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REVIEW ARTICLE

Nanotechnology in Spinal Cord Injury: A New Hope for Overcoming Barriers to Treatment

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ABSTRACT

Incidence of spinal cord injury (SCI) is on the rise affecting the young strata of the society leading to permanent disability in majority of cases with limited treatment to offer. Treatment of SCI has many challenges due to the complex blood spinal cord barrier (BSCB). Nanotechnology presents a substantial solution in neuroprotective treatment by enabling targeted delivery of drugs to the site of injury by overcoming BSCB. Nanofiber scaffolds which are built of biodegradable nanofibers forms structural support for injured spinal cord, guiding and supporting cell growth thereby favoring neural regeneration. Common concerns with nanotechnology include the health hazards due to the difficult degradation and immunomodulation. The lack of proper clinical trials and the lack of centralized monitoring agency are the serious ethical concerns regarding nanotechnology. Nanotechnology is still a developing field and it is unclear exactly what effects it will have on the body or the environment. This fact leads to the greater regulation imposed on nanotechnology, making the process of drug development even more expensive and time consuming. Application of nanotechnology in stem cell research and nanorobotics are promising future research that can revolutionize the treatment strategies in SCI.

Keywords: Barrier, Nanotechnology, Regeneration, Spinal cord.

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INTRODUCTION

The incidence as well as the prevalence of spinal injuries has been on the rise. Every year about 2.5 to 5 lakhs of people suffer from spinal cord injuries (SCI) due to various causes around the world.[1] Spinal cord injury tragically often affects the youngest and the most active segment of our society, with 60% of injuries occurring in those under the age of 30 years. The most common cause, making up greater than 40% of SCI, is road traffic accidents.[2] Spinal cord injury often leads to permanent disability and may render a person dependent on caregivers.

Treatment of SCI poses substantial challenges due to difficulty in targeted drug delivery by overcoming blood spinal cord barrier (BSCB) and due to complexities of post injury cellular environment that complicates the process of neural regeneration.

Nanotechnology presents a substantial solution for the above problem. Recent years have seen an explosion in the number of studies showing the role of nanotechnology in neuroprotection and neuroregeneration.[3]

The concept of nanotechnology was presented in 1959 by Dr Richard P Feynman. The word nano is derived from the Greek word for dwarf. The term 'Nanotechnology' had been coined by Norio Taniguchi in 1974.[4] Nanotechnology is defined as the science that deals with design, synthesis, characterization and application of nano materials which are extremely small particles whose functional organization in at least one dimension is on the nanometer scale (one-billionth of a meter).[5] Nano carriers has enabled targeted delivery of neuroprotective drugs to the site of injury.[6] Nanoparticle scaffolds have been developed which aid in neuroregeneration.[6]

In this review, the role of nanotechnology is discussed in the context of SCI emphasizing its multifunctional capabilities in neuroprotection and neuroregeneration. The safety and ethical issues along with its feasibility in a developing country like India is also discussed.

PATHOPHYSIOLOGY OF SPINAL CORD INJURY

Primary injury of spinal cord involves initial trauma and local tissue injury due to stretching, laceration and compression of the spinal cord. Primary injury mainly damages the gray matter of the spinal cord.[7]

The secondary injury denotes the spread of damage from the original injury site to the adjacent tissue through a cascade of deleterious reactions.[8] The extent of secondary injury is directly proportional to the magnitude of primary injury. The cause of secondary injury includes ischemia due to vascular thrombosis resulting in oxidative damage leading to disruption of cell membrane.[8]

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CHALLENGES IN TREATMENT OF SPINAL CORD INJURY

The BSCB poses special challenges of its own. The endothelial cells that line the capillaries form tight junctions that prevents most drugs from entering the spinal cord parenchyma.[9]

Neuroprotective agents act by preventing the spread of secondary injury.[10,11] Some neuroprotective therapies include antibodies against a cell adhesion molecule present on immune cells,[12] erythropoietin, minocycline[13] and steroids like methylprednisolone.[14] The efficacy of these methods has not been proven so far. Because of the BSCB, neuroprotective therapy faces difficulties in delivering therapeutic agents effectively.

Currently, the drug used to treat SCI is a large dose of methylprednisolone (MP) (30 mg/kg intravenously for the first hour then 5.4 mg/kg/hr for next 23 hours) which is effective only if administered within the first 8 hours of injury. The efficacy of MP treatment is highly controversial.[15-18] In order for drugs like MP to reach therapeutic levels at the injury site, an extremely high systemic dose is required which can result in serious systemic side effects.[19]

To combat these shortcomings, local delivery methods like bolus injection into the intrathecal space and osmotic minipumps had been developed. These methods disrupt the tissue and prevent recovery of the BSCB after injury.[20] Osmotic minipumps faced additional challenges like blockage and infection, which eventually made its use obsolete.[20]

Regenerative therapy focuses on regaining neural circuitry and functionality in the damaged nervous tissue. Regeneration must overcome both intrinsic (lack of intrinsic capacity to regenerate) and extrinsic (glial scarring and production of inhibitory factors) environmental challenges.[21]

The advent of nanomedicine may provide new tools for tackling these problems.

NANOMEDICINE: HOPE FOR OVERCOMING BARRIERS TO TREATMENT

Nanotechnology may be considered a solution to most of the challenges in the neuroprotective and regenerative therapies in SCI.

Nanomaterials can be used as carriers which can cross BSCB because of small size and have the potential to increase the bioavailability of neuroprotective drugs through targeted delivery.[22] The large surface area to mass ratio of nanocarriers allows drugs to be bonded to the surface. Nanocarriers also have the ability to self-assemble and scavenge reactive oxygen species.[23]

Nanomaterials can also aid regeneration by providing a growth permissive environment. This is by blocking inhibitory factors, promoting neurotrophic factors and circumventing glial scarring.[24-28] Scaffolds composed of nanomaterials can mimic the natural cell environment and influence cellular growth and differentiation.[26]

Although, nanomedicine is an upcoming field, great progress has already been made in both neuroprotection and neuroregeneration, as highlighted in the following sections.

COMPOSITION OF NANOPARTICLES

Nanoparticles (NPs) are synthesized using a wide range of materials, including metals (e.g. gold, silver, cadmium), metal oxides (iron oxide, titanium oxide, zinc oxide), silica, polymers, and biological molecules (peptides and DNA).[29]

Recently, NPs are made of a mixture of the above materials. This is achieved by making one layer at a time, called layer-by-layer synthesis.[30] Each layer changes the characteristics and adds functionality making the NP programmable. Such multifunctional NPs become a unique nanomedical system for treating SCI.

NANOMEDICINE STRATEGIES FOR NEUROPROTECTION

Titanium nanowires: Nanowires have been applied in SCI with limited success although there have been several recent studies.[31]

- *Studies: In vitro* study by Sharma et al[23] found that innocuous titanium nanowires were able to improve the efficacy of neuroprotective compounds to which they are attached.
- *Animal study:* In an *in vivo* dorsal horn incision rat model of SCI, the nanowired compounds were locally applied to the injury site. The nanowired compounds performed significantly better than the unwired compounds.[31] Structural framework of nanofiber is shown in Figure 1.

Nanoparticles: The most extensively tested NPs for drug delivery to the spinal cord have been polymeric NPs and silica NPs. Nanoparticles can be coated or functionalized with targeting peptides to improve delivery efficacy.[32]

Polymeric NPs are typically solid and biodegradable, which allows drugs to be chemically linked to the particle through surface modifications.[32]

Animal Studies

- Kim et al[32] investigated polylactic glycolic acid (PLGA) NPs loaded with MP for local delivery in an *in vivo* dorsal hemisection rat model of SCI. Methylprednisolone loaded NPs were compared to equivalent

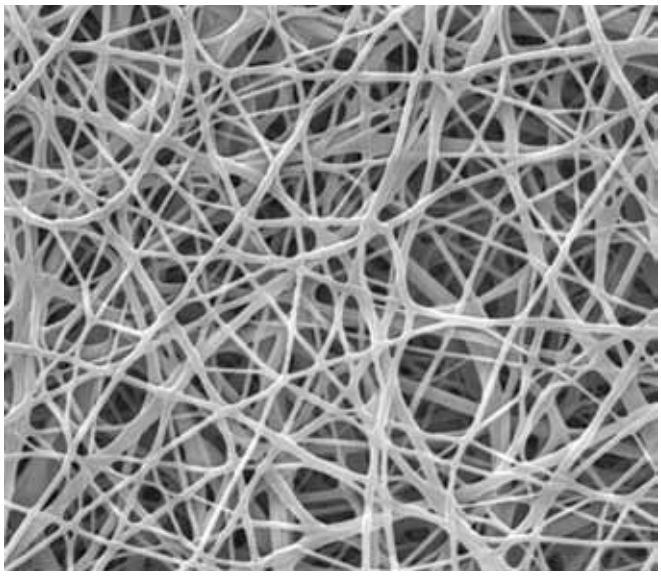

Fig. 1: Structural framework of nanofiber 5000× magnification (*courtesy:* url:www.elmarco.com)

local dose of methylprednisolone. Methylprednisolone-nanoparticles (MP-NP) treated rats recovered earlier than controls.[32]

- Monosialotetrahexosylganglioside (GM-1), which can re-establish function of the damaged central nervous system (CNS),[33] was loaded into the NPs and were tested in a complete transection rat model of SCI. The NPs were applied, and their efficacy was evaluated later using immunohistochemistry methods. Rats treated with GM-1 loaded NPs demonstrated significant histological recovery. Control animals showed no evidence of regeneration.

Silica NPs (SiNPs), which have been demonstrated to be non-toxic *in vivo*, also have been studied in depth for treatment of SCI.

In Vivo Animal Study

Cho et al demonstrated the effectiveness of polyethylene glycol decorated SiNP in *ex vivo* and *in vivo* contusion guinea pig models of SCI.[30]

In Vitro Study

Cho et al also demonstrated the efficacy of hydralazine loaded mesoporous silica NPs functionalized with polyethylene glycol (PEG) in an *in vitro* acrolein challenged neuron cell model.[30] Acrolein is produced during secondary injury as a byproduct of lipid peroxidation and is toxic to spinal tissue.[34]

OTHER NANOPARTICLES

Autocatalytic nanoceria particles[35] are neuroprotective NPs under evaluation which have the ability to harvest reactive oxygen species and undergo catalytic oxidative recovery.

CARBON-BASED NANOMATERIALS

Fullerenes are carbon based NPS which can scavenge more than one free-radical per molecule.[36]

Carbon nanotube is another carbon-based nanomaterial having extraordinary strengths and unique electrical properties. *In vitro* studies showed that they can promote neuritic outgrowths in cell culture.[37] Structure of carbon nanotubes is shown in Figure 2.

NANOMEDICINE STRATEGIES FOR NEURAL REGENERATION

Regeneration of the CNS neurons is more difficult for several reasons. In the CNS, oligodendrocytes forms a smaller proportion compared to Schwann cells in the peripheral nervous system. When oligodendrocytes are damaged axons are affected due to reduced support for regeneration. Degraded myelin also contains growth inhibitors.[33] Cyst and glial scar formation provide significant physical and chemical barriers to regeneration.[38]

The goal in neural regeneration is to provide an environment that is permissive for axonal growth, by promoting neurotrophic factors and by blocking inhibitory factors with drugs.

Several different nanomaterial approaches for neuroregeneration have been explored like nanofiber scaffolds, nanofiber conduits and self-assembled peptide systems and combined approaches.[39]

NANOFIBER SCAFFOLDS

Nanoscaffolds are very small structural complexes built of biodegradable fibers. To bridge the physiological gap caused by injury, scaffolds can be incorporated into the damaged portion of the spinal cord. This can be done either through surgical implantation, or through injection in the case of self-assembling scaffold and hydrogels.[40] Scaffolds provide not only a structural support for the damaged

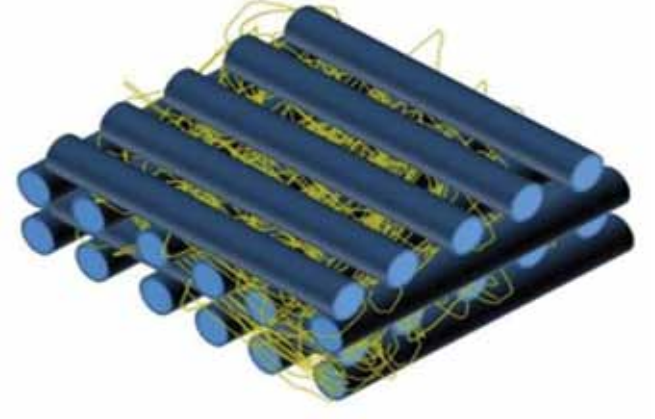

Fig. 2: Hybrid structure of nanofiber scaffolds showing electrospun membrane made of plotted microfibers arranged in three layers with nanofibers entangled in between (*courtesy:* url:www.electrospin)

spinal cord but also a physical surface for regeneration.[39] The nerve cells will attach to scaffoldings by interweaving in between openings. Stem cells attached to scaffolding are shown to be more successful in adapting to their environment. Electrospun nanofiber scaffolds are shown in Figure 2.

STUDIES

In Vitro Study

Ahmed et al[41] attached neurite outgrowth promoting tenascin-C-derived peptides to electrospun polyamide nanofiber scaffolds. They demonstrated that neural cells cultured on the functionalized scaffold had more neuronal attachments, and greater neurite extension.[41]

CONDUITS

Nanofibrous conduits can be formed via electrospinning and have been used for peripheral nerve regeneration. Electrospun nanofibrous conduit is shown in Figure 3.

ANIMAL STUDIES

In one recent study, polycaprolactone nanofibrous conduits were able to close a 15 mm gap in a rat sciatic nerve model.[42]

Liu et al[43] implanted tubular conduits made from electrospun collagen nanofibers in a rat hemisection model of SCI. They found that despite the success of collagen and nanofibrous conduits in peripheral nerve regeneration, nanoscale conduits have been less successful in repairing SCI.

SELF-ASSEMBLING SYSTEMS

Self-assembling peptide systems are synthetic amino acid-based systems that transits from a solution to a gel, within seconds.[44] The gels are generally biocompatible and non-cytotoxic. The gels can also safely encapsulate drugs for combination therapies.[44] Self-assembling peptide amphiphiles have also been successfully tested *in vitro* and *in vivo*.[44]

Fig. 3: Nanofiber conduit

COMBINATION OF SELF-ASSEMBLING AND SCAFFOLDING SYSTEMS

In order to utilize the benefits of both self-assembling systems and scaffolding, combination approaches have also been developed.

STUDIES

Gelain et al[45] developed composite guidance channels constructed from electrospun PLGA based nanofibers filled with RADA16-7-BMHP1 is a pepetide (one that is given in bracket is secondary structure of protein) self-assembling peptides to tackle the challenges of chronic SCI.[46]

IN VIVO STUDIES UTILIZING DRUGS COMMONLY USED FOR SPINAL CORD INJURY

Steroids

Because MP is already used to treat SCI, various groups have attempted to improve its local delivery with the goal of circumventing its side effects and improving efficacy.

Studies

An early study used PLGA based NPs and observed 65% encapsulation efficiency with steroids.[47]

Another study showed improvements in the size of injury when treated with MP loaded NP compared to MP alone *in vivo* study.[32]

Another group used smaller (~109 nm) carboxymethyl chitosan/polyamidoamine dendrimer NPs and were able to observe sustained release of steroids for 14 days.[48]

Targeting Acrolein

Some researchers have focused particularly on massively destructive aldehydes, such as acrolein which is a toxic substance released during secondary SCI. Cho et al synthesized silica NPs to deliver hydralazine to healthy cells that had been exposed to acrolein thus neutralizing its toxicity.[30]

COMMON CONCERNS WITH NANOTECHNOLOGY AND OBSTACLES FOR CLINICAL TRANSLATION

Health Hazards

Although nanotechnology has been found beneficial for mankind, there are safety concerns related to its applications. Nanoparticles are very difficult to degrade.[49] They

interact with immune system at various levels.[50] Nanoparticles also activate complement.[49] Nanoparticles may aggregate together to form larger particles and invade cells which alter physiological properties and chemical reactivity.[51]

Lack of Proper Clinical Trials

Nanotechnology is a novel scientific application. There is scarcity of literature and researches regarding the safety of nanotechnology. Lack of standardization of nanomaterials pose another barrier for undertaking nano-based trials.[52] But when technology advances, knowledge and communication about its safety need to be emphazised for undertaking clinical trials in human subjects. Till now only phase 1 trial has been initiated.[52] Many *in vitro* studies are not following any clinical correlation.[52]

Lack of Proper Monitoring

Another safety concerns with nanotechnology is the lack of a centralized monitoring agency. A major challenge in this area is comparing treatment results. Comparison of treatments across laboratories are difficult due to different injury models, treatment schedules and dosing schemes.[53] For example, prognosis following a contusion injury and a transection injury are very different, and subsequently, recovery looks different for these models. Treatment given at different postinjury time points will have different effects. At this early investigative stage, most studies apply the drug at only one point of time in the post-traumatic phase, in one dosing scheme, and in one animal injury model; a limitation which perhaps confounds effects.[53]

Ethics

As the science and technology of nanomedicine speed ahead, ethics, policies, and the law struggle to catch up. At present, the most significant concern involve risk assessment, risk management of engineered nanomaterials and risk communication in clinical trials. Though *in vivo* animal experiments and *ex vivo* laboratory analyses can increase our understanding of the interaction of engineered nanomaterials in biological systems, they cannot eliminate all of the uncertainties that surround the exposure of a human subject to nanomedicine products in clinical trials.[52] Significant risks can still emerge after a product has cleared the phase I hurdle and is in the phase II or III clinical trial.[49]

Cost

Developing nanotechnology requires even more specialized equipment and a greater level of precision than developing most other drugs, leading to larger costs and longer development timelines. Nanotechnology is still a developing field and it is unclear exactly what effects it will have on the body or the environment. This fact leads to the greater regulation imposed on nanotechnology by the food and drug administration (FDA), making the process of drug development even more expensive and time consuming.

Nanotechnology in India

Indian Institute of Technology, Mumbai, is the premier organization in India in the field of nanotechnology. Government of India launched the Nano Science and Technology Initiative (NSTI) in 2001. In 2007, the Nano Science and Technology Mission 2007 was initiated with an allocation of Rupees 1000 crores for a period of 5 years. This was an umbrella program for capacity building and building international collaborations. The objective was basic research promotion for young scientists, human resources development and infrastructure development. Now 11 core groups have been sanctioned across the country for nanomedicine research. Newer projects and proposals are undertaken yearly. An International Workshop NANO-15 is being planned by Center for Nano Science and Technology, Tamil Nadu in December 2015 to give insight among the medical fraternity about the benefits of nanotechnology.

Nanotechnology in Stem Cell Research

Applications of nanotechnology in regenerative medicine has begun to revolutionize several areas of stem cell research also. Magnetic NPs can be used for *in vivo* stem cell tracking. Stem cell durability can be increased with nanoscaffoldings. Genetic manipulation of stem cells can also be done using nanomaterials.[54]

FUTURE RESEARCH

Nanorobots

Nanorobots[55] are theoretical microscopic devices which can be programmed for targeted drug delivery. They have the capacity to work together and are also capable of replication using environmental resources. Nanorobots are now only in research and development phase, but some molecular machines and nanomotors have been tested *in vitro*. When hypothetical stage is surpassed to clinical setting, it is believed that they can be programmed to work at atomic, molecular and cellular level. It is believed that because of its nanosize, they can easily traverse the human vasculature.[55] Super smooth surface and diamond exterior will lessen the likelihood of triggering immune response.[55] Glucose and oxygen can be used as a source of energy for its forward propulsion *in vivo*.[55] The development of nucleic acid robots (origami robots) hold

Fig. 4: Artist depiction of nanorobots in action traversing the blood stream (*courtesy:* www.nano-man.co.uk)

tremendous promise for future. Artists depiction of nanorobots in blood stream is shown in Figure 4.

CONCLUSION

The treatment of SCI is complicated by a number of factors like BSCB and the complexities of cellular environment for nerve regeneration. Nanotechnology addresses these issues. Nanocarriers have enabled targeted delivery of chemotherapeutics. Nanorobots are theoretical microscopic devices which can be programmed for targeted drug delivery. With regard to neuroregeneration, nanoscale scaffolds have successfully guided the rewiring of nerves with associated functional recovery in animal models. Applications of nanotechnology in regenerative medicine have revolutionized several areas of stem cell research. Unfortunately, there are few promising clinical studies to translate this novel idea into clinics, benefitting patients.

Scientists need to work hard in convincing government agencies, the pharmaceutical industry, and the public, regarding the benefits as well as the toxicity of nanotechnology. Large multi center trials may be undertaken to assess the actual benefit of this novel technique so that its benefit can be applied in patient care.

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