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Historical Perspective of Regeneration in Spinal Cord Injury (SCI)

Faiza Ahmed*, Vamsi Garimella[8], Uzoamaka Nwokorie[1], Adnan Choudhry[4], Godsgift Enebong Nya[1,6], Andre Thompson[2], Gertrude O Bassey[3], Fernand Jean- Baptiste[1], Shanthi Potla[5], Rujina Munim[7] and Timothy Fernandez[9]

[1]*Doctor of Medicine Graduate, University of Science, Arts and Technology, Montserrat*

[2]*Doctor of Medicine Graduate, Washington University of Health and Science, Belize*

[3]*Department of Family Medicine, Bon Secours Medical Group, USA*

[4]*Department of Medical Education, Neuroscience Research & Medical Education Program, Canada*

[5]*Medical Student, Avalon University School of Medicine, Curacao*

[6]*John Hopkins Hospital, USA*

[7]*Visitor Consultant, Bentley University, USA*

[8]*Medical Student, Howard University College of Medicine, USA*

[9]*Resident Physician Internal Medicine, Emory University School of Medicine, USA*

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***Corresponding author:** Faiza Ahmed, MD Program, Avalon University School of Medicine, Curacao

Abstract

Spinal cord restoration has inspired thoughtful discussions and gleaned keen insights from the scientific and clinical community at large. Due to the nature of the health complications which are associated with spinal cord injury, spinal cord restoration holds promising potential in significantly improving the quality of life of spinal cord injury sufferers, especially for those who are young. Research has shown that the nerves found in the Peripheral Nervous System (PNS), exclusively those in the exterior side of the brain and in the spinal cord are capable of regeneration. When these PNS cells were embedded in the damaged spinal cord, it improved restructuring the tissue. However, since spinal cord trauma has become a worldwide problem, several specialists and researchers have put a lot of effort into finding solutions. Axonal restoration, electric invigoration, Netrins, and stem cells among other areas have become fields of focus. Therefore, this research work is aimed at determining insightful abilities on how to regenerate the human motor neurons more so in scientific laboratories. Hence, it would provide robust platforms for the discovery of therapeutic objectives and drug verification.

Keywords: Spinal injury; Regenerating the spine; Stem cells; Spine repair; Spinal cord injury (SCI); Spine therapy

Introduction

Injuries of the spinal cord have been reported for many decades. Analysis of American Egyptologist, Edwin Smith, papyrus records reveals that even during ancient times, society acknowledged spinal cord injury as a dangerous health condition and a menace that could not be treated [1]. Indeed, tremendous efforts undertaken by physicians amongst ancient societies have been recorded. However, their effort never yielded any fruitful outcomes as they too believed that such high caliber injuries could not be managed and that if one loses their spinal cord function to any form of injury, the nerve fibers would not operate optimally. Therefore, they believed that the condition would be synonymous with spinal cord failure [2]. In the modern age, scientists are actively exploring novel therapeutic strategies in order to control or even reverse the adverse effects of spinal cord injury. Although this concerted effort may appear to be in its infancy, many scientists such as Theodor Schwann and Santiago Ramon Cajal in the 1830s as well as in the 1890s discovered that the problem which was generally deemed untreatable was indeed curable [3]. In his research, Santiago discovered that there was a possibility of damaged nerve cells, especially those that comprised the peripheral nervous system, to regrow physiologically in mammals [4].These revelations were later reinforced in the early

1990s by the renowned scientist J.F. Tello, who revealed that an injured spinal cord could regenerate but would require constant nourishment. Nevertheless, this research did not pick up until after the Second World War when the discovery of sophisticated antibiotics and enhanced surgical techniques were developed [5].

Upon discovering that spinal cord nerves were capable of rejuvenation, many scientists then steered their research towards understanding how such nerves could be nourished [6]. Led by Rita Levi-Montalcini and Viktor Hamburger, this team of medical practitioners in the 1960s conducted research with the sole aim of discovering what elements made nourishment possible in nerve cells. During their research, they discovered that there was a Nerve Growth Factor (NGF) which made it possible for the damaged nerve cells to regrow. The discovery of NGF preceded that of Brain-Derived Neurotrophic Factor (BDNF) which was put forward by Yves Barde. These scientists also discovered that the growth factors received different responses from different cells. According to these scholars, the main aim of the research was to ensure that they cure the patients and enable them to regain their full operation [7]. Spinal cord injury represents an epidemic which affects millions of people across the world in both developed and developing countries. Current estimates suggest that more than 130,000 people around the world suffer from spinal cord related trauma. Unfortunately, a significant proportion of spinal cord injury sufferers are young and fall under the age of 19 [8]. According to a report released by the International Campaign for Cures of Spinal Cord Injury Paralysis Online (ICCSCIP), spinal cord injury is associated with a bevy of health complications including disability in the form of wheelchair assistance. The effects were evident, stretching from economic aspects to social destabilization. As witnessed in the United States of America, both long term costs and those associated with the social wellbeing of such patients increased drastically, culminating in a staggering $7.7 billion. The situation was found to be similar in Canada and Britain [9].

Discussion

Advances in Research

Based on the immense socio-economic burden wrought by the spinal cord injury epidemic, it was evident that there was a need to conduct more research by the various agencies [10]. This outcome prompted many rigorous studies to be carried out by several medical institutions, individual researchers, and medical practitioners. However, unless thoughtful work and effort are devoted to this issue, such research may still prove unhelpful towards eliminating the problem [11]. It should be noted that some effects of spinal cord injury such as loss of sexual functionality, bladder and bowel infections, loss of breathing capacity, inability to ambulate and cognitive impairment are very serious to the overall well-being of any person [12]. This underscores the importance of focused research that is primarily scoped to discovering viable therapeutic options for patients with spinal cord injuries in order to alleviate their physical disease burden. As illustrated, these new research findings are directed towards discovering the viable therapeutic options for spinal cord problems. Different scientists focused on distinctive areas of concern in an attempt at converging a specific set of conclusions. One of the significant areas where recent research has focused on is axon growth. In early 1988, a renowned physician, Martin Schwab put forward two key factors that hindered the growth of the wounded mammalian spinal cord [13]. Since then, his findings have been buttressed by other discoveries, such as in 2009, where the regeneration of any mammalian spinal cord was found to be triggered by anti-Nogo-A, an antibody that promotes neuronal reorganization and character advancement [14]. During his research, Martin Schwab conducted murine studies in which he observed that after administering the antibody, there was a steady growth [15]. Also, he realized that after using both the antibody IN-1 and the earlier nourishment booster NT-3, there was a vast, unexpected regrowth of the damaged rat nerves [16].

Researchers also observed that amongst the injured spinal cord nerve cells, there was a minor rate of necrosis [17]. This led them to conclude that antibodies not only promoted the regrowth of damaged nerve cells, but also prevented necrosis [17,18] These factors included the NT-3 which is a Neurotrophin, BDNF (brain-derived neurotrophic factor), FGF (Fibroblast Growth Factor) and NGF [16,19]. Following these discoveries, Dr. Ida Black and his coworkers achieved a significant milestone in 2000, when they successfully attempted to make transplantation possible and used it to treat some of the neurological infections. Using NT-3 and BDNF, they were able to prove that such a treatment was possible; hence triggering research extensions in the field [16,19,20]. Apart from the axon being the primary aspect investigated by many researchers, scientists have also shifted concern to investigate how such damaged nerves can grow beyond the injury site to reconnect with other parts of the nerve. Dr. Mark Tessier-Lavigne, for instance, established that proteins such as netrins are essential in rejoining the damaged nerve to the central nervous system [21,22]. In addition, scientists from the Centre for Paralysis Research at the University of Purdue came up with validation points on the use of Polyethylene Glycol (PEG) in guinea pigs to facilitate the immediate restoration of nerve functionality, especially at the membrane [23]. During this process, the team realized that the fibroblast, which is the cell outside the skin covering the spinal cord, helped to produce neurotrophin-3, which facilitates the proper healing of damaged nerves. According to Dr. Marion Murray from the University of MCP Hahnemann, this was the reason why rats that were used as test subjects due to their ability to regenerate faster [21,24]. However, apart from the use of proteins, the research team from Purdue University also concluded that electrical invigoration could be used as one of the methods for nerve rejoining [25]. During their study, they planted a tiny battery pack around a small dog, and after some days, they realized that the dog's damaged nerve had rejoined [26]. Despite the heavy work done on the axon and protein front,

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researchers have developed interests in many potential target-areas for cure of the spinal cord. In recent years, some of the emerging areas include neuroprotection, which focused mainly on methylprednisolone, glutamate (AMPA) Receptor Blockers, and 4-Aminopyridine, among others [27]. These are the clinical aspects that were also aligned towards improving the time taken for the healing processes of the damaged tissues [28]. Even though the methodologies were proven to be effective, it was recommended that further research was required before such drugs could be administered to human beings as all the tests were carried out using animals. To be precise, its effectiveness on human anatomy was not validated [29].

Role of Stem Cells

In 1994, Fred Gage made a significant discovery. He proposed that the human skin cells could produce growth factors and neurotransmitters, which subsequently trigger spinal cord sensory cells which in turn stimulate regeneration [30]. This hypothesis developed by Fred Gage was re-emphasized by Lars Olson from the Institute of Karolinska. Together, they supported this hypothesis with observations made from studies conducted on rats. However, they recommended that such results would be realistic if conducted with a larger sample [31]. From the research analysis, it is clear that most researchers were only focused on why spinal cord regeneration was impossible. The researchers failed to investigate the aspect from a broader perspective. To be precise, they failed to establish and evaluate the core reasons that triggered the difficulties in rejoining the nerves after injuries [32]. This was what prompted the 2000 research which revealed that in any damaged tissue, there is more protein fibrinogen which in most cases prevents clotting, thus hindering proper healing [33,34]. This unique finding led to the use of enzymes in the treatment of such illness. This discovery is regarded as one of the significant breakthroughs in the rehabilitation of human health but requires further testing [35].

Conclusion

Even though many studies are still on-going, the notion that spinal cord illnesses are incurable is no longer accurate (refer to Figure 1). Figure 1 lists all the cell types that are utilized as therapy for SCI patients with references associated with each variety of cells. To sum up, cellular therapies in combination with different regeneration approaches are the new promising solution to SCI problems. In the past, most spinal cord injuries were permanent and negatively impacted upon their individual personal development through financial and social constraints [36-45]. This revolutionary discovery paves path forward to restore function in SCI patients after traumatic injury. Therefore, people are advised that even if there has been tremendous progress in the development of curative measures for the spinal cord epidemic, there is a pressing need for therapy to prevent the deleterious sequelae of spinal cord injury and other associated negative health outcomes [37,46-56].

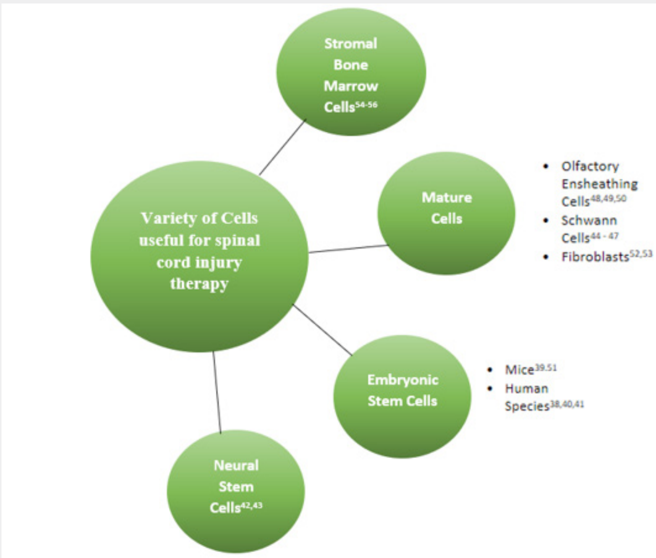

Figure 1: Different types of cells that are useful as therapy in SCI patients.

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