which are causing neuropathic pains, A2M being a matrix metalloproteases inhibitor (MMPI) can be a solution that will provide relief of symptoms and thus form part of the regenerative injection therapies.

References

1. Stoll G, Jander S, Myers RR.(2002) Degeneration and regeneration of the peripheral nervous system: from Augustus Waller's observations to neuroinflammation. *J Peripheral Nerv Syst.*; 7: 13-27.
2. Chaudry V, Comblath DR. Wallerian (1992) degeneration in human nerves: serial electrophysiological studies. *Muscle Nerve*; 15(6): 687-683.
3. Weerasuriya A. Hockman CH.(1992) Perineurial permeability to sodium during Wallerian degeneration in rat sciatic nerve. *Brain Res.*; 581(2): 327-33.
4. Mizisin AP, Weerasuriya A (2011). Homeostatic regulation of the endoneurial microenvironment during development, aging and in response to trauma, disease and toxic insult. *Acta Neuropathol.* 2011; 121(3): 291-312.
5. Gaudet AD, Popovich PG, Ramen MS.(2011) Wallerian degeneration: gaining perspective on inflammatory events after peripheral nerve injury. *J Neuroinflammation*; 8: 110.
6. Lee HK, Shin YK, Jung J, Seo SY, Baek SY, et al (2009). Proteasome inhibition suppresses Schwann cell dedifferentiation in vitro and in vivo. *Glia.*; 57(16): 1825-1834.
7. Trapp BD, Hauer P, Lemke G. (1988) Axonal regulation of myelin protein mRNA levels in actively myelinating Schwann cells. *J Neurosci.* 8(9): 3515-3521.
8. Pellegrino RG, Politis MJ, Ritchie JM, Spencer PS(1986) Events in degenerating cat peripheral nerve: induction of Schwann cell S phase and its relation to nerve fiber degeneration. *J Neurocytol*; 15(1): 17-28.
9. Murinson BB, Archer DR, Li Y, Griffin JW (2005). Degeneration of myelinated efferent fibers prompts mitosis in Remak Schwann cells of uninjured C-fiber afferents; 25(5): 1179-1187.
10. Stoll G, Griffin JW, Li CY, Trapp BD.(1989) Wallerian degeneration in the peripheral nervous system: participation of both Schwann cells and macrophage in myelin degradation. *J Neurocytol* ; 18(5): 671-683.
11. Myers RR, Sekiguchi Y, Kikuchi S, Scott B, Medicherla S, et al (2003). Inhibition of p38 MAP kinase activity enhances axonal regeneration. *Exp Neurol*; 184: 606-614.
12. Nadeau S, Fillali M, Zhang J, Kerr BJ, Rivest S, et al (2011), Vaccari JPR, Keane RW, Lacroix S. Functional recovery after peripheral nerve injury is dependent on the pro-inflammatory cytokines IL-1beta and TNF: Implications for neuropathic pain. *J Neurosci.*; 31 (35):12533-12542.
13. Taskinen HS, Olsson T, Bucht A, Khademi M, Svelander L, et al (2000). Peripheral nerve injury induces endoneurial expression of IFN-gamma, IL-10, TNF-alpha mRNA. *J Neuroimmunol*; 102: 17-25.
14. Shamash S, Reichert F, Rotshenker S.(2002) The cytokine network of Wallerian degeneration: tumor necrosis factor-alpha, interleukin-1alpha, and interleukin-1beta. *J Neurosci*; 22: 3052-3060.
15. Menge T, Jander S, Stoll G.(2001) Induction of the proinflammatory cytokine interleukin-18 by axonal injury. *J Neurosci.*; 65: 332-339.
16. Reichert F, Levitzky R, Rotshenker S(1996) Interleukin 6 in intact and injured mouse peripheral nerves. *Eur J Neurosci.*; 8: 530-535.
17. Wagner R, Myers RR.(1996) Endoneurial injection of TNF-alpha produces neuropathic pain behaviors. *Neuroreport* 7; 7: 2897-2901.
18. Sorkin LS, Xiao WH, Wagner R, Myers RR.(1997) Tumor necrosis factor-alpha induces ectopic activity in nociceptive primary afferent fibers. *Neuroscience*; 81: 255-262.
19. Myers RR, Campana WM, Shubayev VI.(2006) The role of neuroinflammation in neuropathic pain: mechanisms and therapeutic targets. *Drug Discov Today*; 11:8-20.
20. Gordon S.(2003) Alternative activation of macrophages. *Nat Rev Immunol.*; 3: 23-25.
21. Mantovani A, Sica A, Sozzani S, Allavena P, Vecchi A, et al (2004). The chemokine system in diverse forms of macrophage activation and polarization. *Trends Immunol.*; 25: 677-686.
22. Rehman AA, Khan FH, Ahsan H. Alpha-2-macroglobulin:(2013) A physiological guardian. *J Cellular Physiol*; 228: 1665-1675.
23. Sottrup-Jensen L.(1987) In the plasma proteins. Academic Press; 5: 192-291.
24. Wolf BB, Jayanand V, Gonias SL.(1993) Reaction of nerve growth factor gamma and 75 nerve growth factor complex with human and murine alpha-2-macroglobulin. *Biochemistry.*; 32: 1875-1882.
25. Jeng D, Rahman MM, McFadden G, Essani K.(2011) Tumor necrosis factor inhibitors from poxviruses with an emphasis on tanapoxvirus-2L protein. *Recent Pat DNA Gene Seq* 5; 97-103.
26. Athipozhy A, Huang L, Wooton-Kee CR, Zhao T, Jungsuwadee P, et al (2011) M. Differential gene expression in liver and small intestine from lactating rat compare to age-matched virgin controls detects increased mRNA of cholesterol biosynthetic genes. *BMC Genomics.*; 12: 95-111.
27. Gunnarsson M, Jensen PEH. (1998) Binding of soluble myelin basic protein to various conformational forms of alpha-2-macroglobulin. *Arch Biochem Biophys*; 359: 192-198.
28. Liu CJ, Kong W, Ilalov K, Yu S, Xu K, et al (2006), Di Cesare PE. ADAMTS-7: A metalloproteinase that directly binds to and degrades cartilage oligomeric matrix protein. *FASEB J.* ; 20: 988-990.
29. Liu CJ, Kong W, Xu K, Luan Y, Ilalov K, et al, (2006) Di Cesare PE. ADAMTS-12 associates with and degrades cartilage oligomeric matrix protein. *J Biol Chem.* b; 281: 15800-15808.
30. Luan, Y Kong L, Howell DR, Ilalov K, Fajardo M, et al, (2008) Di Cesare PE, Goldring MB, Abramson SB, Lin CJ. Inhibition of ADAMTS-7 and ADAMTS-12 degradation of cartilage oligomeric matrix protein by alpha-2-macroglobulin. *Osteoarthritis Cartilage.*; 16: 1413-1420.
31. Armstrong PB, Quigley JP(1999) Alpha-2-macroglobulin: an evolutionary conserved arm of the innate immune system. *Dev. Comp. Immunol*; 23: 375-390.
32. Arandjelovic S, Dragojlovic N, Li X, Myers RR, Campana WM, Gonias SL.(2007) A derivative of the plasma protease inhibitor alpha-2-macroglobulin regulates the response to peripheral nerve injury. *J Neurochem.* ; 103(2): 694-705.
33. Lysiak JJ, Hussaini IM, Gonias SL.(1997) Alpha-2-macroglobulin synthesis by the human monocytic cell line THP-1 is differentiation state-dependent. *J Cell. Biochem.* ; 67: 492-497.
34. Shimomura R, Nezu T, Hosomi N, Aoki S, Sugimoto T, et al (2018) T, Alpha-2-macroglobulin as a promising biological marker of endothelial function. *J Atheroscler Thromb.* 2018; 25: 350-358.
35. Montesano PX, Cuellar JM,(2017) Scuderi GJ. Intradiscal injection of an autologous alpha-2-macroglobulin concentrate alleviates back pain in FAC-positive patients. *Ortho & Rheuma.* ; 4(2): 555634.

