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From basics to clinical: A comprehensive review on spinal cord injury

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ABSTRACT

Spinal cord injury (SCI) is a devastating neurological disorder that affects thousands of individuals each year. Over the past decades an enormous progress has been made in our understanding of the molecular and cellular events generated by SCI, providing insights into crucial mechanisms that contribute to tissue damage and regenerative failure of injured neurons. Current treatment options for SCI include the use of high dose methylprednisolone, surgical interventions to stabilize and decompress the spinal cord, and rehabilitative care. Nonetheless, SCI is still a harmful condition for which there is yet no cure. Cellular, molecular, rehabilitative training and combinatorial therapies have shown promising results in animal models. Nevertheless, work remains to be done to ascertain whether any of these therapies can safely improve patient's condition after human SCI. This review provides an extensive overview of SCI research, as well as its clinical component. It starts covering areas from physiology and anatomy of the spinal cord, neuropathology of the SCI, current clinical options, neuronal plasticity after SCI, animal models and techniques to assess recovery, focusing the subsequent discussion on a variety of promising neuroprotective, cell-based and combinatorial therapeutic approaches that have recently moved, or are close, to clinical testing.

Contents

Abbreviations: BBB, Basso, Beattie and Bresnahan; BDA, biotinylated dextran amine; ChABC, chondroitinase ABC; CSPGs, chondroitin sulphate proteoglycans; CST, corticospinal tract; CTB, cholera toxin B; ECM, extracellular matrix; GAG, glycosaminoglycan; GFAP, glial fibrillary acidic protein; GRPs, glial-restricted precursors; ICCP, international campaign for cures spinal cord injury paralysis; IL, Interleukin; Ips, induced pluripotent stem; MAG, myelin-associate glycoprotein; MAP-2, microtubule-associated protein 2; MP, methylprednisolone; MSCs, mesenchymal stem cells; NASCIS, national acute spinal cord injury study; NF, neurofilament; NRPs, neuronal-restricted precursors; NSCs, neural stem cells; OECs, olfactory ensheathing cells; OMgp, oligodendrocyte myelin glycoprotein; OPCs, oligodendrocytes progenitor cells; PEG, polyethylene glycol; ROS, reactive oxygen species; SCs, Schwann cells; SCI, spinal cord injury; SPCL, starch poly-caprolactone; TNF-α, tumor necrosis factor-alpha.

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1. Introduction

The Edwin Smith papyrus, an ancient Egyptian physician textbook, described, in 1700BC, Spinal Cord Injury (SCI) as an "ailment not to be treated" (Porter, 1996). Now, almost 4000 years later, the treatment of SCI remains largely palliative: preventing injury progression; handling spasticity, dysautonomia, and deafferentation pain syndromes; implementing bowel and bladder training regimens; managing complications of sensory loss; and teaching patients how to cope with their disabilities. Fortunately, ongoing advances in neurobiology research promise to change this paradigm from palliation to more curative interventions.

The number of people in the United States who currently live with SCI is estimated to be around 253,000 with 11,000 new cases occurring each year. Causes include penetrating bullet wounds and other forms of violence (26%) and non-penetrating lesions from vehicular accidents (38%) and sports accidents (7%), as well as falls (22%), especially in elderly persons (Dobkin and Havton, 2004). This condition usually leads to devastating neurological deficits and disabilities that provoke not only the loss of sensory and motor capabilities (paraplegia or tetraplegia) but other common problems related with SCI such as frequent infections in bladder, kidneys, bowel problems, and cardiac and respiratory dysfunctions. All of these problems have a strong impact on the physiologic, psychological and social behavior of SCI patients. For all of these reasons, it is urgent to develop therapeutic strategies that can specifically target this problem.

This review intends to provide an extensive overview of the SCI field. It will expand from the basic biology to the current state of research and clinical areas and finish with the future trends for this field.

2. Physiology and anatomy of the spinal cord

The spinal cord provides a means of communication between the brain and the peripheral nerves that enter the cord. Besides that, it is also able to produce reflexes, called the spinal reflexes.

The spinal cord extends from the base of the brain (in medulla oblongata) through the *foramen magnum* of the skull to the firsts lumbar vertebras. The cord only extends to the L1 vertebra in human, or L3 in the case of rats, because the vertebral column grows faster than the spinal cord. For this reason, and below the cervical levels, the spinal nerves run parallel downwards to their intervertebral foramina. The spinal cord is protected by the vertebral column, which is composed of individual vertebrae. Like the brain, it is also protected by three membranes of connective tissue called meninges. From the outside in, the meninges are the *dura mater*, *arachnoid mater* and *pia mater*. Finally and helping to protect the spinal cord, there are the subarachnoid space (between arachnoid and pia) filled with cerebrospinal fluid and the epidural space (between dura and periosteum) filled with loose fibrous and adipose connective tissues (Van-De-Graaff, 2001; Vander et al., 2001).

The gray matter of the spinal cord is located centrally, surrounded by white matter. The gray matter is made up of interneurons, the cell bodies and dendrites of efferent neurons, the entering fibers of afferent neurons, and glial cells. The surrounding white matter (except when the dorsal horns touch the margins of the spinal cord) is composed mostly of groups of myelinated axons. These groups of axons, called fiber tracts or pathways, run longitudinally through the cord, some descending to relay information from the brain to the periphery, others are ascending to transmit information to the brain (Fig. 1).

The names of the ascending tracts usually start with the prefix spino- and end with the name of the brain region where the spinal cord fibers first synapse. The anterior spinothalamic tract, for instance, carries impulses to the thalamus; from there the sensory information is relayed to the cerebral cortex. The names of descending motor tracts, conversely, begin with a prefix denoting the brain region that gives rise to the fibbers and end with the suffix spinal. The corticospinal tract (CST), for instance, begins in the cerebral cortex and descends the spinal cord. It is important to note that the tracks location in the spinal cord may vary between species. There is a major difference on the position of the CST fibers (responsible for voluntary skilled movements) in humans and in rodents. In humans, the major corticospinal bundle is found in the lateral column while in rodents it is found in the ventral part of the dorsal funiculus (Fig. 2). More information about the tracts that run in the spinal cord can be found in the Watson, Paxinos and Kayalioglu book (Watson et al., 2009).

The above mentioned fiber tracts are crucial in the communication between spinal cord and brain. Groups of afferent (sensory) fibers that enter the spinal cord from the peripheral nerves enter on the dorsal side of the cord *via* the dorsal roots. Small bumps on the dorsal roots, the dorsal root ganglia, contain the cell bodies of the afferent neurons. The axons of efferent (motor) neurons leave the spinal cord on the ventral side *via* the ventral roots. Near the cord, the dorsal and ventral roots from the same level combine to form a spinal nerve, one on each side of the spinal cord. The spinal nerves are designated by the five

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