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Research Article

Spinal Cord Injury Intensity Modifies the Expression of Inflammation-Related Gene Expression after Immunization with Neural Derived Peptides

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Abstract

Previous studies revealed that the intensity of Spinal Cord Injury (SCI) plays a key role in the therapeutic effects induced by Immunizing With Neural-Derived Peptides (INDP), as severe injuries abolish the beneficial effects induced by INDP. In the present study, we analyzed the expression of some inflammation-related genes (IL6, IL12, IL-1β, IFNɣ, TNFα, IL-10, IL-4, and IGF-1) by quantitative PCR in rats subjected to SCI and INDP. We investigated the expression of these genes after a moderate or severe contusion. In addition, we evaluated the effect of INDP by utilizing2 different peptides: A91 and Cop-1. After moderate injury, both A91 andCop-1 eliciteda pattern of genes characterized by a significant reduction of IL6, IL1β,andTNFα but an increase in IL10, IL4, and IGF-1expression. There was no effect on IL-12 and INFɣ. In contrast, the opposite pattern was observed when rats were subjected to a severe spinal cord contusion. Immunization with either peptide caused a significant increase in the expression of IL-12, IL-1β, IFNɣ, (pro-inflammatory genes), and IGF-1. There was no effect on IL-4 and IL-10 compared to controls. After a moderate SCI, IND Preduced pro-inflammatory gene expression, and generated a microenvironment prone to neuroprotection. Nevertheless, severe injury elicits the expression of pro-inflammatory genes that could be aggravated by INDP. These findings correlate with our previous results demonstrating that severe injury inhibits the beneficial effects of protective autoimmunity.

Keywords: Gene Expression; Neural Derived Peptides; Spinal Cord Injury

Introduction

Several auto-destructive mechanisms arise after Spinal Cord Injury (SCI) including massive entry of calcium into the cellular compartment, neural fiber damage, metabolic disturbances, destruction of microvessels, and breakdown of the blood-spinal cord barrier. One of the most important subsequent events is the recruitment of immunological cells (neutrophils, hematogenous macrophages, and T lymphocytes) to the site of injury; accompanied by the activation of resident microglia that triggers an inflammatory reaction at the damaged area increasing the inflammatory response [1]. This inflammatory reaction is carried out by different cells and pro-inflammatory cytokines, which exacerbate lipid peroxidation, free radical production, and demyelination; leading to extensive secondary tissue damage [2,3]. The exacerbated inflammatory response can trigger a pathological auto reactivity reaction that is mostly mediated by the activation of T lymphocytes. In these pathological circumstances, activation of T cells shifts towards a Th1phenotype (pro-inflammatory), there by promoting a higher demyelination and increasing injury size. Nevertheless, if the response is activated towards a Th2 phenotype (anti-inflammatory), it could regulate the secondary damage by creating a neuroprotective microenvironment [3 – 5]. The immune system plays a pivotal role in the pathophysiology secondary to SCI [6]. It has been demonstrated that modulation rather than inhibition of the immune response is beneficial and promotes neurological recovery after injury [7,8]. Protective autoimmunity (PA) is an innovative strategy based on the modulation of the immune response after trauma to the central nervous system (CNS) [9-11]. PA is boosted by immunizing with non-encephalogenic neural derived peptides (INDP) such as A91 or Cop-1 [4,12]. A91 is a myelin basic protein (MBP) -derived peptide (sequence of amino acids 87-99), originated by replacing lysine with alanine at residue 91 [12-14].Another peptide capable of modulating PA is Cop-1,a random polypeptide synthesized from four amino acids (L-tyrosine, L-glutamic acid, L-alanine, and L-lysine) with an average molar fraction of 0.141, 0.427, 0.095 and 0.0338, respectively [15,16].

At the moment, the way through which PA exerts its beneficial actions is not entirely understood, as there is a broad spectrum of mechanisms that have not yet been explored. Gene expression is one of the main phenomena that could provide some interesting information about how PA exerts its protective effects. Inflammation-related genes like Interleukin (IL)-6, IL12, IL1β, Interferonγ (IFNγ), Tumor Necrosis Factor Alpha (TNFα), IL-10, IL-4, and Insulin-like Growth Factor-1 (IGF-1), could influence cell function over minutes to hours - or a much longer period of time - in a pro or anti-inflammatory manner [6].

On the other hand, previous studies have demonstrated that severe injury avoids the neuroprotective effect elicited by INDP [17]. In these instances, we hypothesize that the lack of a neuroprotective effect is related to the upregulation of pro-inflammatory and downregulation of anti-inflammatory genes. For that reason, we

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Table 1: PCR primers.

PCR primers			
Gene	**Reference sequence number**	**Sequence**	**Product length**
18 s Ribosomal	NM_0010076	Forward5'-ACATTGGAAGCCTCATCTGC-3' Reward 3' - CCATGTCATCCTCGGATTCT - 5'	157pb
Interleukin6 IL 6	NM_012589	Forward 5'-TGTGGAAGACAAAC ATGTTGCCG- 3' Reward3'-TATTGCAGGTGAGCTGGACGTTCT-5'	117pb
Interleukin12 IL12	NM_053390	Forward 5'-TGCCAGTGTCTTAAACCAGTCCCA- 3' Reward3' TGATCGATGTCTCCAGCAGTGCAA-5'	111pb
Interleukin- 1β IL1β	NM_031512.2	Forward5'- CAGTCTTTTGCCCTCCTGTC -3' Reward 3'- GACACTGTTGGTGTAGGGAC-5'	120 pb
Interferon gamma IFNγ	NM_138880	Forward5'-CAACCAGGCCATCAGCAACAACAT - 3' Reward3'-TCTGTGGGTTGTTCACCTCGAACT- 5'	128 pb
Tumor necrosis factor alpha TNF α	NM_012675	Forward5'-CTCTTCTGTCTACTGAACTTCGGG-3' Reward3'-GAGAAGATGATCTGAGTGTGAGGG-5'	115 pb
Interleukin 4 IL4	NM_201270	Forward 5'- GGCTTCCAGGGTGCTTCGCAA- 3' Reward 3'- GTGGACTCATTCACGGTGCAGC -5'	150 pb
Interleukin10 IL10	X60675	Forward5'- GGGGTGACAATAACTGCA -3' Reward3'- GGGGCATCACTTCTACCA-5'	216 pb
Insulin growth factor -1 IGF-1	NM_001082477	Forward5'- GCTGAAGCCGTTCATTTAGC -3' Reward3'-AACAACTTAAACCGGAGGAG-5'	171 pb

explored the expression of eight inflammation-related genes in two models of SCI (moderate and severe contusion) in rats immunized either with A91 or Cop-1 peptides.

Materials and Methods

Study design

The sample size for this experiment was calculated using an alpha of 0.05 and beta of 0.20. Two experiments were performed with twenty animals used in each experiment. In the first, fifteen rats were subjected to a moderate SC contusion and then were randomly allocated into 3 groups (GraphPad QuickCalcs: http://www.graphpad.com/quickcalcs/): 1) Rats immunized with PBS (n=5); 2) Rats immunized with A91-peptide (n=5); 3) Rats immunized with Cop-1 (n=5). In the second experiment, fifteen rats were subjected to a severe SCI and then allocated into 3 groups as described in experiment 1. Sham-operated rats (n= 5) were used to normalize the values of all groups in both experiments. Seven days after injury, animals of all groups were euthanized, and the spinal cord was analyzed for expression of inflammation related-genes.

Animals

Adult Fischer 344 (F344; 13-14 weeks old, 200-230 g) female rats (n=40) were used. Animals were supplied by Proyecto Camina A.C. and were handled according to the NIH guidelines for management of laboratory animals. All the procedures were carried out in accordance with the National Institutes of Health Guide for the care and use of laboratory animals, and the Mexican Official Norm on Principles of Laboratory Animal Care (NOM 062-ZOO-1999).Also, all animal procedures were approved by the Animal Bioethics and Welfare Committee (ID:57204; CSNBTBIBAJ 090812960).

Spinal cord injury

Rats were anesthetized with an intramuscular injection of ketamine (100 mg/kg; Probiomed, Mexico City) and xylazine (10 mg/kg, Fort Dodge Laboratories, Fort Dodge, IA), and their spinal cords were exposed by laminectomy at the T9 level. A 10 g rod was dropped onto the exposed spinal cord from a height of25 mm for moderate injury and50 mm for severe injury using the New York University impactor (Basso et al., 1996; Basso, Beattie, & Bresnahan, 1995). Subsequently, muscles and skin were closed in layers, and animals were placed in a temperature-controlled room. During the first 7 days post-surgery temperature was maintained at 23°C.Manual voiding of the bladder was performed twice per day. Antibiotic (Enrofloxacin 64mg/kg/day; Marvel Mexico City) and analgesic therapy were given daily throughout the study to avoid complications.

Active immunization

Sixty minutes after SCI rats were immunized subcutaneously at the base of the tail with 150 µg of A91 or Cop-1 dissolved in 0.15M phosphate-buffered saline (PBS) (experimental groups),or only with PBS (control groups: SC injury + immunization with PBS and sham-operated animals). Both peptides and PBS alone were emulsifiedin an equal volume of complete Freund's adjuvant (CFA) containing 0.5 mg/ml of Mycobacterium tuberculosis.A91 peptide was purchased from Invitrogen Life Technologies (San Diego, CA), and its purity (higher than 95%) was confirmed by reverse-phase HPLC. Cop-1 was purchased from Sigma (St. Louis, MO).

Quantitative polymerase chain reaction

A 3cm long segment of the spinal cord was obtained 7 days after injury. The total RNA was then isolated using the phenol-chloroform extraction method with Trizol (Life Technologies, Carlsbad, CA). RNA concentration and purity was evaluated by UV spectrophotometry, integrity by electrophoresis, and complementary DNA (cDNA) was obtained by reverse transcription. The cDNA synthesis was performed with oligo (dT)at 55°C for 50 min in a final volume of 20µl from 2µg of total RNA, following the manufacturer's instructions for Superscript reverse transcriptase-RNase H (Invitrogen, Carlsbad, CA). The template cDNA was normalized to the ribosomal RNA. Real-time RT-PCR was performed using a Light Cycler 2.0 instrument (Roche, México D.F., MX). Three independent experiments for every set of RT- PCR analyses were performed. We assayed the expression of cDNA by quantitative PCR using the selected gene-specific primers pairs listed in Table 1. For the initial denaturation step, samples were heated up to 95°C for 10 min, followed by the first cycle consisting of a denaturation step (95°C, 10 sec), a primer annealing step (60°C, 10 sec), an extension step (72°C, 10 sec), a melting curve (65°C, 1 min), and a cooling step (40°C, 30 sec). The reaction was carried out in 40 cycles. Expression levels of individual genes were represented in arbitrary units after

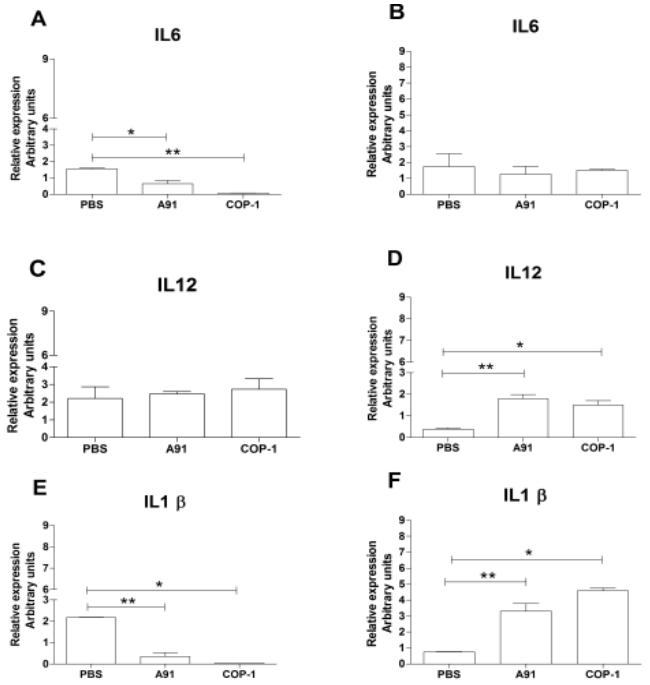

Figure 1: IL6, IL12, and IL1β gene expression after moderate (A,C,E) or severe (B,D,F) SCI, seven days after immunization with A91 or Cop-1 (INDP). INDP downregulates the expression of IL6 andIL1β genes after moderate SCI.INDP upregulates the expression of IL12 and IL1β genes after sever injury. Bars represent mean +/- SD of five animals. *p<0.05, ** p < 0.01, Kruskal-Wallis followed Mann-Whitney U test. Each experiment is one of three in which we observed the same effect.

normalization with ribosomal RNA. All experiments were performed per triplicate. Each reaction was subjected to melting curve and melting temperatures to confirm single amplified products using the Light-Cycler software (build 4.1.1.21). The crosspoint value was used to obtain the delta 1 and delta 2 analyses, which reported the relative expression for each group.

Statistical analysis

Data is displayed as the mean ± Standard Deviation (SD), and statistical significance was established when $p < 0.05$. Graph Pad Prism 5.0 (GraphPad Software, Inc. La Jolla, CA, USA) was employed in statistical the analysis. All data were analyzed using Kruskal-Wallis test or Mann-Whitney U test.

Results

First, we analyzed pro-inflammatory gene expression subsequent to immunization with A91 or Cop-1 (INDP).INDP was performed in rats with moderate or severe SCI. Immunization either with A91 or Cop-1 caused a significant reduction of IL-6, IL-1β (Figure 1A and 1E) and TNFα ($p < 0.05$, Kruskal-Wall is followed by Mann Whitney Utest; Figure 2C) in rats with moderate SCI. In contrast, immunization with any of these peptides induced a significant increaseofIL-12, IL-1β (Figure 1D and 1F) and IFNγ, (See Figure 2B; $p < 0.05$; Kruskal-Wallis followed by Mann Whitney U test) after severe SCI.

In the case of anti-inflammatory genes, INDP provoked a significant increase of IL10 and IL4 after a moderate SCI (Figure 3A and C). Meanwhile, there was no significant effect on these cytokines

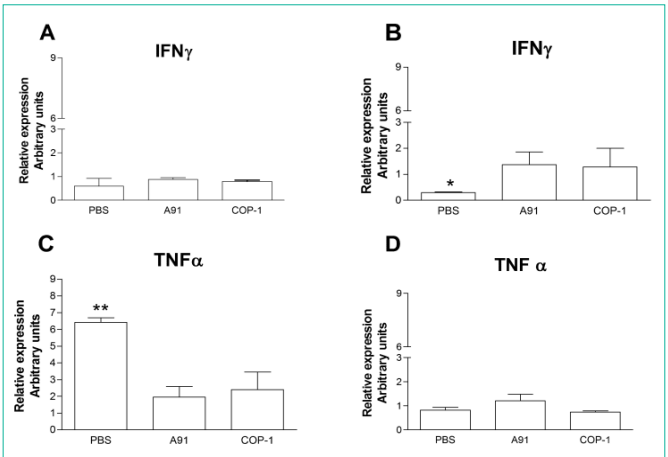

Figure 2: Expression of INFγ and TNFα genes after moderate (A,C,E) or severe (B,D,F) SCI, seven days after immunization with A91 or Cop-1 (INDP). INDP induced a downregulation of TNFα in moderate SCI. INDP caused upregulation of INFγ in rats with severe SCI. Bars represent mean +/- SD of five animals. *p<0.05, ** p < 0.01, Kruskal-Wallis followed Mann-Whitney U test. Each experiment is one of three in which we observed the same effect.

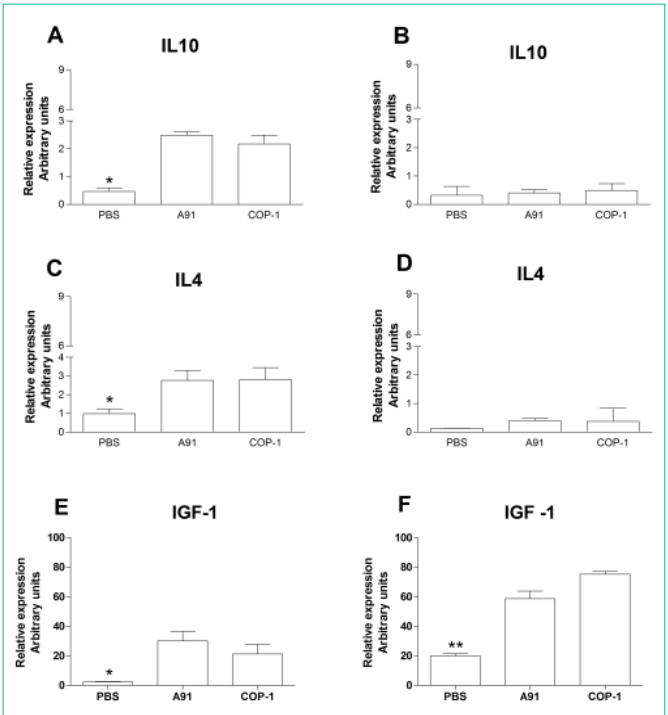

Figure 3: Expression of IL10, IL4, and IGF-1 genes after moderate (A, C, E) or severe (B, D, F) injury, seven days after A91 or Cop-1 immunization (INDP).After moderate SCI, INDP induced a significant upregulation of IL10, IL4, and IGF-1 genes. IGF-1 expression was increased after INDP in severely injured rats. Bars represent mean +/- SD of four animals. *p<0.05; ** p <0.01 Kruskal-Wallis followed Mann-Whitney U test. Each experiment is one of three in which the same effect was observed.

when animals were subjected to a severe SCI (Figure 3B and 3D). Finally, IGF-1 was significantly increased in both moderately and severely injured rats ($p < 0.05$, Kruskal-Wallis followed by Mann Whitney U test; Figure 3E and 3F).

Discussion

Changes in gene expression have been documented in diverse in

vivo models as an early response to SCI [18-20]. The up regulation of diverse transcription factors and molecules involved in signaling pathways suggests that changes in the expression of many genes can develop as a result of the traumatic insult. Several in vivo studies have been carried out to analyze the post-traumatic gene expression in an attempt to establish the biological and functional after math of SCI [21,22]. Here, we analyzed changes in the expression of eight different genes: IL6, IL12, IL1β, IFNγ, TNFα, IL10, IL4, and IGF-1, in moderate and severe SCI. It was evident that moderate injury allows INDP to create a microenvironment where cytokines like IL4 and IL10 prevail; which could play an important role in protecting and restoring neural tissue [23,24].

The cytokine profile induced by INDP in the present SCI model is capable of collaborating with the modulation of the inflammatory response, due to its necessary role in activation, differentiation, and proliferation of Th2 lymphocytes [25]. Likewise, this cytokine microenvironment promotes an M2 macrophage differentiation, increases the macrophage expression of the Major Histocompatibility Complex class II (MHC-II), and decreases IL1, IL6, and TNFα production [26 – 30].

The latter was corroborated in the present work since INDP-treated rats with moderate SCI presented a significant reduction of inflammatory cytokines. The relevance of this effect is evidenced with the regulation of TNFα, a pro-inflammatory cytokine that stimulates a variety of factors that aggravate inflammation, such as IL8, IL6, IL1, nitric oxide, peroxide, and prostaglandin [31,32]. Previous studies in our laboratory have demonstrated that INDP is capable of reducing inflammation and lipid peroxidation [33]. In contrast, after a severe contusion, INDP was not capable of inducing the same effect [34]. In this case, INDP did not induce any sign of motor improvement. In the present work, we intended to delve into the cause of this lack of effect and found a prevailing inflammatory environment that could be inhibiting the beneficial effects induced by INDP. After severe SCI, immunization with any peptide (A91 or Cop-1) significantly increased the expression of inflammation-related genes and reduced the amount of those related to the anti-inflammatory response.

Of note, an interesting pattern of gene expression was observed in this SCI model, where INDP produced a higher expression of IL12, IL1β, and IFNγ. The reason why INDP induced the expression of this gene pattern is not clear yet. Nevertheless, it is well known that inflammatory gene expression could be increased by the action of the NFkB signaling pathway, which is activated by high concentrations of tissue protein-like DAMPs (Damage-Associated Molecular Patterns) [35,36]. With this in regard, when compared to moderate SCI, severe injury causes a more pronounced release of DAMPs and neural constituents, in such a way that the high concentration of these molecules along with INDP could be shifting the immune response towards a Th1 encephalitogenic phenotype [37]. This predominant phenotype (Th1) –which could be directed against other immunogenic determinants- could also inhibit the proliferation of Th2 protective lymphocytes, and thereby its beneficial actions [34]. Previous investigations in our laboratory have proven that severe injuries or the excessive administration of INDP inhibit the beneficial action of protective autoimmunity [17,34]. On the other hand, we found a significant increase of IGF-1 in A91 and Cop-1-immunized groups in severe SCI. This finding may be due to the arrival of peripheral and resident macrophages, as these cells produce pro-fibrotic mediators, including insulin growth factor 1 (IGF-1), transforming growth factor (TGF)-β, and Platelet-Derived Growth Factor (PDGF). IGF-1 is also produced by astrocytes and endothelial cells, it down regulates several pro-inflammatory cytokines, such as TNFα, IL1 β, and IL6 [38]. The increase of IGF-1concentrationsin treated animals - especially in those with severe injury -could be the response to the high concentrations of pro-inflammatory cytokines (TNFα, IL1 β, and IL6), that result from a failed effort to modulate the hostile microenvironment. Finally, IL10 -a cytokine involved in the anti-inflammatory response, by altering immune cell activities- is able to reduceIL1α, IL1β, IL8, IL12, IFNα, iNOS, and TNFα production [39-41]. Evidence suggests that application of IL10 after SCI could decrease the inflammatory response and augment neural survival [42,43]. Here, animals with INDP subjected to severe SCI did not present any significant production of this cytokine; however, INDP-immunized rats with moderate injury showed a significant production of IL-10.These results support our hypothesis, as the effect of INDP was avoided and an inflammatory microenvironment prevailed in severe SCI; while after a moderate SCI, INDP was capable of promoting its beneficial effect mediated by a microenvironment propitious for neuroprotection and neuroregeneration.

The present study provides evidence supporting the fact that neuroprotection induced by INDP could be the result of an upregulation of IL10 and IL4 accompanied by a down regulation of TNFα, IL1β, and IL-6 genes. This information correlates with previous studies from our laboratory that elucidated some of the protective mechanisms induced by INDP; for instance, the reduced expression of the Inducible Nitric Oxide Synthase (INOS) and decreasing nitric oxide production. INOS expression is down regulated by IL10 and IL4 [7].Further studies on the effect of INDP are warranted in order to completely understand how this strategy provides its neuroprotective effects after SCI.

References

1. Bethea JR, & Dietrich WD. Targeting the host inflammatory response in traumatic spinal cord injury. Current Opinion in Neurology. 2002; 15: 355–360.

2. Hausmann ON. Post-traumatic inflammation following spinal cord injury. Spinal Cord. 2003; 41: 369–378.

3. Ibarra A, García E, Flores N, Martiñón S, Reyes R, Campos MG, et al. Immunization with neural-derived antigens inhibits lipid peroxidation after spinal cord injury. Neuroscience Letters. 2010; 476: 62–65.

4. Schwartz M. Harnessing the immune system for neuroprotection: Therapeutic vaccines for acute and chronic neurodegenerative disorders. Cellular and Molecular Neurobiology. 2001; 21: 617–627.

5. Schwartz M & Kipnis, J. Protective autoimmunity: Regulation and prospects for vaccination after brain and spinal cord injuries. Trends in Molecular Medicine. 2001; 7: 252–258.

6. Donnelly DJ & Popovich PG. Inflammation and its role in neuroprotection, axonal regeneration and functional recovery after spinal cord injury. Experimental Neurology. 2008; 209: 378–388.

7. Garcia E, Silva-Garcia R, Mestre H, Flores N, Martinon S, Calderon-Aranda ES, & Ibarra A. Immunization with A91 peptide or copolymer-1 reduces the production of nitric oxide and inducible nitric oxide synthase gene expression after spinal cord injury. J Neurosci Res. 2012; 90, 656–663.

8. Rodríguez-Barrera R, Fernández-Presas AM, García E, Flores-Romero A, Martiñón S, González-Puertos VY et al. Immunization with a neural-derived peptide protects the spinal cord from apoptosis after traumatic injury. BioMed

Research International. 2013.

9. Berger T, Weerth S, Kojima K, Linington C, Wekerle H, & Lassmann H. Experimental autoimmune encephalomyelitis: the antigen specificity of T lymphocytes determines the topography of lesions in the central and peripheral nervous system. Laboratory Investigation; a Journal of Technical Methods and Pathology. 1997; 76: 355–364.

10. Hauben E, Nevo U, Yoles E, Moalem G, Agranov E, Mor F, et al. Autoimmune T cells as potential neuroprotective therapy for spinal cord injury. Lancet. 2000.

11. Linington C, Berger T, Perry L, Weerth S, Hinze-Selch D, Zhang Y, et al. T cells specific for the myelin oligodendrocyte glycoprotein mediate an unusual autoimmune inflammatory response in the central nervous system. European Journal of Immunology. 1993; 23: 1364–1372.

12. Gaur A, Boehme SA, Chalmers D, Crowe PD, Pahuja A, Ling N, et al. Amelioration of relapsing experimental autoimmune encephalomyelitis with altered myelin basic protein peptides involves different cellular mechanisms. Journal of Neuroimmunology. 1997; 74: 149–158.

13. Katsara M, Yuriev E, Ramsland PA, Tselios T, Deraos G, Lourbopoulos A , et al. Altered peptide ligands of myelin basic protein (MBP87–99) conjugated to reduced mannan modulate immune responses in mice. Immunology. 2009; 128: 521–533.

14. Samson MF & Smilek DE. Reversal of acute experimental autoimmune encephalomyelitis and prevention of relapses by treatment with a myelin basic protein peptide analogue modified to form long-lived peptide-MHC complexes. J Immunol. 1995; 155: 2737–2746.

15. Guan L, Eisenstein TK, Adler MW, & Rogers TJ. Inhibition of T cell superantigen responses following treatment with the kappa-opioid agonist U50,488H. Journal of Neuroimmunology. 1997; 75: 163–8.

16. Liu J, Johnson TV, Lin J, Ramirez SH, Bronich TK, Caplan S, et al. T cell independent mechanism for copolymer-1-induced neuroprotection. European Journal of Immunology. 2007; 37: 3143–3154.

17. Martiñon S, García E, Flores N, Gonzalez I, Ortega T, Buenrostro M, et al. Vaccination with a neural-derived peptide plus administration of glutathione improves the performance of paraplegic rats. European Journal of Neuroscience. 2007; 26; 403-412.

18. Carmel JB, Galante a, Soteropoulos P, Tolias P, Recce M, Young W.et al. Gene expression profiling of acute spinal cord injury reveals spreading inflammatory signals and neuron loss. Physiological Genomics. 2001; 7: 201–213.

19. Song G, Cechvala C, Resnick DK, Dempsey RJ, & Rao VL. GeneChip analysis after acute spinal cord injury in rat. Journal of Neurochemistry. 2001; 79: 804–815.

20. Tachibana T, Noguchi K, & Ruda MA. Analysis of gene expression following spinal cord injury in rat using complementary DNA microarray. Neuroscience Letters. 2002; 327: 133–137.

21. Aimone JB, Leasure JL, Perreau VM, & Thallmair M. Spatial and temporal gene expression profiling of the contused rat spinal cord. Experimental Neurology. 2004; 189: 204–221.

22. Giovanni S. Di, Knoblach SM, Brandoli C, Aden SA, Hoffman EP, & Faden AI. Gene Profiling in Spinal Cord Injury Shows Role of Cell Cycle Neuronal Death. Ann Neurol. 2003; 53: 454–468.

23. Walsh JT, Hendrix S, Boato F, Smirnov I, Zheng J, Lukens JR, et al. MHCII-independent CD4+ T cells protect injured CNS neurons via IL-4. The Journal of Clinical Investigation. 2015; 125: 699–714.

24. Zhou Z, Peng X, Insolera R, Fink DJ, & Mata M. IL-10 promotes neuronal survival following spinal cord injury. Experimental Neurology. 2009; 220: 183–190.

25. Hausmann ON. Post-traumatic inflammation following spinal cord injury. Spinal Cord. 2003; 41: 369–378.

26. Becker S, & Daniel EG. Antagonistic and additive effects of IL-4 and Interferon-gamma on human monocytes and macrophages: Effects on Fc receptors, HLA-D antigens, and superoxide production. Cellular Immunology. 1990; 129: 351–362.

27. Cao H, Wolff RG, Meltzer M S & Crawford RM. Differential regulation of class II MHC determinants on macrophages by IFN-gamma and IL-4. Journal of Immunology, 1989; 143: 3524–3531.

28. Crawford RM, Finbloom DS, Ohara J, Paul WE & Meltzer MS. B cell stimulatory factor-1 (interleukin 4) activates macrophages for increased tumoricidal activity and expression of Ia antigens. Journal of Immunology. 1987; 139: 135–141.

29. Gerrard TL, Dyer DR & Mostowski HS. IL-4 and granulocyte-macrophage colony-stimulating factor selectively increase HLA-DR and HLA-DP antigens but not HLA-DQ antigens on human monocytes. Journal of Immunology, 1990; 144: 4670–4674.

30. Hart PH, Vitti GF, Burgess DR, Whitty GA, Piccoli DS & Hamilton JA. Potential antiinflammatory effects of interleukin 4: suppression of human monocyte tumor necrosis factor alpha, interleukin 1, and prostaglandin E2. Proceedings of the National Academy of Sciences. 1989; 86: 3803–3807.

31. Esposito E & Cuzzocrea S. TNF-alpha as a therapeutic target in inflammatory diseases, ischemia-reperfusion injury and trauma. Current Medicinal Chemistry. 2009; 16: 3152–3167.

32. Esposito E & Cuzzocrea S. Anti-TNF therapy in the injured spinal cord. Trends in Pharmacological Sciences. 2011.

33. Ibarra A, Correa D, Willms K, Merchant MT, Guízar-Sahagún G, Grijalva I, & Madrazo I. Effects of cyclosporin-A on immune response, tissue protection and motor function of rats subjected to spinal cord injury. Brain Research. 2003; 979: 165–178.

34. Martiñón S, García E, Gutierrez-Ospina G, Mestre H & Ibarra A. Development of Protective Autoimmunity by Immunization with a Neural-Derived Peptide Is Ineffective in Severe Spinal Cord Injury. PLoS ONE. 2012; 7: 32027.

35. Kigerl KA, Gensel JC, Ankeny DP, Alexander JK, Donnelly DJ & Popovich PG. Identification of two distinct macrophage subsets with divergent effects causing either neurotoxicity or regeneration in the injured mouse spinal cord. The Journal of Neuroscience : The Official Journal of the Society for Neuroscience 2009; 29: 13435–13444.

36. Mills KHG. TLR-dependent T cell activation in autoimmunity. Nature Reviews Immunology. 2011.

37. Bielekova B, Goodwin B, Richert N, Cortese I, Kondo T, Afshar G. et al. Encephalitogenic potential of the myelin basic protein peptide (aminoacids 83-99) in multiple sclerosis: results of a phase II clinical trial with analtered peptide ligand. Nat Med. 2010; 6: 1167–1175.

38. Higashi Y, Sukhanov S, Anwar A, Shai SY & Delafontaine, P. IGF-1, oxidative stress and atheroprotection. Trends in Endocrinology and Metabolism. 2010.

39. Clemens Ja, Ho PP & Panetta Ja. LY178002 reduces rat brain damage after transient global forebrain ischemia. Stroke; a Journal of Cerebral Circulation. 1991; 22: 1048–1052.

40. Howard M, & O'Garra A. Biological properties of interleukin 10. Immunology Today. 1992; 13: 198–200.

41. Moore KW, de Waal Malefyt R, Coffman RL & O'Garra, A. I IL-10 and the IL-6 receptor. Annual Review of Immunology, 2001; 19: 683–765.

42. Abraham KE, Mcmillen D & Brewer KL. The effects of endogenous interleukin-10 on gray matter damage and the development of pain behaviors following excitotoxic spinal cord injury in the mouse. Neuroscience. 2004; 124: 945–952.

43. Brewer KL, Bethea JR & Yezierski RP. Neuroprotective effects of interleukin-10 following excitotoxic spinal cord injury. Experimental Neurology. 1999; 159: 484–93.

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