Peripheral nerve injuries (PNI) are common following blunt or penetrating trauma and can lead to disability and chronic pain in affected individuals, with limited options available to promote regeneration and functional recovery. From an animal model, it is known that the regenerative capacity of the peripheral nervous system (PNS) is heavily dependent upon the remarkable ability of Schwann cells to undergo a phenotypic shift from a supportive/myelinating/maintaining phenotype to one that encourages neural regeneration. In rodents, a great deal is known about the molecular signals that control this process or mark to the cells and cellular changes involved (Boerboom et al., 2017; Jessen and Mirsky, 2019). Effective translation of the wealth of animal model data into a human paradigm of nerve injury would be of great benefit in the development of improved clinical treatments. However, progress has been limited by ethical and practical challenges associated with studying human nerve injury (Hewitt et al., 2008; Wilcox et al., 2019). Moreover, the intricate anatomy and diverse range of injuries make PNI a heterogeneous pathology to study. To address this issue, in our recent article entitled Characterizing cellular and molecular features of human peripheral nerve degeneration, we analyzed nerve tissue retrieved from patients undergoing reconstructive nerve procedures (Wilcox et al., 2020). Since the patients had a range of differing time intervals between injury and surgery, it was possible to construct an impression of the phenotypic changes of Schwann cells within a population over acute and chronic time points of denervation. The findings reveal novel information about the cellular and molecular features that underpin human nerve degeneration. The patterns of changes seen in the human nerve samples were similar to those previously reported in rodent models of neural degeneration. Schwann cells adopted a repair phenotype in acutely injured nerve samples which faded over time with chronic denervation. This finding may assist clinicians to optimize the timing of surgical nerve repair, to understand how phenotypic adaptations and similarities in the cellular and molecular responses seen following injury. In an attempt to start to address this we explored the presence of four biomarkers, associated with changes in rodent Schwann cell phenotype, in human tissue obtained from patients following nerve injury (Wilcox et al., 2020). These included the transcription factor c-Jun which is a pivotal mediator of the Schwann cell phenotypic shift (Arthur-Farraj et al., 2012), the neurotrophin receptor p75NRTR which is upregulated in repair Schwann cells, the transcription factor EGR2 which is associated with myelination and the pan-Schwann cell marker SOX10.

Human nerve tissue samples are challenging to obtain since most nerve repair procedures focus on preserving tissue during surgery and repairing nerves as soon as possible after damage. Our study capitalized on an opportunity to obtain acutely and chronically denervated tissue from patients undergoing nerve transfer procedures, in which excess tissue (which would normally be disposed of) was used for histological and gene expression analysis. For gene expression analysis using real-time quantitative polymerase chain reaction, we first needed to develop a protocol that enabled sufficient yields of mRNA to be extracted, which requires rapid processing and careful avoidance of degradation of the reagents used in the operating theater (Wilcox et al., 2019). Rather than being a problematic uncontrollable variable, the heterogeneity in the duration of denervation experienced by the individuals in the study provided a way to start to understand the time course of changes in the biomarkers.

The hypothesis for the study was that characteristic changes in Schwann cells, specifically expression of c-Jun, p75NRTR, EGR2 and SOX10, identified in rodent studies would also be present in denervated human nerves, and regulated after injury in a similar way to that seen in rodents. The study showed that markers associated with repair Schwann cells in rodents, c-Jun and p75NRTR were upregulated in acutely injured human nerves and then declined during long term denervation. There were also changes in Schwann cell markers in acutely denervated human nerves, with increased Schwann cell density in acutely denervated tissue which then reduced in chronic denervation. These changes mirror the pattern seen in rodents, suggesting that basic molecular features associated with regeneration are conserved between these species. The timing for phenotypic changes in the Schwann cells of human nerve tissue appeared to follow a pattern whereby the initial switch to repair phenotype was detected at the earliest time points explored (4–50 days), then declined after 100 days (Figure 1). This decline is a significant reason for regeneration failure, and is also seen in rodents where it has been characterized in some detail. Repair cells do, however, appear to deteriorate rather faster in humans than in rodents that are used to study regeneration. This indicates that by 100 days there is already a substantial reduction in expression of c-Jun, p75NRTR and trophic factors such as brain-derived neurotrophic factor and glial cell line-derived neurotrophic factor, cell numbers and regenerative support.

The use of surplus human tissue samples from a relatively small yet diverse patient population.
can only provide limited information, but this study helps to bridge between laboratory models and nerve injury in humans. The predicted clinical time frame for optimal functional recovery following nerve injury and repair in humans has largely been based on knowledge about what happens in denervated muscles, which have been shown to require sufficient reinnervation within 1 year. Our study indicates that the capacity to support regeneration of denervated nerve tissue distal to an injury may reduce over a considerably shorter time frame. Understanding this process, and assessment of individual variation in this, will guide clinical decision making between repair or reconstructive options for nerve injury. It will allow stratification of associated implications and risks versus likely mean outcome and allow greater patient education and shared decision making.

In addition to helping extrapolate findings from basic scientific animal studies towards application in human medicine, studies such as this help inform the direction of laboratory-based translational research. This is important to consider. New technologies emerging from the field of regenerative medicine have the potential to revolutionize treatment options for nerve injury, but there is a long history of potential new treatments that are effective in animal models failing to benefit patients (Standing, 2020). Increased understanding about how the distal nerve segment can provide regeneration support, and how this declines over time, presents researchers with an exciting array of new opportunities for therapeutic interventions. Such interventions are inevitably developed and tested in the well-established in vitro and in vivo research models that have proved fruitful in revealing details of nerve biology. However, for new approaches to translate into useful treatments they need to work effectively in humans, so studies which help to identify similarities and differences between rodent and human responses to nerve injury are an important contribution.

The study we report focuses on a small number of markers of Schwann cell phenotype and does not correlate this with functional recovery. It would be interesting in future studies to explore exactly how the duration of denervation and consequent changes in Schwann cell phenotype in the distal nerve influences motor and sensory recovery in patients. It would also be valuable to explore additional changes in human Schwann cells to understand the similarities and differences compared with rodents, e.g. by transcriptome analysis. The results of our study show a general pattern of change over time but if additional samples could be tested this could be refined and improved, for example to reveal details about the timing of initial molecular events leading to phenotypic switch. By understanding the cell signalling events that control the increase then decrease of the regenerative environment in damaged nerves, pharmacological approaches to enhance or prolong the favorable environment can be developed. In conclusion, our exploration of human peripheral nerve regeneration revealed that hallmark changes in Schwann cell phenotype known to occur in rodents are also present in humans, providing an important translational link between fundamental nerve biology research and future applications in delivering improved patient care and clinical outcomes.

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