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Review article

The age factor in axonal repair after spinal cord injury: A focus on neuron-intrinsic mechanisms

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ABSTRACT

Age is an important consideration for recovery and repair after spinal cord injury. Spinal cord injury is increasingly affecting the middle-aged and aging populations. Despite rapid progress in research to promote axonal regeneration and repair, our understanding of how age can modulate this repair is rather limited. In this review, we discuss the literature supporting the notion of an age-dependent decline in axonal growth after central nervous system (CNS) injury. While both neuron-intrinsic and extrinsic factors are involved in the control of axon growth after injury, here we focus on possible intrinsic mechanisms for this age-dependent decline.

Contents

1. Introduction

Age is an important factor for spinal cord injury (SCI) and repair. SCI is increasingly inflicted in the middle aged and aging populations [21,90]. The average age of incidence for SCI has risen substantially in recent years, from ~29 in the 1970s to ~42 since 2010 in the United States (National Spinal Cord Injury Statistical

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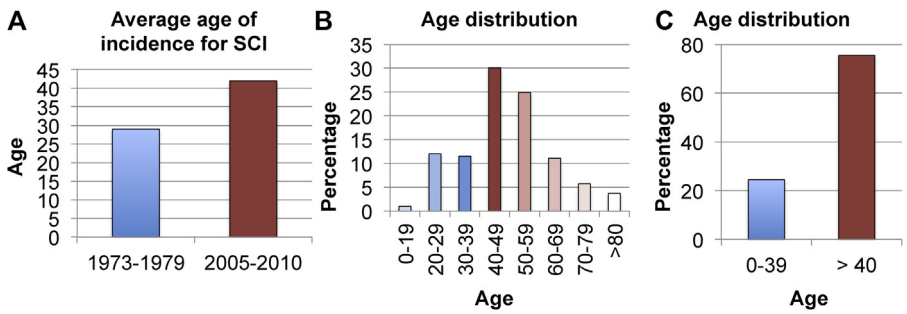

Fig. 1. Spinal cord injury and age. A: Average age of incidence for SCI increased from ~29 in the 1970s to ~42 since 2010 in the US (from National Spinal Cord Injury Statistical Center); B–C: Age distribution for people who live with a paralyzing spinal cord injury in the US.
(Adapted From *One Degree of Separation*, 2009, Christopher and Dana Reeve Foundation.)

Center), partly due to an increasingly active older population. In a census study initiated by the Christopher and Dana Reeve Foundation, the average age of people in the United States who reported being paralyzed due to a SCI is now at ~48, with the peak age group of 40–49 followed closely by the 50–59 age group (Fig. 1). Together, the 40 and above age groups represent about 75% of all people with a paralyzing SCI. Thus, whereas SCI used to preferentially affect young individuals, today this condition most widely impacts older individuals and especially the middle-aged group. These changing demographics call for a critical need to better understand how age and aging impact recovery and repair after SCI.

The field of SCI has certainly recognized the importance of age in both the basic and clinical arenas [24,30,38–40,101]. However, our understanding of how age and aging impact repair and recovery after SCI is still rather limited. In particular, despite the critical importance of axon regeneration in central nervous system (CNS) repair and the rapid progress in understanding its molecular regulation [6,9,11,61,64,73,74,80,84,89,91,93], a major gap exists in our knowledge of how age impacts CNS axon regeneration. This is in large part due to the fact that CNS axons even in young adult mammals have a very limited natural ability to regenerate after injury. Meanwhile, most of the studies in the field use young animals as the model system, corresponding at best to teenagers/young adults in humans. It is understandable that studying how aging impacts spinal cord repair can be intimidating: it is extremely time and resource consuming, and experimental manipulations may be less likely to have a detectable effect relative to experiments performed in young animals.

As this dichotomy in age between human spinal cord injury populations and experimental animal models will inevitably impede translational efforts for restorative therapies, it is of special importance to better understand the impact age has on spinal cord repair. A parallel can be drawn in the field of stroke research, where age has been recognized as an important variable in translating basic research findings into clinical practice [31]. In this review, we will discuss the evidence for an age-dependent decline in axon growth after CNS injury. Although both neuron-intrinsic and -extrinsic factors are likely to play significant roles in this age-dependent decline, here we focus on potential neuron-intrinsic mechanisms as the first step to start a discourse on this important topic.

2. Age-dependent decline in axon growth after injury in diverse systems

In model organisms, axon regeneration has been reported to decline with age. In aging zebrafish, axon regeneration occurs at a reduced speed with an increased latency, both of which were tentatively attributed to factors intrinsic to the neurons [37]. Similarly, in *C. elegans*, efficiency of axon regeneration declines with age, and intra-neuronal mechanisms seem to be at play [13]. An important question in the relationship between aging and axon regeneration is whether molecular pathways involved in lifespan and organismal aging also play a significant role in aging-associated alterations in regeneration. Indeed, worms deficient in the insulin/IGF1 (insulin-like growth factor 1) receptor DAF-2, which have an increased lifespan, exhibit enhanced regeneration in aged but not young adults [13]. These effects require the activity of the downstream forkhead transcription factor DAF-16/FOXO. However, DAF-16 appears to regulate axon regeneration independently of its role in lifespan as it is required in different cell/tissue types for these two functions. On the other hand, DAF-18/PTEN inhibits regeneration in both young and old worms via the TOR pathway independently of age. Unlike in organismal aging, the DAF-2/DAF-16 pathway does not appear to cross-talk with DAF-18/TOR in regulating age-dependent regeneration. These complex relationships, which remain to be fully elucidated, indicate that the molecular pathways involved in organismal aging can regulate axon regeneration in aging adults, but the same molecular machinery can regulate lifespan and regeneration independently.

In the mammalian peripheral nervous system (PNS), where axons regenerate robustly compared to in the CNS, an age-dependent decline in regeneration has been known for over 30 years [83,99,100]. There has been a debate on whether this age-dependent decline is mediated by neuron-intrinsic or extrinsic mechanisms [32,53,57]. Recent evidence from in vivo imaging and reciprocal nerve graft experiments between young and old animals implicates a neuron-extrinsic mechanism in which Schwann cells have a reduced ability to clear up axon and myelin debris in aging adults, thus impeding regeneration [51,79]. However, the molecular underpinnings for the proposed extrinsic mechanism have not been identified and it remains possible that manipulating neuron-intrinsic factors may alleviate this age-dependent decline in PNS regeneration.

In experimental models of mammalian spinal cord injury, relatively few studies have assessed the relationship between age and various outcome measures. Aging reduces locomotor recovery after SCI and is linked to changes in inflammation and myelination [33,40,55,88]. Even fewer studies have examined the effect of age or aging on axon growth after injury. Obviously, since CNS axons have a very limited natural ability to regenerate, it would be difficult, if not impossible, to detect a further reduction in regeneration at an increased age. One study reported that aging impacts axon growth in a tract-specific manner, reducing sprouting of the corticospinal tract (CST), serotonergic (5-HT), raphespinal and catecholaminergic (TH) coerulospinal tracts rostral to the injury site, while the regenerative growth of 5-HT, TH and calcitonin gene-related peptide positive (CGRP+) sensory axons into the lesion site is not impaired by aging [47]. However, this study did not examine true axon regeneration beyond a lesion site.

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