After major discoveries she made two decades ago, neuroscientist Dr Nurit Kalderon explains how well-established clinical procedures can be adapted to treat debilitating spinal cord injury.

Could you provide an overview of your work on the cellular responses and mechanisms following injury to the spinal cord?

Spinal cord injury (SCI) results structurally in permanent damage and chronic tissue decay at the trauma site and in destruction of the brain-spinal cord fibre connectivity, leading to paralysis below the lesion site. The severed brain-to-cord fibres fail to cross the widening wound gap, and brain motor control below the lesion site becomes permanently impaired.

My research approach is focused on the pathology and chronic decay, assuming that preventing the pathology would also enable the regrowth of spinal cord fibre. The funded research project was based on my fundamental discovery that the spinal cord is able to repair itself in the early days after injury but is thwarted in its efforts during the second or third week post-injury.

Which components are critical in inducing the chronic decay?

Using my discovery, we developed an effective procedure to treat SCI in laboratory animals based on the simple principle that if one specifically targets and eliminates these intrusive cells — applying clinical radiation therapy as commonly used to eliminate tumour cells — one can allow the natural injury repair processes to proceed to completion as they function in any other tissue.

Injury to the blood vessels and the related broken neurovascular barrier (ie. cord blood barrier) plays a critical role in the irreversible pathology. Identifying these cells and understanding their action/function and how the inherent repair is aborted at the compromised neurovascular barrier is the main objective of the research.

How does radiation therapy promote this recovery?

Radiotherapy is a life-saving clinical modality used specifically to eradicate solid tumours. Ionising irradiation at the appropriate dosage levels selectively kills dividing cells and causes minimal damage to the resting, nondividing cells. Generally speaking, since specifically timed cell elimination enables the natural repair process to take its normal course, this implies that radiotherapy eliminates some cells that are generated in response to injury and which presumably interfere with the natural repair process.

In more recent studies, our data suggest that radiation therapy prevents hypervascularisation and the target is probably the dividing blood vessel cells (endothelial cells), thereby leading to the repair of the neurovascular barrier.

Could you discuss how your work has advanced existing preclinical research on SCI repair?

There are several aspects of my work which have significantly advanced and opened novel areas of research into developing a treatment for SCI using conventional clinical procedures. First and foremost, my research has established that, contrary to the common belief among researchers, spinal cord tissue has a complete repertoire of wound repair machineries which proceed normally, at least in the first week after injury. The repair process is halted and chronic inflammation is triggered during the second to third week post-injury, presumably by the hypervascularisation. Next, my work demonstrated it is possible to enable the normal wound repair processes to proceed, including neuronal regrowth beyond the lesion site, by timed cell-elimination.

Further, being enclosed within a bony structure, brain and spinal cord injuries entail severe consequences of haemorrhaging and built-in pressure, both of which can lead to severe secondary damage. My research established that in crush/fracture injuries, tissue decay is exacerbated by the secondary damage caused by massive swelling as fluids build up from the injured blood vessels, therefore to obtain any repair, it is essential to remove the fluid within the first day post-injury.

What challenges have you faced during your research? How have these been overcome?

The main challenge, which still has not been overcome, is not having other investigators reproduce my studies. In 2003, the National Institute of Neurological Disorders and Stroke (NINDS) launched a new programme called Facilities of Research Excellence in SCI. This programme provided funding via contracts to carry out independent replication of published studies reporting experimental interventions that reduce secondary injury, improve recovery or enhance axon regeneration after SCI. Of the three centres that received these funds none attempted to reproduce any of the data published by my laboratory.

Innate repair in injured cord

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Restoring innate repair and building up the nerve

Exciting discoveries are changing the prevalent attitudes toward the irreversibility of spinal cord injury. Recent studies conducted by Dr Nurit Kalderon have led to a combination therapy that could eventually put an end to the permanence of paralysis.

THE NERVE FIBERS that pass between the brain and the spinal cord are generally perceived within the medical community to be unrepairable following trauma. Consequently, spinal cord injury (SCI) – most often seen in vehicular and sporting accidents or sustained combat injuries – results in lifelong paralysis as current available treatments such as surgery and drugs can only reduce further secondary tissue damage.

Recent advances in understanding of injuries to the central nervous system – brain and spinal cord – have widened consensus within the scientific community that SCI no longer represents an insuperable challenge but is rather a neurological dysfunction receptive to existing therapies. Following Dr Nurit Kalderon’s breakthrough research conducted almost 20 years ago, it is now known that spinal cord tissue is imbued – like other tissues – with the innate capacity for self-repair. However, the repair is halted by some cells that are generated at end of the second week after injury, leading to a permanent wound gap. Through a combination of several conventional clinical procedures: radiation therapy to destroy harmful cells, and microsurgery to drain excess fluids, it is hoped that patients with SCI may soon benefit from a treatment that is simple, effective and inexpensive.

Results of an ongoing study, led by Kalderon, – a neuroscientist formerly engaged at The Rockefeller University and Memorial Sloane-Kettering Cancer Centre (MSKCC) in New York – suggest a potential treatment for SCI that makes use of radiotherapy to unlock the inherent wound repair mechanism, leading to the regrowth of the severed brain fibers across the damaged region of the cord. This work was funded by the US National Institutes of Health (NIH) and has benefited from the collaborative efforts of Dr Zvi Fuks at MSKCC and Dr V Reggie Edgerton at the University of California, Los Angeles.

DECIPHERING WOUND REPAIR

Injury to the blood vessels and the related broken neurovascular interface play a critical role in SCI pathology. A major characteristic of SCI is the formation of a glial scar, the accumulation of layers of reactive astrocytes at the damage site. Opinion is divided over the role of these reactive astrocytes in SCI; Kalderon initially maintained that it interferes with the repair of the injured neurovascular barrier. In the pilot study that tested this hypothesis, it was demonstrated that the glial scar can be effectively reduced/eliminated when radiation is applied during the third week post-injury. In more recent studies, the data suggest that radiation therapy prevents hypervascularisation by targeting the dividing endothelial cell, and elimination of the glial scar is secondary to the repair of the neurovascular barrier.

Aimed at enabling victims of SCI to regain at least some of their former physical abilities, Kalderon’s research encompasses two primary objectives. The first is to prevent the pathology and obtain an optimised wound repair that would consequently re-establish connectivity between the brain and the spinal cord by providing the required terrain for the regrowth of the brain nerve fibres beyond the trauma site. The second objective is to achieve neurorehabilitation by training the patient for stepping and weight support, which is known to manipulate the local spinal cord circuitry thereby restoring, to a certain extent, the patient’s capacity for voluntary motor control. Though full recovery of motor control is not expected, the prospect of having limited physical ability instead of paralysis is a life-changing concept.

ADAPTED THERAPY

The hallmark of spinal cord injury is progressive tissue decay at the damage site. In earlier research on rats with severed cords, Kalderon was able to show that wound-localised radiation therapy, administered during the third week following injury facilitated healing by eliminating the cells that interfere with its natural repair processes. Once the wound healed, the severed nerve fibres could grow across the lesion site, restoring the connection between the brain and the spinal cord and, consequently, voluntary muscle function. Thus, Kalderon’s research established a connection between the body’s ability to repair the wounded cord and recovery of motor function.

Fractionated radiation therapy, as used clinically in cancer treatment, involves repetitive daily doses of irradiation at the range of 2-4 gray units, usually given over a course of several weeks. Experiments are conducted to identify the parameters of optimal radiation protocols in SCI therapy. The optimal timing after injury at which radiation therapy should be started has
improvements that were significant for standing and stepping capacity, and yielded a significant direct correlation between standing and stepping performance. In contrast, the training in the unirradiated group resulted in no apparent beneficial effects and yielded an inverse correlation between standing and stepping performance, eg. subject with good standing showed poor stepping capacity. “Most importantly, for restoring beneficial motor function following radiotherapy, training seems to be crucial,” summarises Kalderon.

CLINICAL ANIMAL TRIALS

For individuals suffering from SCI crush, Kalderon’s tripartite treatment programme of micro-incision, radiotherapy and training sessions could mean a whole new lease of life for those otherwise facing indefinite paralysis. In order to validate this combination treatment programme it is essential to see how it is tolerated by real life patients, particularly the micro-incision procedure to remove the fluid. Hence, before human trials can begin, injured animal testing is needed in a real life setting – a canine-feline veterinary hospital – to include any confounding variables that a non-controlled environment brings. In reality, SCI is often accompanied by injury to other vital organs that affect the entire clinical picture. In addition to this, the varying timescales in which the injured animals are brought to the veterinary hospital adds a vital random element to the trial process – a varying factor that is also consistent with human injury – which would be useful for further determining the best time to carry out the micro-incision procedure and its associated feasibility. Once funds are raised, animal trials will start, in collaboration with Dr Humberto Cerrel Bazo at a veterinary hospital in Naples, Italy.

Kalderon’s work shows that SCI is increasingly becoming less of an absolute. Though members of the scientific community may be wary of radiotherapy, these studies illustrate how well established and conventional clinical procedures can be utilised firmly within the boundaries of existing safety protocols. Though clinical trials with human patients currently remain a distant goal, Kalderon’s breakthroughs in SCI treatment have brought the reality of a cure considerably closer.