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"The role of inflammatory cytokines in the recovery of spinal cord injury: Recent data on NF-κB."

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ABSTRACT

Spinal cord injury is damage to the spinal cord, resulting from physical trauma as well as other pathological conditions, causing temporary or permanent changes in its function. SCI demonstrates increased mortality and morbidity placing a great financial burden to health systems worldwide. The physiology of post-injury spinal cord recovery is complicated and includes primary and secondary damage mechanisms. Inflammation and inflammatory cytokines hold a central role in this procedure. This is a review of the existing literature on the role of inflammatory cytokines in the recovery process following spinal cord injury, with emphasis on the role of the transcriptive factor NF-κB. NF-κB is the ultimate signaling molecule in pathophysiological mechanisms regulated by inflammatory cytokines, such as TNF-α and IL-1β. Its activation includes a complicated network of pathways that interact with one another through several checkpoints. NF-κB modification influences gene expression in the post-injury spinal cord and regulates intracellular procedures that mediate the recovery of the neuronal tissue. These procedures include inflammation, cellular death, oxidative stress and myelination of neuraxons. Therapies that affect NF-κB-mediated pathways influence the functionality and the prognosis of patients who have sustained a spinal cord injury.

KEY WORDS: spinal cord injury, recovery, cytokines, NF-κB

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Introduction

Spinal cord injury, a damage to the spinal cord causing temporary or permanent changes in its function, results to increased mortality and morbidity rates. Globally, it is estimated that approximately 250,000-500,000 people are affected by this condition [1,2]. Spinal cord injury usually affects young males before the 3rd decade of life, while recently there is a marked shift towards persons older than 60 years, mostly attributed to preventive medicine programs aimed at younger ages and to the phenomenon of population ageing in industrialized countries [3].

The most common mechanisms resulting to spinal cord injury include primarily traffic accidents and falls, with national distributions fluctuating according to the country's demographic curve and the existing socioeconomic conditions [4]. An increased percentage of those who suffer acute spinal cord injury die instantly, about 10% die during first hospitalization while the prognosis of patients who finally undergo rehabilitation is influenced by the resulting neurological condition according to ASIA staging [3,5]. About a half of SCI patients are diagnosed with cervical spine lesions and suffer from severe neurological complications, mostly quadriplegia and paraplegia [6].

Despite its low incidence, SCI results in disproportionate burden for health care systems not only in terms of human loss but also financially. Its great cost is an equation of multiple hospital admissions, required for spinal cord injury patients, the expensive and long-lasting rehabilitation programs, as well as the social allowances and the loss of productivity [7]. The existing predicting models describe an increase in healthcare costs resulting from spinal cord injury in the next decade, primarily attributed to an extended hospitalization period and to the treatment of multiple co-morbidities due to the age of the affected population [8].

Up to this moment, there are no existing national studies to evaluate the epidemiology of SCI in Greece. An estimated prevalence of around 34 patients per million is the most realistic scenario according to some sporadic studies that have included Greek patients and this number is considered as increased when compared to other European countries [1,9]. Although detailed data on the exact numbers is still lacking, it can be alleged that the structure of the national healthcare system, the shortage of rehabilitation facilities and the unavailability of effective social policies targeting disabled persons, do not favour the management of SCI patients in Greece [10].

Research on recovery mechanisms following spinal cord injury utilizes animal models to clarify the underlying pathophysiological mechanisms and to test possible treatment regimens that amplify subjects' neurological status [11,12]. Issuing novel guidelines regulating data exchange and increased sharing of acquired knowledge will contribute highly to breakthroughs in the study of spinal cord injury [13].

In the molecular level, the pathophysiological mechanisms that take place following SCI are very complicated. The "primary injury" develops acutely after trauma and includes the direct implications of the injury mechanism to the spinal cord structures [14]. The "secondary injury" follows and is further divided in an acute (0-48 hours), subacute (2-14 days), intermediate (2 weeks-6 months) and chronic phase (>6 months) [15]. This secondary phase includes several pathophysiological mechanisms that promote the expansion of the injury within the spinal cord structures [16]. The most important ones are: deranged blood perfusion, imbalance in the concentration of ions and neurotransmitters, oxidative stress and production of free radicals, cellular death and inflammation [12]. The above mechanisms, primarily represented by the inflammatory one, are mediated by a variety of signaling molecules and develop both in the intra- and extracellular levels. These include cytokines, such as TNF-α, IL-1β, IL-6 andIL-12, which regulate the procedure of secondary spinal cord injury and progressively lead to the recovery of neuronal tissue. The above procedures result in intranuclear modifications and gene expression, primarily mediated by transcription factors, such as NF-κB [17]. Formation of a scar tissue within the spinal cord, is a dynamic balance between the infiltrate of inflammatory cells and molecules of the extracellular matrix. This fibrous

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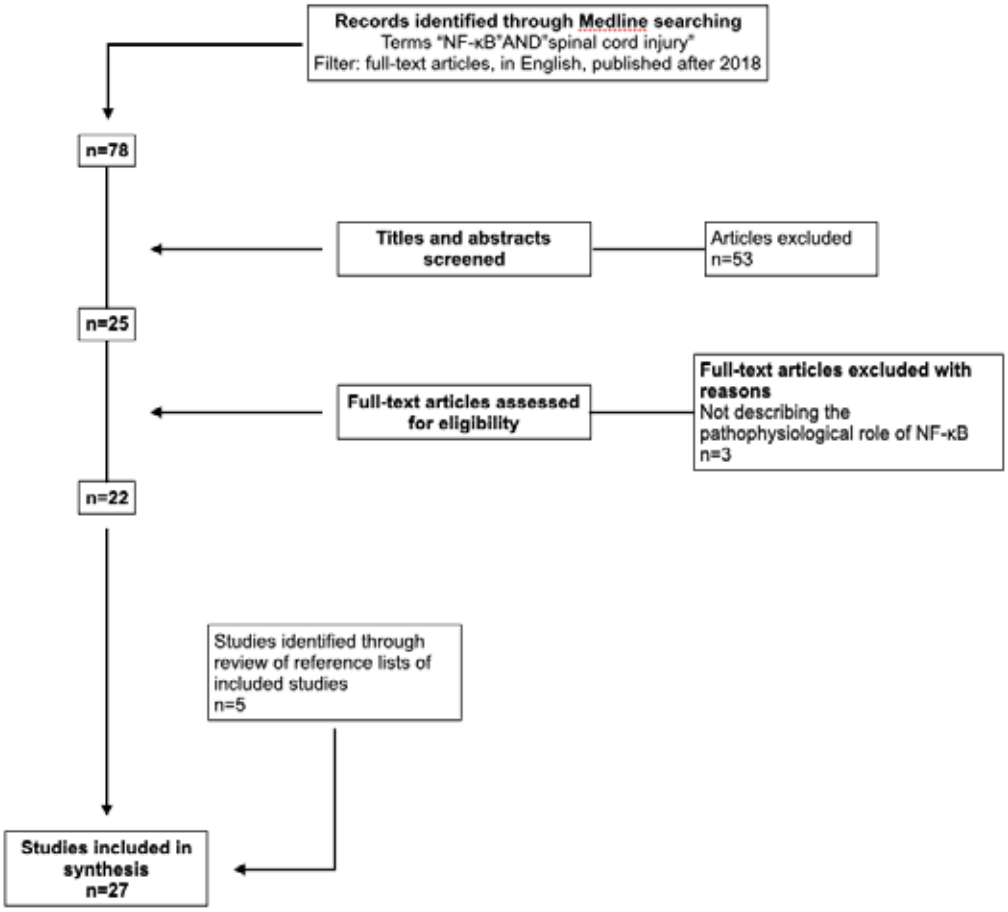
TABLE 1. CURRENT REVIEW FLOW CHART.



tissue surrounding primary injury prevents from spreading through secondary injury mechanisms and partly facilitates the recovery of the neuronal tissue through axial reformation [18].

Given the above facts, the present study is a literature review aiming to summarize the present knowledge on the role of NF-κB in the recovery of spinal cord following injury. In March 2020, an initial search using suitable MeSH terms was performed in the database Medline-Pubmed. From the 78 articles included in the search results only 22 were relevant to the pathophysiological role of NF-κB in SCI after injury. Subsequently, a scan of the articles' reference list was performed to check for more eligible articles to be included in the study. Following the above procedure, 27 articles were finally included in this literature review. (**Table 1**)

Discussion

NF-κB is a transcriptive factor that exists in the nuclei of all eukaryotic cells. In the normal spinal cord, it has been detected both in neuronal cells (neurons, astrocytes, oligodendrocytes) and in microglia [19]. It is a complex molecule that is kept inactive by protein inhibitors (IKK) and by epigenetic modifications [20,21].

Structure of NF-κB

Three molecular complexes contribute to the formation of the entire NF-κB molecule: the NF-κB family proteins, the NF-κB inhibitors (IKB) and the IKK complex.

• The NF-κB family, also described as NF-κB/Rel family, includes the molecules NF-κB1 (p50), NF-κB2 (p52), RelA (p65), c-Rel and RelB.

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• The IκB inhibitor family is comprised of the molecules IκBα, IκBβ and IκBε.

• The IKK complex is a protein with a high molecular weight which regulates the phosphorylation of the NF-κB inhibitors (IκB).

In the deactivated state, IκB inhibitors cover the NF-κB sequencing that facilitate its binding to the nuclear gene promoters and thus its activity as a transcription regulator is annihilated [22]. When activated, NF-κB moves to the nucleus and modifies the transcription of genes which regulate several intracellular procedures and relate to the recovery of neural tissue following spinal cord injury [19].

Activation of NF-κB and signaling

The activation of NF-κB is mediated by many molecules. IL-1β activates NF-κB and enhances inflammation through the TLR/MyD88 or through the TLR4/TRAM/TRIF trail. The first pathway is more rapid and facilitates the acute inflammatory phase by promoting a more acute activation of NF-κB, while the second one leads to a more delayed activation of NF-κB in the subacute inflammatory phase [23,24]. Medicines, such as the natural extract chlorogenic acid, inhibit the IL-1β-mediated activation of NF-κB and result to better neurological outcomes [25]. Other interventions, such as treatment with hyperbaric oxygen (HBO), also deactivate NF-κB by influencing the above pathway and thus ameliorate prognosis after spinal cord injury [26].

Moreover, TNF-α binds to its receptor on the cellular surface (TNFR1) and activates the RIPK1/TAK1/NIK pathway by enhancing the phosphorylation of the inhibitory complex IKK. Prior to binding, the receptor rests in deactivated status connected with ubiquitin molecules. This ubiquitination process is mediated by the TNFAIP3 or A20 molecule. These molecules are possible targets for future therapies that could deactivate TNF-α receptor and thus inhibit inflammation [27]. The unbinding of the RIPK1 molecule from the TNFR1 complex activates the TAK1 molecule, which in turn enables the NEMO-IKK (NIK) molecule to phosphorylate the IKK complex of the NF-κB. Consequently, the inhibitory molecules IκBα, IκBβ are phosphorylated and NF-κB is released. The phosphorylated IκB then binds with ubiquitin and is then decomposed by the 26S proteasome. The free NF-κB inserts the cellular nucleus and enhances the expression of genes which deter cell death and enhance inflammation [28].

Another mechanism of potential activation is the cross-talk between NF-Kb and TWEAK (TNF-like weak inducer of apoptosis). This molecule binds to its Fn14 receptor (Fibroblast growth factor–inducible 14) and activates NF-κB to enter the nucleus and exert its pro inflammatory role through the synthesis of TNF-α and IL-1β[29].

Additionally, Micro-RNAs (miRNAs) regulate the expression of NF-κB by binding on relevant gene promoters that encode signaling molecules included in the mechanisms described above. For example, miR-136-5p and miR-96 induce inflammation by reducing the transcription of IKKβ and by increasing the release of NF-κB [30]. The molecules miR-199b and miR-124 have an opposite action: they increase the transcription of IKKβ and promote the binding of NF-κB to its inhibitor complex. Thus, these molecules could represent targets for the development of novel molecular therapies with the aim to ameliorate neurological burden of SCI patients [31]. The regulatory path is reversible: NF-κB binds to the promoter of certain miRNAs and regulates their activity. For instance, the miRNA-372 has an anti-inflammatory role in the spinal cord following NF-κB binding to its promoter [32].

The presence of free myelin, produced by damaged neuraxons during the primary SCI, has been shown to regulate NF-κB. Literature data support NF-κB activation and the promotion of inflammation through the FAK/P13K/Akt trail initiated by NogoA (neurite outgrowth inhibitor A) and the glycoprotein of oligodendritic myelin [33].

The role of epigenetic modifications is still unclear but they can both enhance and annihilate the activity of NF-κB. In macrophages, methylation and phosphorylation of serine amino-acids in the molecule's promoter (the so-called nuclear localization signals - NLS) enables its traffic to the macrophage nucleus, increases its transcriptive activity and promotes inflammation in the spinal cord [34]. The acetylation of the RelA (p65) molecule in lysine po-

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sitions retains its inactive status and is the output of a subtle balance between histone acetyltransferases (HATs) and histone deacetylases (HDACs) [21]. The AMPK/SIRT1 trail leads to the deacetylation of NF-κB and suppresses inflammation following SCI. Treatment agents, such as resveratrol, enhance neuronal recovery by inducing the early apoptosis of inflammatory cells in the above trail [21,35] and the traditionally used valproic acid has also been reported to suppress SCI inflammation by interacting with these epigenetic modifications [36].

Pathophysiological role of NF-κB

Despite recent progress in the detection of several novel signaling pathways and their cross-talks, associated with NF-κB, their exact pathophysiological roles remain unknown. It is well understood that NF-κB facilitates inflammation by regulating the chemotaxis of inflammatory cells and the intracellular communication during inflammation [16]. NF-κB increases the expression of genes that produce the molecules ICAM and VCAM, which enable the adhesion and immigration of neutrophils through the blood vessel wall. Furthermore, the inflammatory cells that mediate inflammation (astrocytes, T-lymphocytes and macrophages) communicate with chymokines and cytokines, which initiate various signaling mechanisms. Many of these mechanisms end up to the activation of NF-κB. For example, pro-inflammatory cytokines including TNF-α, IL-1β and IL-6 lead to an increased expression of NF-κB, while lower levels of the latter are related to an increased circulation of anti-inflammatory molecules, such as IL-12 [12].

Free oxygen and nitrate radicals (ROS, NOS) activate NF-κB and preserve inflammation in the spinal cord by preventing autophagy and apoptosis of inflammatory cells [37,38]. The mechanism includes an increase in the expression of the mitochondrial enzyme MnSOD and a decrease in the production of free radicals through a reverse feedback mechanism. As a result, the free-radical-mediated apoptosis of inflammatory cells is inhibited, a phenomenon which exacerbates inflammation in the spinal cord [37]. Another mechanism includes the activation of kinase JNK1 by NOS and the consequent phosphorylation of Bcl-2 (Beclin 1 / B-cell lymphoma-2) and of IKKb of the NF-κB complex. The free NF-κB increases the expression of genes that annihilate the autophagy of inflammatory cells (c-Fos, c-Jun) [38]. In animal models, the commencement of ketotic diet (rich in fat, poor in carbohydrates, medium protein intake) reduces oxidative stress and prevents inflammation as early as the 4th week after injury. This procedure is mediated by NF-κB [39].

Moreover, cellular death associated with NF-κB is regulated by TNF-α and by the TWEAK molecule. A study performed by Xu et al in 2016 proved the anti-apoptotic role of TWEAK in inflammatory cells following spinal cord injury in a procedure mediated by RIPK1/caspase 8. Through this mechanism, TWEAK preserves inflammation within the spinal cord by binding to its Fn14 receptor that leads to the activation of NF-κB [26]. TNF-α also activates RIPK1/caspase 8 after binding to its receptor in the membrane of inflammatory cells that appear in the acutely damaged spinal cord. Through the RIPK1/RIPK3/MLKL complex ("necrosome") TNF-α promotes the necroptosis of inflammatory cells in a strictly regulated procedure that includes gene transcription mediated by NF-κB [28]. This anti-apoptotic role of TNF-α through NF-κB-mediated gene transcription is further supported by experimental data that show an increase in the cell death rates of inflammatory cells within the spinal cord when gene transcription was inhibited by using actinomycin D or cycloheximide [40]. Medications, such as the natural extract Paeoniflorin, influence the above pathway, by deactivating NF-κB, thus deterring inflammation and exerting a neuroprotective influence [41]. Other molecules, such as DUSP19, inhibit apoptosis by enhancing the transcription of NF-κB and are suitable targets for future therapies [42]. Last, resveratrol is a polyphenol of red wine that promotes the recovery of neuronal tissue after spinal cord injury. Its role is performed by an increase in the expression of SIRT1 and AMPK in the spinal cord macrophages. Resveratrol deters inflammation by rendering inflammatory cells vulnerable to apoptosis, a procedure which relates to a decrease in the expression of NF-κB, decreased levels of

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TNF-α and increased levels of IL-12 [43].

Axon demyelination and remyelination are also under NF-kB modulation. The phagocytosis of free myelin by microglia cells promotes the activation NF-κB and preserves inflammation. Rat models that underwent intrathecal infusion of E6020, a factor that activates NF-κB through the TLR pathway of the precursor oligodendritic cells (OPCs), showed an estimated increase in the levels of pro-inflammatory cytokines such as TNF-α, IL-1β and IL-6 and the percentage of remyelinated neuraxons increased [44,45].

In conclusion, the transcriptive factor NF-κB is a central regulatory molecule in the recovery process following SCI and is included in several pathophysiological pathways. More research is required to clarify the exact role of NF-κB in the cellular functions and for the development of targeted therapies against molecules that affect its functionality, to ameliorate the neurological function of patients suffering from SCI.

Conflict of interest

The authors declare no conflicts of interest.

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