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Effect progress of complement system in neural repair after spinal cord injury

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Abstract: Spinal cord injury has the characteristics of high mortality and disability rates, and the treatment of spinal cord injury has been a worldwide problem. With the deepening of spinal cord injury research and the advancement of treatment methods, the survival rate of patients has improved, but the clinical efficacy is still not ideal. New research has found that the immune response is involved in the entire process of pathological changes and regeneration and repair after spinal cord injury. Among them, the complement system plays an important role in the occurrence and development of spinal cord injury. This article mainly reviews the role of the complement system in secondary spinal cord injury and regeneration and repair after spinal cord injury, including the double-edged sword effect of the complement system, the impact of the complement system on axonal regeneration and synaptic maintenance, and possible signaling pathways, with a view to improving the treatment of spinal cord injury, providing new treatment ideas.

Keywords: Spinal cord injury; Complement; Nerve regeneration; Axonal regeneration

Fund program: Xuzhou Municipal Health Commission, Pengcheng Yingcai-Medical Young Reserve Talent (XWRCHT20220035); Key Project of Medical Science and Technology Innovation Project of Xuzhou Municipal Health Commission (XWKYHT20230055)

1 Overview of spinal cord injury

Spinal cord injury refers to damage to the integrity of the spinal column structures due to various causes such as trauma, tumor compression, lumbar tuberculosis, etc. This includes damage to the vertebrae, intervertebral discs, ligaments stabilizing the spine, and muscles surrounding the spine, leading to impairment of the neural structures within the spinal canal (including the spinal cord and nerve roots) and their functions. This results in disorders of spinal cord functions such as movement, sensation, reflexes, etc., below the level of injury [1]. Traumatic injuries, such as those from traffic accidents and falls from heights, are the primary causes, with fewer reports on the specific etiology of non-traumatic spinal cord injuries [2]. Globally, the incidence of traumatic spinal cord injuries ranges from 236 to 4,187 per million population, with rates in China ranging from 14.6 to 60.6 per million [3]. Spinal cord injury imposes a heavy economic burden on families and society [4-5].

The spinal cord injury is divided into primary and secondary injuries. The former primarily refers to mechanical damage to the spinal cord caused by external forces, which is usually irreversible. Secondary injury is the result of cellular responses to primary injury, characterized by a cascade of secondary injury reactions such as ischemia, apoptosis promotion, inflammatory cell infiltration, and excitotoxicity [6]. The complex cascade of inflammatory reactions following secondary injury is a key factor determining the extent of damage and patient prognosis [7]. Therefore, current research mainly focuses on improving the post-spinal cord injury inflammatory and immune microenvironment.

Currently, there are many treatment methods for spinal cord injury patients, including timely surgical decompression and fixation, local application of methylprednisolone, neurotrophic drug therapy, stem cell transplantation, and comprehensive measures to prevent complications [8-10]. Acute spinal cord injuries are mainly treated through surgical intervention to limit the extent of injury and minimize secondary damage, but decompression surgery also entails significant risks [8]. Furthermore, because the functional reconstruction during the recovery period determines the patient's prognosis and quality of life, corticosteroids can prevent secondary injury after spinal cord injury by decreasing oxidative stress, enhancing impulse conduction, improving blood flow, reducing oxidative stress, and regulating immune responses to protect the spinal cord's structure, thereby aiding in maintaining spinal cord ultrastructure stability. Neurotrophic factors are molecules that control neuronal growth, survival, proliferation, and differentiation, playing a crucial role in regulating immune responses and autoimmunity [11-12]. Clinical trials over the past decade have demonstrated the feasibility and long-term safety of transplanting stem cells into injured spinal cords. Additionally, as research progresses, the use of biomaterials to enhance cell transplantation effectiveness provides a feasible direction for future spinal cord injury treatment [13]. However, due to the complex pathophysiological mechanisms of spinal cord injury, these treatment methods still have a long way to go before achieving satisfactory clinical outcomes.

Zhao *et al.* [14] through high-throughput sequencing of spinal cord tissue cells in spinal cord hemisected mice found that 24 complement components, including Clq, C3, C5, and MAC, were upregulated 72 hours after spinal cord injury. qPCR results also showed a corresponding increase in the mRNA levels of these complement components, indicating an increase in the expression levels of the complement system during the acute phase of spinal cord injury. Previous studies by our research group have also found a significant increase in serum C1QB level in spinal cord injury patients compared to simple spinal fractures patients, and C1QB level was closely related to the severity of spinal cord injury, suggesting that serum C1QB may be a potential serological marker for spinal cord injury [15].

2 Complement System

2.1 Complement and complement system

Complement is a group of proteins present in normal human and animal sera and tissue fluids, which exhibit enzymatic activity upon activation. The complement system consists of over 50 secreted proteins and membrane-bound proteins, which exert their functions through highly ordered interactions. Complement cascades are key components of the innate immune system, rapidly supplementing and efficiently identifying and clearing pathogens through cascading enzymatic reactions, while also promoting tissue repair. Under pathology conditions, dysregulation of the complement cascade can lead to chronic inflammation, persistent pain, and neurological dysfunction. Increasing evidence suggests that the complement system plays important roles in central nervous system development, maintenance, and restoration of homeostasis, as well as in regulating neuronal plasticity [16-20]. Recent studies have found that complement protein C1Q can promote the migration and repair of neural stem cells by mediating receptors on the surface of neural stem cells [21]. These studies confirm the significant role of the complement system in the occurrence and development of spinal cord injury, clarifying its relationship with the pathophysiological mechanisms of spinal cord injury and bringing new hope for the treatment of this debilitating disease.

2.2 Activation pathways of the complement cascade

The activation pathways of the complement cascade include the classical pathway, the lectin pathway, and the alternative pathway. Among them, C3a and C5a are two core effector molecules in the activation pathways, and their receptors play important roles in brain development and neuroplasticity. The receptor for C3a is C3aR, and there are two receptors for C5a: one is C5aR1, a G protein-coupled pro-inflammatory receptor expressed on myeloid-derived cells; the other is C5aR2. The C3a-C3aR axis plays an important role in neuronal migration, while the C5a-C5aR1 axis regulates the proliferation and differentiation of progenitor cells, which are also crucial in human embryonic brain development [22].

3 Complement system and spinal cord injury

3.1 The dual role of the complement system

The complement pathway participates in the body's defense responses and immune regulation and also mediates inflammatory responses after central nervous system injury. The neuroinflammation after central nervous system injury is the result of activation of the innate immune system, mediated by cytokines and chemokines released by astrocytes, microglia, endothelial cells, and immune cells from peripheral sources [23]. Additionally, primary central nervous system injury can activate the complement pathway. The inflammation and immune responses mediated by complement pathway activation are central components of secondary injury, and complement cascades are critical components of the inflammatory response after secondary injury. Relevant experiments have shown that Clq, C4, factor B, MAC, and others are deposited in neurons and oligodendrocytes in the spinal cord injury area, and the staining of Clq and factor B in axons is particularly significant, indicating their possible correlation with axonal degeneration or demyelination reactions after spinal cord injury [24]. Studies have found that inhibiting the activation pathways of complement can reduce the area of inflammatory invasion, decrease inflammatory cells and factors, and improve motor function in animal models [25]. As mentioned earlier, the inflammatory response induced by spinal cord injury is an important factor in secondary injury, with complement pathway activation playing a crucial role in the occurrence of inflammation [26-27].

However, research has shown that the complement system induces inflammatory cascades in spinal cord injury models and plays a role in promoting injury repair. Beck *et al.* found that 14 days after spinal cord injury in rats, administration of a C5aR antagonist increased demyelination of neurons, infiltration of macrophages, and activation of microglia in the spinal cord injury area, exacerbating motor function and histopathological damage [28]. Benavente *et al.* [21] found that complement protein C1Q can promote the migration and repair of neural stem cells by mediating receptors on the surface of neural stem cells, improving motor function in rats. Components of the innate immune system can alter the fate and migration of human neural stem cells (hNSCs). Similarly, research has found that when treating spinal cord injury with C1Q+C3a, the PI3K/AKT pathway is activated, promoting the growth of hNSCs toward the center of spinal cord injury. Migration of hNSCs was not induced when the PI3K/AKT pathway

was blocked, and the addition of C1Q Ab and C3a Ab inhibited the migration of hNSCs [29]. Therefore, the complement pathway has a dual role in spinal cord injury. On the one hand, complement activation can exacerbate secondary injury of spinal cord injury; on the other hand, complement activation can promote injury repair at certain stages of spinal cord injury.

3.2 Complement system affects axon regeneration and synaptic maintenance

The inflammatory response following spinal cord injury is mediated by a variety of cells and proteins, which have diverse, overlapping, and sometimes opposing roles in histological and behavioral recovery. Although complement components have been associated with axons and myelin phospholipids after spinal cord injury, current research has only confirmed that complement proteins can promote neural repair and motor function recovery by activating surface mediators of neural stem cells. However, whether complement proteins directly influence axon growth or neuronal cell regeneration remains unclear. As the injury transitions from acute to chronic phases, persistent inflammatory stimuli and apoptosis of necrotic cells leave behind multiple microcavities, whose fusion further restricts axon regeneration and cell migration. These microcavities consist of a dense network woven by astrocytic processes and deposits of chondroitin sulfate proteoglycans (CSPGs), forming a physical and biochemical barrier to neural axon growth and regeneration, ultimately forming tough scars [30]. It has been reported that complement C1Q plays a crucial role in axon growth and spinal cord injury-induced axon regeneration *in vitro*. Studies have found that C1Q can increase axon length on myelin. Subsequent protein and molecular analyses revealed a direct interaction between C1Q and myelin-associated glycoprotein (MAG) in myelin, leading to reduced activation of growth-inhibitory signals in neurons [31]. Peterson *et al.* [32] conducted a study involving dorsal hemi section with peripheral reflex condition damage, and found that at 6 weeks post-injury, spinal sensory axon regeneration increased twofold in C3 (-/-) mice compared to wild-type C3 (+/+) mice. *In vitro* experiments showed that adding C3 to myelin phospholipids increased myelin phospholipid-mediated neurite growth inhibition and neuronal loss by twofold compared to using myelin phospholipids alone. ELISA experiments showed that myelin phospholipase cleaved C3 into active fragments. Adding purified C3b to cultured neurons resulted in C3b exhibiting growth inhibition, neurotoxicity, or anti-adhesive activity. These data suggest that C3 inhibits neurite growth and neuronal viability *in vitro* and inhibits axon regeneration *in vivo*. These studies demonstrate that complement proteins indeed promote axon and neuronal regeneration *in vitro*, but given the complex physiological effects within the human body, further research is needed to understand the role of complement proteins in neural regeneration *in vivo.*

4 Summary and outlook

This review summarizes the current research status of the complement system in the pathogenesis of spinal cord injury and suggests that complement proteins may be key therapeutic factors for improving motor function recovery and neural repair after spinal cord injury. Previous studies have found that C1QB may be a potential serum biomarker for spinal cord injury. However, whether complement proteins can promote spinal cord repair and regeneration remains to be verified. Therefore, future research will continue to explore the positive effects of complement proteins on the prognosis of spinal cord injury and conduct a series of clinical and basic research to provide a theoretical basis for further exploration.

Conflict of Interest None

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· 研究进展 ·

补体系统在脊髓损伤后神经修复中的作用进展

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摘要：脊髓损伤具有高致死率与高致残率的特点，其治疗一直是世界性难题。随着脊髓损伤研究的深入和治疗手段的进步，脊髓损伤患者的生存率有所提升，但其预后仍不理想。最新研究发现，免疫反应参与脊髓损伤后的病理变化和再生修复全过程，其中，补体系统在脊髓损伤的发生发展中扮演了重要角色。本文主要综述补体系统在继发性脊髓损伤及脊髓损伤后再生修复中的作用，包括补体系统的双刃剑作用，补体系统影响轴突再生与突触维持，及可能存在的信号通路，以期为脊髓损伤患者提供新的治疗思路。

关键词：脊髓损伤；补体；神经再生；轴突再生；免疫反应

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Abstract: Spinal cord injury has the characteristics of high mortality and disability rates, and the treatment of spinal cord injury has been a worldwide problem. With the deepening of spinal cord injury research and the advancement of treatment methods, the survival rate of patients has improved, but the clinical efficacy is still not ideal. New research has found that the immune response is involved in the entire process of pathological changes and regeneration and repair after spinal cord injury. Among them, the complement system plays an important role in the occurrence and development of spinal cord injury. This article mainly reviews the role of the complement system in secondary spinal cord injury and regeneration and repair after spinal cord injury, including the double-edged sword effect of the complement system, the impact of the complement system on axonal regeneration and synaptic maintenance, and possible signaling pathways, with a view to improving the treatment of spinal cord injury, providing new treatment ideas.

Keywords: Spinal cord injury; Complement; Nerve regeneration; Axonal regeneration; Immune reaction

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1　脊髓损伤的概述

脊髓损伤是指各种原因(如创伤、肿瘤压迫、腰椎结核等)导致的脊柱结构的完整性被损害，包括椎骨、椎盘、稳定脊柱的韧带及椎旁肌肉的损伤导致椎管内神经结构(脊髓和神经根)及其功能的损害，出现损伤水平及以下脊髓功能(运动、感觉、反射等)障碍[1]。其中交通事故、高处跌落等创伤性损伤是主要原因，非创伤性脊髓损伤的具体病因报道较少[2]。据统计，全球创伤性脊髓损伤发生率为(236～4 187)/100 万，中国的发生率为(14.6～60.6)/100 万[3]。脊髓损伤给家庭和社会带来沉重的经济负担[4-5]。

脊髓损伤可分为原发性损伤和继发性损伤。原发性损伤主要指外力对脊髓造成的机械损伤，通常是不可逆的。继发性损伤是细胞对原发性损伤的反应结果，是以缺血、促凋亡、炎性细胞浸润和兴奋性毒性为特征的继发性损伤级联反应[6]。因继发性损伤后复杂的炎症级联反应是决定损伤程度及患者预后的关键因素[7]。因此目前研究主要关注于改善脊髓损伤后的炎症及免疫微环境。

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现阶段，临床上对于脊髓损伤的治疗方法很多，包括及时的手术减压固定，甲泼尼龙局部封闭，神经营养药物应用，干细胞移植，以及预防并发症发生等综合治疗措施[8-10]。其中急性脊髓损伤主要通过手术治疗，限制损伤范围，尽可能减少继发性损伤，但是减压手术同时也伴随着巨大的风险[8]。此外，因为恢复期的功能重建决定了患者的预后和生活质量。皮质类固醇可以预防脊髓损伤后的继发性损伤，并通过减少自由基氧化，增强冲动传导，改善血流，减少氧化应激和调节免疫反应，从而有助于保护脊髓的超微结构稳定。神经营养因子是控制神经元生长、存活、增殖和分化的分子，在调节免疫应答和自身免疫中也起着关键作用[11-12]。在过去十余年中，临床试验已证实将干细胞移植到受伤脊髓中的可行性和长期安全性。并且随着研究的不断深入，目前可以通过使用生物材料来增强干细胞移植的效果，这为以后脊髓损伤的治疗提供了可行的方向[13]。但由于脊髓损伤复杂的病理生理机制，这些治疗方法距离令人满意的临床效果仍有很长的路要走。

Zhao 等[14]通过对脊髓半切小鼠的脊髓组织细胞的高通量测序结果发现，脊髓损伤后 72 h，C1q、C3、C5、MAC 等 24 种补体成分上调，且 qPCR 结果显示上述补体的 mRNA 水平也相应升高，表明在脊髓损伤急性期补体系统的表达即增加。本课题组前期研究发现，脊髓损伤患者与单纯脊柱骨折患者相比，血清补体 C1q 亚基 BL（C1QB）水平在脊髓损伤后明显升高，且与脊髓损伤严重程度密切相关，表明血清 C1QB 可能是脊髓损伤潜在的血清学标志物[15]。

2　补体系统

2.1　*补体及补体系统*　补体是存在于正常人和动物血清与组织液中的一组经活化后具有酶活性的蛋白质。补体系统由 50 多种分泌蛋白和细胞膜结合蛋白组成，通过高度有序的相互作用发挥其功能。补体级联是先天免疫系统的一个关键组成部分，通过级联酶反应迅速补充，并迅速识别、清除病原体，同时促进组织修复。在各种病理条件，补体级联失调会导致慢性炎症、持续疼痛和神经功能障碍。越来越多的证据表明，补体系统在中枢神经系统的发育，维持和恢复中枢神经系统内稳态以及调节神经可塑性中发挥重要作用[16-20]。近年来有研究发现补体蛋白 C1q 可以通过介导神经干细胞表面的受体，从而促进神经干细胞的迁移与修复[21]。这些研究证实，补体系统在脊髓损伤的发生发展中扮演了重要角色，明确其与脊髓损伤的关系可进一步揭示脊髓损伤的病理生理机制，并为其治疗带来新的希望。

2.2　*补体级联的激活途径*　补体级联的激活途径包括经典途径、凝集素途径和旁路途径。其中，C3a 和 C5a 是三条激活途径中两个核心效应分子，其受体在大脑发育和神经可塑性中起着重要作用。C3a 的受体是 C3aR，C5a 有两种受体：一种是 C5aR1，该受体为 G 蛋白偶联促炎受体，表达于髓系起源的细胞上；另一种为 C5aR2。C3a-C3aR 轴在神经元迁移中具有重要作用，C5a-C5aR1 轴可调节祖细胞的增殖和分化，在胚胎期脑神经发育中至关重要[22]。

3　补体系统与脊髓损伤

3.1　*补体系统的双刃剑作用*　补体途径参与机体的防御反应和免疫调节，也介导中枢神经系统损伤后的炎症反应。中枢神经系统损伤后的神经炎症是先天免疫系统激活的结果，由星形胶质细胞、小胶质细胞、内皮细胞和外周来源的免疫细胞释放的细胞因子和趋化因子介导[23]。此外原发性中枢神经系统损伤可激活补体途径。补体途径激活介导的炎症与免疫反应是继发性损伤的核心环节，补体级联是继发性损伤后炎症反应的关键组成部分。相关实验证明 C1q、C4、B 因子、MAC 等在脊髓挫伤区的神经元和少突胶质细胞中均有沉积，且 C1q 和 B 因子在轴突中的染色甚为明显，意味着二者可能与脊髓损伤后的轴突变性或脱髓鞘反应存在相关性[24]。研究发现，抑制补体的活化途径可以减少动物模型中的炎症侵袭面积，减少炎症细胞和细胞因子，降低运动功能[25]。如前所述，脊髓损伤诱导的炎症反应是继发性损伤的重要因素，其中补体途径的激活在炎症反应的发生中起关键作用[26-27]。

然而，研究表明，补体系统在脊髓损伤模型中诱导炎症级联反应，并在促进损伤修复中起作用。Beck 等[28]发现，大鼠脊髓损伤 14 d 后，给予 C5aR 拮抗剂，脊髓损伤区域的神经元脱髓鞘、巨噬细胞浸润和小胶质细胞活化增加，运动功能和组织病理学损伤增加。Benavente 等[21]发现，补体蛋白 C1q 可以通过介导神经干细胞表面的受体，从而促进神经干细胞的迁移与修复，改善大鼠运动功能。先天免疫的细胞和体液成分会改变人类神经干细胞（hNSC）的命运和迁移。同样有研究发现，当使用 C1q+C3a 治疗脊髓损伤时，PI3K/AKT 途径被激活，促进了 hNSC 向脊髓损伤中生长。当阻断 PI3K/AKT 途径后，C1q+C3a 无法诱导 hNSC 的迁移；当加入 C1q Ab 与 C3a Ab 后同样抑制了 hNSC 的迁移[29]。因此，补体途径在脊髓损伤中起双重作用。一方面，补体激活可加重脊髓损伤的继发性损伤；另一方面，补体激活在脊髓损伤的一定阶段可促进损伤修复。

3.2　*补体系统影响轴突再生和突触维持*　脊髓损伤后的炎症反应是由一组不同的细胞和蛋白质介导的，这些细胞和蛋白质对组织学和行为恢复具有不同的、重叠的和相反的作用。尽管脊髓损伤后补体成分与轴突和髓磷脂相关性增加，目前已有相关研究证实补体蛋白可以通过激活神经干细胞的细胞表面介质促进神经的修复与运动功能的恢复，但补体蛋白是否直接影响轴突生长或神经元细胞再生尚不清楚。随着损伤由急性期进入慢性期，持续的炎症刺激和凋亡坏死细胞死亡，留下多个微囊腔，囊腔合并进一步限制了轴突再生和细胞迁移。这些微囊腔由星型胶质细胞突起紧密编织网络和硫酸软骨素蛋白聚糖（chondroitin sulfate proteoglycans，CSPGs）形成的致密纤维沉积组成，作为神经轴突生长和再生的物理和生物化学屏障，最终形成质韧的疤痕[30]。据报道，补体 C1q 在体外轴突生长和脊髓损伤后轴突再生中发挥重要作用。经研究发现，C1q 可增加髓鞘上的轴突长度。通过蛋白质和分子

分析发现,C1q 与髓鞘中的髓鞘相关糖蛋白(MAG)直接相互作用,导致神经元中生长抑制信号的激活减少[31]。Peterson 等[32]进行了一项背侧半切伴外周条件反射损伤实验,伤后 6 周时 C3(-/-)小鼠与野生型 C3(+/+)小鼠相比,脊髓感觉轴突再生增加了 2 倍。在体外实验中,与单独使用髓磷脂相比,添加 C3 可以使髓磷脂介导的神经突生长抑制和神经元损失增加 2 倍,ELISA 实验显示髓磷脂丝氨酸蛋白酶裂解 C3 产生活性片段。将纯化的 C3b 添加到培养的神经元中,结果发现 C3b 具有 C3 的生长抑制和神经毒性或抗黏附活性。这些数据表明,C3 在体外抑制神经突生长和神经元活力,在体内抑制轴突再生。这些研究证明补体蛋白在体外研究中确实起到了促进轴突与神经元再生的作用,但介于人体内部复杂的生理作用,补体蛋白在体内对神经再生的作用仍需要进一步的研究。

4　总结与展望

本综述总结归纳了目前脊髓损伤发生机制领域的补体系统研究现状,补体蛋白可能成为改善脊髓损伤后运动功能恢复及神经系统修复的关键治疗因子。前期研究发现,血清 C1QB 可能是脊髓损伤潜在的血清学标志物,但是关于补体蛋白能否促进损伤脊髓修复与再生尚未予以验证。因此未来的研究将继续致力于探索补体蛋白对脊髓损伤预后的积极作用,同时进行一系列的临床及基础研究为下一步探索提供理论基础。

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