

## New Functions for the Proprioceptive System in Skeletal Biology

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**Abstract**

Muscle spindles and Golgi tendon organs (GTOs) are two types of sensory receptors that respond to changes in length or tension of skeletal muscles. These mechanosensors have long been known to participate in both proprioception and stretch reflex. Here, we present recent findings implicating these organs in maintenance of spine alignment as well as in realignment of fractured bones. These discoveries have been made in several mouse lines lacking functional mechanosensors in part or completely. In both studies, the absence of functional spindles and GTOs produced a more severe phenotype than that of spindles alone. Interestingly, the spinal curve phenotype, which appeared during peripubertal development, bears resemblance to the human condition adolescent idiopathic scoliosis. This similarity may contribute to the study of the disease by offering both an animal model and a clue as to its etiology. Moreover, it raises the possibility that impaired proprioceptive signalling may be involved in the etiology of other conditions. Overall, these new findings expand considerably the scope of involvement of proprioception in musculoskeletal development and function.

**Keywords:** Muscle spindle, Golgi tendon organs, Adolescent idiopathic scoliosis, Proprioception, Musculoskeleton, Fracture repair

## Introduction

Proprioception, in the original Sherringtonian concept of detection of mechanical stimuli arising within the musculoskeletal system itself, is a component of the sense of the relative position of one's own body parts as well as of the level of effort exerted by acting muscles. As such, it is a necessary part of the control of movement and posture. In the musculoskeletal system of humans and other terrestrial vertebrates, the two main types of mechanosensors involved are the muscle spindle [1] and the Golgi tendon organ (GTO) [2]. By virtue of their respective positions in parallel and in series with the force-producing muscle fibres that form the great bulk of skeletal muscles, they respond predominantly to length and changing length of the muscle (muscle spindles) and to actively generated muscle force (GTOs). Although muscle spindles and GTOs are often lumped together as proprioceptors, it is important to recognize that they respond to stimuli whether arising from internal or external (e.g. gravitational) forces. Despite differences in morphology, location, measured input, effect and other characteristics [3-5], these two organs share the ability to respond to mechanical conditions in their local muscle, initiate a rapid response in specialized sensory afferent fibres, often loosely termed proprioceptive neurons, and ultimately modulate local muscle tension through segmental and longer monosynaptic and polysynaptic reflexes [6, 7]. True proprioception is typically short range, may be tonic or phasic, and is relatively weak compared to voluntary or externally evoked forces [8]. Nevertheless, here we present our recent evidence that constant disturbance in proprioception, as might occur during abnormal development or following a limb fracture, is extremely important. In order to understand some of the genetic and molecular aspects involved, we begin with a brief overview of the normal development of muscle spindles and GTOs.

Over the years, several molecular pathways have been identified to regulate proprioceptor formation, connectivity and function [9-13]. Proprioceptive neurons transmit mechanical sensations from muscles and tendons via the dorsal root ganglia (DRG) to the spinal cord. These neurons express the neurotrophic tyrosine tropomyosin receptor kinase C (*TrkC*; also known as neurotrophic tyrosine kinase receptor type 3 (*Ntrk3*) [14] along with neurogenin 2 (*Ngn2*) and Runt related transcription factor 3 (*Runx3*), all essential for the generation and development of DRG sensory neurons [15, 16]. In particular, *Runx3*, a member of the Runt domain-containing family of transcription factors, is highly expressed by DRG *TrkC*-positive neurons and is essential for their survival, axonal projection and connectivity to the spinal cord [17, 18]. *Runx3* knockout (KO) mice display severe limb ataxia, a phenotype that was recently recapitulated upon deletion of the genomic elements driving *Runx3* expression in DRG *TrkC* neurons in mice [19]. In skeletal muscles, differentiation of intrafusal (i.e., situated inside the muscle spindle) fibres begins with the establishment of neuromuscular connection between sensory afferent (Ia) neurons and primary myotubes, followed by induction from the sensory neurons. This process is regulated by neuregulin 1 (NRG1) and its receptor Erb-B2 receptor tyrosine kinase 2 (ErbB2, also known as HER2) [20]. NRG1-ErbB2 signalling activates downstream targets such as early growth response 3 (*Egr3*), a member of the zinc-finger family of transcription factors [13, 21, 22] and the Ets transcription factors *Pea3* and *Erm* [9]. Further developed intrafusal fibres express specific intrafusal molecules, including the *TrkC* ligand neurotrophin 3 (NT3) [23] and Ets transcription factor *Er81* [9]. These molecules, along with *Egr3*, *Pea3* and *Erm*, were shown to affect the survival of proprioceptive sensory neurons and maintain functional sensory axon-myotube connection during embryonic and early postnatal muscle spindle development [9, 13].

Most of the research of the proprioceptive system has focused on its well-known function in motor control. Yet, accumulated evidence shows that this system is also involved in nonautonomous regulation of skeletal development and function. In this review, we describe recent findings pertaining to the roles of proprioception in the maintenance of proper spinal alignment, as well as in morphological restoration of fractured bones.

### **The involvement of the proprioceptive system in maintaining spinal alignment**

The vertebral column serves as the central axis of the body, playing essential roles in supporting weight and maintaining posture while allowing movement. As other skeletal elements, the spine is subjected to high stresses created by body weight and by loads exerted by the attached muscles. The unique structure of the spine restricts movement between its parts to provide inherent stability and, thereby, reduces the need for continuous external stabilization by contraction of adjacent muscles [24]. The dynamic maintenance of body posture requires tight regulation of the position and orientation of numerous vertebrae and intervertebral discs. Yet, despite its importance, surprisingly little is known about this regulatory mechanism.

Scoliosis is a condition in which the spinal column is curved laterally by 10° or more [25]. The most common type of the disease is adolescent idiopathic scoliosis (AIS), which appears during puberty without a known cause or other skeletal anomalies in around 3% of school-aged children worldwide. Treatment includes back bracing, with aim to stop the progression of deformity. In severe or rapidly progressing curves, surgical correction may be required [26]. To date, despite substantial efforts to decipher the pathogenesis of acquired scoliosis, the mechanisms underlying this condition are still elusive [27].

Because the onset of AIS is not preceded by other skeletal abnormalities, uncovering the mechanisms underlying its pathogenesis has been particularly challenging. Yet, the appearance of a curve in spines comprising morphologically intact elements suggests the involvement of a nonautonomous regulatory mechanism in maintaining spinal alignment. Indeed, we recently reported that *Runx3* knockout mice, which lack TrkC neurons connecting between proprioceptors and spinal cord, developed peripubertal scoliosis without prior vertebral dysplasia or muscle asymmetry [28]. Similar results were obtained by conditional deletion of *Runx3* in peripheral nervous tissue or specifically in peripheral sensory neurons, but not in skeletal tissue. Moreover, deletion of enhancer elements driving *Runx3* expression in proprioceptive neurons induced a similar phenotype. A less severe phenotype was exhibited by *Egr3* knockout mice, which lack muscle spindles but not Golgi tendon organs. Functional assays revealed a decrease in gait regularity, which was also more pronounced in *Runx3* KO than in *Egr3* KO mice. These findings implicate impaired proprioceptive signalling in acquired scoliosis and suggest that both receptor types are required for this regulatory mechanism.

Over the years, numerous attempts to develop genetic [29, 30], neuroendocrine [31, 32] or surgical perturbation [33, 34] models for AIS have come short of producing a model that recapitulates the unique features of the disease [27]. Our mouse model displays several hallmark features of AIS, including apparently intact skeletons prior to the appearance of scoliosis, the temporal dynamics of the deformative process, and an accentuated right-sided curve of the thoracic spine.

A large body of evidence supports the idea of neuromuscular involvement in the etiology of scoliosis. These include abnormal morphology and function of neuromuscular elements identified in the central nervous system [35, 36], the somatosensory [37] and vestibular [38]

systems and in trunk muscles [39, 40] of AIS patients. Moreover, the association between neural insults, such as stroke [41] and cerebral palsy [42], and the development of trunk imbalance and deformity is well-established in the clinical practice. In addition, both stroke [43, 44] and cerebral palsy [45] have been shown to substantially impair proprioceptive functions, suggesting a mechanistic cause for the acquired deformity. In animal models, removal of the spinal cord [46] or nerve roots [47-49] resulted in scoliosis, demonstrating the cross-species conservation of the association.

There are several observations that support the notion that proprioceptive function is impaired in AIS patients. These include reported alterations in postural balance [50, 51], and gait [52], as well as reduced number of muscle spindles in paravertebral muscles [53]. Additionally, abnormal neural proprioception-related responses, such as inability to reproduce joint angle [54], vibratory sensation [55] and the size-weight illusion, integrating proprioception and visual inputs [56] have also been seen in these patients. Also, the onset time of AIS during the second decade of life is consistent with the maturation of the proprioceptive system (refs 111, 112). Indeed, it has been speculated that proprioception is involved in the control of spine stability, with muscle spindles acting as a regulatory feedback mechanism [57, 58]; yet, direct evidence for this involvement has been lacking.

Our work may provide the missing link between proprioception and scoliosis. Our findings indicate that the proprioceptive system may not only provide dynamic control of spine alignment, but also prevents progressive spinal deformation. Moreover, our data indicate that this unique relationship between proprioception and spinal alignment requires the synergistic action of both muscle spindles and GTOs. The clinical implication of this notion is that treatment should aim at restoring the balance between motor output and sensory feedback.

In our study, the appearance of spinal deformity (between mouse postnatal days 40 and 60) coincided with highly relevant anatomical and physiological changes, namely maturation of muscle mechanosensors [59, 60] and substantial increases in muscle mass [61] and mobility. Thus, peripubertal scoliosis could result from the combination of increasing mechanical loads and a malfunctioning proprioceptive system. Interestingly, our proprioceptive-deficient mouse strains also developed ataxia, which is not seen in AIS patients. Given the close functional and anatomical interactions between central and peripheral proprioceptive circuits, it is yet to be determined whether ataxia could contribute to the scoliotic phenotype.

From a genetic perspective, while our findings underscore the involvement of *Runx3* and *Egr3* in the mechanisms underlying AIS, the etiopathogenesis of this disease has long been considered polygenic in nature [62, 63]. To date, various loci has been identified as been associated with susceptibility to AIS [64-68]. Based on the etiological explanation we propose, the search for the genetic background of AIS should focus on genes, loci and pathways associated with proprioception. This proposed etiology may also promote development of evaluation and screening tests based on, for example, the performance of proprioception-dependent tasks. Altogether, the shift in focus in the research of AIS towards viewing it as a neuromuscular disease may lead to advances in diagnostics, in progression assessment and, possibly, to future treatment.

### **Proprioception and morphological repair of fractured bones**

Correct bone morphology is essential for the function of the musculoskeletal system [69-73]. The evidence-based textbook model for bone fracture repair describes four distinct stages, from hematoma formation through to bone modelling [74-82]. Yet, despite extensive clinical research



into the association between fracture realignment and functional outcome [83-85], little attention has been paid to the mechanisms that restore the general shape of the fractured bone immediately after the injury and before union has been achieved. It is reasonable to assume that the ability to restore skeletal morphology after a traumatic insult to bone integrity would have granted vertebrates a considerable evolutionary advantage. Indeed, several pieces of evidence support the existence of a robust mechanism that rapidly restores bone morphology following injury. In human neonates, humeral birth fractures with severe angulations usually heal well without intervention and with little residual deformity [86]. Additionally, studies of primate skeletons have documented high rates (up to 30%) of well-healed fractures, mostly occurring in youth, which were also marked by minimal residual deformity, further indicating that effective morphological restoration occurs spontaneously and frequently [87-90]. These findings suggest that during evolution, vertebrates have acquired a mechanism that realigns fractured bones [91]. Previously, we demonstrated the existence of such a mechanism by showing that fractured humeri of neonatal mice undergo realignment without any intervention [92]. The realignment process, which we dubbed natural reduction, involved substantial movement of the two fracture fragments. However, we did not identify the mechanism that senses the location and orientation of the fracture fragments to guide realignment. More recently, we found that muscle spindles and GTOs play this role together [93]. We showed that natural reduction failed in fractured bones of *Runx3*-KO mice. Conditional deletion of *Runx3* in peripheral nervous system, but not in limb mesenchyme, recapitulated the null phenotype, as did inactivation of muscles flanking the fracture site. *Egr3* KO mice displayed a less severe phenotype, suggesting that both receptor types, as well as muscle contraction, are required for this regulatory mechanism.

Bones have long been known to possess autonomous mechanosensing capabilities [71-73, 91, 94]. To cope with a dynamic mechanical environment, bones adapt their morphology [95, 96], mineral composition and density [97, 98] in response to changes in mechanical loading. At the cell level, chondrocytes [99, 100], osteoblasts [101] and osteocytes [102] have all been reported to be mechanosensitive. Fracture callus also has mechanosensing capabilities, as has been shown both clinically [103] and experimentally [104, 105]. The finding of a proprioception-mediated mechanism that monitors and restores bone integrity adds a nonautonomous level of regulation to the current view of mechanosensing in fracture repair.

Interactions among different tissues regulate the development and growth of the musculoskeletal system [106-109]. For example, skeletal muscles have been shown to regulate the commitment of joint lineage cells [107] as well as the circumferential shape and mineral distribution of developing long bones [95]. In the same vein, it was recently suggested that muscle-derived satellite cells actively participate in fracture repair by expressing various growth factors [110]. The findings that proprioceptive circuitry and muscle activity regulate fracture repair further demonstrates the importance of such interactions between musculoskeletal tissues.

Interestingly, we showed that natural reduction becomes more effective with age. While this finding is at odds with the common knowledge on repair processes, it is consistent with the maturation of the proprioceptive system. In mice, the sensory endings of muscle spindles continue to develop until 30-40 days postnatally [59, 60]. In humans, the ability to perform proprioception-specific tasks was shown to increase from childhood into adolescence [111, 112]. These findings support the notion that proprioceptive efficiency improves with increased age, which would explain our observation.

The research of fracture repair has largely ignored the role of muscle pull in restoring bone alignment. Based on our findings, we suggest that muscle proprioceptors detect the position of the fracture fragments and guide natural reduction. According to this revised model, the breakage of the bone causes changes in length and tonus of attached muscles. Consequently, asymmetric muscle activation controlled by proprioceptive signals correct the position of misaligned fracture fragments rapidly and effectively by pulling more strongly on the parts that are farther away from their proper location. The activation of this mechanism immediately after the injury may optimize the healing process and its outcome substantially.

### **Proprioception in aging**

Increased longevity in developed countries has long been considered an indication of great scientific and medical advancements. Nonetheless, it also poses considerable clinical and socioeconomic challenges, including a steep rise in healthcare expenditure. With advancing age, the musculoskeletal system undergoes several gradual changes leading to decline in function. For example, sarcopenia is defined as the loss of muscle mass that occurs with aging, a process that includes reduction in the muscle cross-sectional area as well as a morphologic change, ultimately resulting in a 60% reduction in muscle power [113]. A concurrent reduction in bone mineral content, known as osteopenia or osteoporosis, further exposes the aging skeleton to low-energy fragility fractures. Finally, accelerated denervation of motor neurons [114] may also contribute to increased fragility in advanced age. Similarly, various elements of the proprioceptive system also change during aging. Muscle spindles in aged animals, for example, have been shown to possess fewer intrafusal fibres [115] as well as an altered morphology of their sensory endings [116]. In addition, electrophysiological studies showed that mature muscle spindles are altered, displaying

a much lower dynamic response of primary endings compared to those of young animals [116]. Taken together, both primary alteration in neural and muscular elements of the musculoskeleton and proprioception-specific changes result in a gradual decline in proprioceptive function in elderly individuals.

One of the more substantial results of this decline is general fragility, manifested in an increased tendency to fall and sustain injuries, most notably hip fractures. By providing a better sense of position, proprioception training was shown to be highly useful in the prevention of falls [117] as well as in the rehabilitation of injured patients [118].

To summarize, similar to other elements of the neuromuscular axis, the proprioceptive system undergoes significant changes with advancing age, contributing to the increased risk to sustain a fragility fracture. Better understanding of proprioceptive pathways may assist in developing specific treatments directed at halting their functional decline, or regaining it during a rehabilitation process, thereby greatly improving the well-being of the mature population.

### **The regulatory role of the proprioceptive system in musculoskeletal system: future directions**

Proprioceptive mechanosensors provide constant regulation of skeletal muscle length and tension to coordinate motor control [119]. Our recent studies implicate the proprioceptive system in regulation of both maintenance and repair of the skeleton. This increases substantially the scope of known physiological functions of this system. Moreover, this raises the possibility that the proprioceptive system is involved in regulating other processes and that its dysfunction may contribute to the etiology of various musculoskeletal pathologies.

The regulatory role of the proprioceptive system can be either nonautonomous or mediated by autonomous mechanisms. Our two recent reports provide examples for nonautonomous regulation, where the proprioceptive system serves as the sensor that activates muscles to achieve skeletal integrity and alignment. Given that the skeleton is a mechanosensitive tissue, it is tempting to speculate that the proprioceptive system can also influence the autonomous response of the skeleton to a changing mechanical environment. By modulating muscle tonus and activity, the proprioceptive system can control the load exerted on bones, joints, tendons and ligaments. These loads can then be translated into molecular signals by mechanosensors installed within these tissues, thereby regulating both growth and steady state. The existence of such an axis implies that abnormal proprioceptive function could lead to musculoskeletal pathology.

Conceptually, there is a fundamental difference between these two modes of involvement. In mediated regulation, mechanosensors in the affected tissue convert the mechanical loads into biological input. By contrast, during nonautonomous regulation the mechanosensors within the muscle need to identify deviation in organization or morphology of skeletal tissue. The ability of the muscle via its intrinsic sensory organs to detect morphological abnormality in neighbouring tissues implies that this regulatory mechanism contains a "setpoint" from which deviations are identified and that also signals the termination of the correction process.

One mechanism that may contribute to the setpoint is the fusimotor system. The motor innervation of intrafusal fibres by gamma neurons, which innervate the polar regions of these fibres and regulate their contractile states, allows the central nervous system to control muscle spindle responsiveness to a given length or length change. In particular, increased static gamma activity produces increased tonic firing in spindle afferents. Better understanding of the fusimotor system may resolve any potential involvement in determining the aforementioned

setpoint. The mechanical properties of the different intrafusal fibres are also relevant here. There are three types of intrafusal fibres, namely bag1, bag2 and chain fibres. Most muscle spindles contain one bag1, one bag2 and several chain fibres, and the action of static gamma neurons on the responsiveness of spindle afferents is due to their innervation of the bag2 and chain fibres. Better understanding of their mechanical properties and the molecular mechanism that control them may reveal important insight into the activity of the spindle.

Finally, we know relatively little on the molecular mechanisms that regulate the development, structure and activity of proprioceptive sensory organs. Their involvement in so many important functions should encourage efforts to uncover these mechanisms in order to better understand how the proprioceptive system regulates processes such as skeletal maintenance, repair and function.

### **Competing interests**

We have no competing interests.

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