Translational Research in Anatomy 1 (2015) 11–16

Contents lists available at ScienceDirect

Translational Research in Anatomy

journal homepage: http://www.journals.elsevier.com/translational-research-in-anatomy

Review

Engraftment of neural stem cells in the treatment of spinal cord injury

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ARTICLE INFO

Article history:
Received 22 February 2015
Received in revised form
12 October 2015
Accepted 12 October 2015
Available online 23 October 2015

Keywords:
Stem cell therapy
Engraftment
Intramedullary
Intrathecal
Intravascular
Intraventricular

ABSTRACT

Spinal cord injury is one of the main causes of disability in the young population. Based on the underlying pathological changes, many modalities of treatments have been trialed. However, the most promising so far, has been the replacement of lost cellular elements, using stem cells and non-stem cells transplantation. The route of cellular administration and engraftment into the site of injury is an important determining factor for functional outcome, and should be chosen to be safe and efficacious in human patients. Herein, we will review the underlying changes following spinal cord injury, and the possible routes of cellular transplantation.

Contents

1. Introduction

In 1944, Woolsey et al. [1] reported the first spinal cord transplantation in known history. A 16- year-old male presented with

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http://dx.doi.org/10.1016/j.tria.2015.10.002

complete loss of motor and sensory function after he was shot in his right shoulder with the bullet reaching the superior border of the fourth thoracic vertebra. Following laminectomy, the injured spinal cord was completely transected and replaced with a cadaveric spinal cord that had been fixed in 10% formalin for twelve days, and cleaned and sterilized with running and distilled water and 70% alcohol. No improvement in the patient's condition was noted, and the patient died almost 4 months after the surgery. Autopsy showed exceptional preservation of the transplanted graft, although with restricted regeneration and limited tissue reaction. The preservation was attributed to the preoperative use of formalin, and no explanations or related conclusion on the microscopic findings could be made.

2. Spinal cord injury

The world wide annual incidence of spinal cord injury (SCI) is 15–40 cases per million. The incidence is approximately 12,000 cases in the United States. Of these, 4000 die before reaching the hospital and 1000 during hospitalization, mostly due to pneumonia and septicemia [2]. Most of these injuries occur in otherwise healthy and young patients, and are mainly due to fracture and/or dislocation of the vertebral column [3]. Based on gross findings, SCI can be classified into four groups: (1) solid cord injury, the least common type, associated with normal appearance of the spinal cord after injury; (2) contusion/cavitation, the most common type, associated with areas of hemorrhage, and expanding necrosis and cavitation, but with no disruption of the surface of the spinal cord; (3) laceration, where there is a clear-cut disruption of the surface anatomy; and (4) massive compression, where the cord is macerated or pulpified to varying degrees. However, despite the differences in anatomic disruption of the spinal cord, these findings carry no significant differences in the consequent histological changes. This disparity is dependent on the different phases of SCI (see below), leading to progressively deteriorating neuronal function [4].

2.1. Pathological changes

Pathological changes following SCI can be divided into two, partially overlapping, phases: primary and secondary [3]. With more thorough analysis, four main phases also have been described: immediate hyperacute, acute, intermediate, and late phases [4]. In the following text, we will discuss these phases with focus on their effects on the neural cells, oligodendrocytes (OL), and oligodendrocytes progenitor cells (OPC), which are the main determinant of regeneration and cellular replacement therapy.

The immediate hyperacute phase is caused by the primary insult of injury, and usually takes place within the first 1–2 h of injury. During this phase, the initial insult, whether it is a contusion, compression, shearing, or stretching of the spinal cord, will lead to disruption of the neural and endothelial tissue. This is associated with hemorrhagic necrosis that is mainly localized in the gray matter and the center of the cord. The localization is due to the high vascularity of the gray matter and the epicentric movement of the injured tissues, which, in turn, places the most damage on the centrally located cells, and the least on the subpial ones. Moreover, at the site of injury, myelinated axons exhibit more pathological injury than unmyelinated ones. This is because the longitudinal force (especially in spinal cord contusion) stretching the fibers is concentrated at the nodes of Ranvier. In many cases, however, no abnormalities are seen following the initial trauma, and most of the consequent changes depend on more insidious, though devastating, secondary injury [3,4].

Following the first 3 h of injury, the secondary phase begins. This phase can be further divided into acute phase (hours to 3 days), intermediate (days to weeks), and late phase (weeks to months) [4]. However, as most of the processes that occur during the secondary injury are interconnecting, we do not prefer the use of this subdivision.

During the secondary injury, expansion of the hemorrhagic sites appears early, and is related to cellular death, which is precipitated, by acute necrosis and subacute apoptosis. Inflammatory response is an important determinant in this process. It starts during the first day of injury, and is initiated by the release of the chemical mediators that attract the early inflammatory cells (i.e. neutrophils) to the site of injury. Neutrophils release inflammatory mediators and free radicals that will exacerbate and accelerate the secondary phase of injury [4]. Necrosis starts as a wave that spreads in centripetal and rostro-caudal directions from the site of primary injury. This necrosis occurs via various mechanisms, including, infarction, excitotoxicity, and reperfusion injury [3,5].

Infarction, which begins during the primary injury phase, occurs early due to disruption of the vascular bed, which, in turn, interrupts the blood perfusion to the neural tissue, and leads to release of toxic digestive proteolytic enzymes. Thereafter, inflammatory changes associated with vasospasm, thrombosis, and neurogenic shock play important role during the secondary phase. The resulted hypoperfusion is associated with inhibition of both oxidative phosphorylation and glycolytic pathways, and leads to loss of energy production and consequent necrosis. *Reperfusion* of the site of injury during this stage will exacerbate cellular death. This is due to reactive oxygen species (ROS) formation from the ischemic endothelial cells. This, added to the ROS produced by the inflammatory cells, will cause direct damage and necrosis to the reperfused cells. *Excitotoxicity* is initiated by the accumulation of the glutamate within the extracellular spaces at the sites of injury. This accumulation is mainly due to defected absorption, excessive release from the damages cells, and exocytosis of the glutamate synaptic vesicles. Glutamate will then lead to over activation of the neural depolarization by activation of the glutamate receptors. Such persistent depolarization will create ionic and osmotic imbalance across the plasma membrane that will cause water influx and consequent lyses. It also leads to excessive calcium influx into the cell and the activation of the auto-destructive calcium-dependent enzymes [3]. Moreover, the release of glutamate and adenosine triphosphate (ATP) at the site of injury will activate the glutamate and P2X7 receptors, respectively, on the OL and OPC. These receptors attract the OL and OPC to the site of injury and cause further cellular loss in similar mechanism as described above [6].

Apoptosis begins as early as 6 h following injury, and spreads in a wave similar to that in necrosis. During the early phase, almost any cell type can be involved. Later on, the OL and myelinated cells are predominantly involved [3]. This programmed cell death occurs due to the secretion of inflammatory mediators and the extravasation of toxic substances following the injury [6]. Some authors, however, deny the presence of apoptosis during SCI in humans [4]. The above-mentioned processes, although extending through the following phases, comprise the main components of the acute phase of the secondary injury.

Over the ensuing days and weeks, more inflammatory cells will invade the site of injury in order to clear the debris and initiate the process of healing via neural fibrosis or gliosis. This starts with accumulation of the myelin and OL debris followed by activation and migration of microglia and macrophages which phagocyte these debris. At this early stage, the phagocytosis may enhance the regenerative process. Moreover, microglia may contribute, via the secretion of various cytokines including IL-1β, Il-6, and TNFα, to facilitate neural protection and regeneration. However, overtime,