Toward Precision Medicine to Treat Spinal Cord Injury: Distinct Neurite Morphology of DRG Neurons from Mice Expressing Human ApoE3 or ApoE4

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Promising spinal cord injury (SCI) therapies in preclinical animal models have failed to translate into the human population. One potential explanation is that individuals have a genetic predisposition which can either enable or discourage regeneration and sprouting following SCI. The clinically relevant ApoE4 allele, present in 25% of the human population, corresponds to an increased incidence of Alzheimer's disease (AD). Its role in recovery from SCI is poorly understood, although two clinical studies have found that individuals with the ApoE4 allele have less motor recovery and a longer rehabilitation time following SCI. To better define the relationship between ApoE4 and recovery after SCI, we first investigated the impact of ApoE4 on sprouting and neurite outgrowth. To this end, we cultured dorsal root ganglia (DRG) neurons from E3FAD and E4FAD mice, which express either the human ApoE3 or E4 gene under the control of the mouse ApoE promoter. We then analyzed differences in 1) robustness of outgrowth and 2) neurite complexity between genotypes. We found that neurons from E3/E3 animals had more robust outgrowth ($p<0.0001$) than neurons from E4/E3 counterparts, as indicated by a higher total combined neurite length. E3/E3 neurons also had a higher degree of neurite complexity ($p=0.0006$) than E4/E3 neurons, as indicated by a higher ratio of neurite end points to neurites at the soma. Promoting regeneration and sprouting can partially mediate recovery after SCI; therefore, impairments in inherent sprouting and outgrowth capacity can impede recovery. These foundational studies address not only the possible genetic influence of ApoE alleles on recovery from SCI, but also a critical gap in knowledge—whether or not there is a genetic contribution underlying responses to treatment in spinal cord injured individuals.