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Review

Spinal muscular atrophy: Factors that modulate motor neurone vulnerability

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ABSTRACT

Spinal muscular atrophy (SMA), a leading genetic cause of infant death, is a neurodegenerative disease characterised by the selective loss of particular groups of motor neurones in the anterior horn of the spinal cord with concomitant muscle weakness. To date, no effective treatment is available, however, there are ongoing clinical trials in place which promise much for the future. However, there remains an ongoing problem in trying to link a single gene loss to motor neurone degeneration. Fortunately, given successful disease models that have been established and intensive studies on SMN functions in the past ten years, we are fast approaching the stage of identifying the underlying mechanisms of SMA pathogenesis Here we discuss potential disease modifying factors on motor neurone vulnerability, in the belief that these factors give insight into the pathological mechanisms of SMA and therefore possible therapeutic targets.

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1. Introduction

Spinal muscular atrophy (SMA) is an autosomal-recessive neurodegenerative disorder, caused by homozygous mutations in survival of motor neurone 1 (*SMN1*). It is characterised by the loss of a large number of lower motor neurones and muscle denervation. In general, there

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are four different types of SMA categorised according to the age of onset and level of motor function achieved (Lunn & Wang, 2008). Type 1 (Werdig Hoffman disease), the most severe type is also the most common genetic cause of infant mortality. Type 2 has a delayed onset around 0.5–1.5 years of age but still usually leads to death before adulthood. Patients with type 3 or type 4 diseases typically can live a normal life with little assistance. The molecular basis for disease severity is associated with both the quality and quantity of SMN protein. In man, a unique gene called *SMN2*, which is a duplication of *SMN1* and can be present in multiple copies. *SMN2*, has a near identical sequence but a crucial C to T substitution in exon 7 frequently results in exclusion of this exon and an unstable transcript, thus causing a low yield of full-length protein product (Fig. 1) (Lefebvre et al., 1995; Lefebvre et al., 1997). Also, some mutations in *SMN1* do not cause complete loss of its function (Burghes & Beattie, 2009). As a result, the disease severity is determined by both the preserved function of mutated *SMN1* and the number of copies of *SMN2* found in the patient genome.

The *SMN1* mutation primarily affects lower motor neurones, the resulting motor neurone loss causing paralysis and early death due to respiratory failure. However, the reason why loss of a ubiquitously expressed protein causes motor neurones to be particularly more vulnerable than other cell types is an intriguing subject.

Fortunately, given the studies on SMN function and a number of disease models established in the past ten years, we are beginning to understand what factors cause motor neurones to more prominently succumb to disease. These factors can be categorised into three major groups depending on external and internal effects on diseased motor neurones: First, it is known that as with other neurodegenerative diseases, other cell types contacting with the primary affected target cell also play a role in modulating disease severity: Motor neurones are surrounded by, and interact with, glia, such that faulty communication between these cells may exaggerate motor neurone pathology – so-called non-cell autonomous effects. Second, SMN is a multifunctional protein involved in a number of processes including RNA maturation and transportation in axons. The low quality or quantity of SMN protein may dysregulate genes which are crucial for motor neurone development and survival, but less crucial for other cell types. Thirdly, there may be motor neurone-specific disease modifiers of SMN effects or gene production. Here, we review factors that have either been demonstrated to, or have the potential to, influence motor neurone vulnerability.

2. Non cell-autonomous effects on motor neurone vulnerability

Since the identification of the *SMN* gene and its role in SMA (Lefebvre et al., 1995), multiple efforts have been made to understand how SMN restoration or deprivation in the motor neurone affects the disease phenotype. It has been shown that specifically elevating SMN in the motor neurones of SMA mice profoundly improves many morphological and physiological defects associated with motor neurones such as neuromuscular junction, (NMJ), breakdown, abnormal synaptic transmission, motor function, and motor neurone viability. However, there is still room for further functional improvement (Lee et al., 2012; Gogliotti et al., 2012; Martinez et al., 2012). In addition, specific SMN deprivation in mouse motor neurones or delaying the induction of *smn* expression in fish does not necessarily generate manifestations of disease (Park et al., 2010), thereby implying some other factor(s) or cell type(s) play a part in motor neurone vulnerability.

To produce a movement, spinal motor neurones propagate the signal generated from the sensory neurone and inter-neurone, and then coordinate the signal to muscle fibres. Their normal function is highly regulated by neuroglia cells. In other words, the communication between all of these cell types is essential not only for effective motor movement but also for cell survival. In SMA, cells communicating with motor neurones are also under the stress of SMN malfunction, and as a result, they may contribute to motor neurone vulnerability. How these contacting cells respond to SMN malfunction and whether they negatively regulate motor neurone health will be considered in turn.

2.1. The role of muscle

The bi-directional nature of communication at the NMJ has long been shown to play an essential role in the function of both the axon terminal and innervated muscle (Rimer et al., 1997; Brenner et al., 1987; Thompson, 1983; Marques et al., 2000). Cultures of neonatal chicken spinal neurones treated with muscle extracts from SMA patients show inhibition of neurite outgrowth (Henderson et al., 1987). Because of the accessibility and apparent malfunction of SMA muscle, many experiments have been carried out to determine whether muscle could be an effective therapeutic target or if there might be a retrograde effect from the muscle to the motor neurone compartment.

Thus, selective knockdown of SMN levels in mouse skeletal muscle recapitulates the atrophic muscle fibres seen in SMA whilst motor neurone number and NMJ are spared (Cifuentes-Diaz et al., 2001). Similarly, increased expression of SMN specifically in mature muscle (driven by the promoter of human skeletal actin, HSA, which is active only in mature myofibres) shows no benefit in nerve or muscle preservation, and little extension in lifespan in the SMN2 mouse model ($smn^{-/-}$; $SMN2^{+/+}$) (Gavrilina et al., 2008). A further investigation used MyoD (myogenic differentiation), whose expression begins at embryonic stage, to drive the expression of SMN in muscle in SMNΔ7 mice ($smn^{-/-}$; $SMN2^{+/+}$; $SMN\Delta7^{+/+}$). Whilst this resulted in slightly increased survival and fully rescued muscle size, it again did not restore the motor neurone number, NMJ pathology, or motor behaviours such as the righting reflex (Martinez et al., 2012).

A further study demonstrated that whilst muscle could grow and function normally even when SMN is reduced to the disease level, and again no rescue was seen using an alternative promoter, (Myf5), to drive the muscle SMN expression in SMAΔ7 mice (Iyer et al., 2015). This result combined with previous work suggests the muscle weakness seen in SMA is a secondary change to the motor neurone pathology and there is minimal retrograde impact of defective SMN protein levels in muscle to motor neurones.

2.2. Is a sensory neurone defect involved in inducing motor neurone pathology?

The significance of communication between sensory and motor neurones has been widely demonstrated. For example, NMJ formation is greatly facilitated by the presence of dorsal root ganglion neurones (DRG) in a co-culture system (Kobayashi et al., 1987; Anne-Sophie et al., 2012). Evidence for an impaired sensory system, including myelination loss and ganglion cell degeneration (Marshall & Duchen, 1975; Rudnik-Schöneborn et al., 2003), and absence of the refractory reaction following muscle spindle stimulation (H-reflex) are reported in some severe SMA cases (Renault et al., 1983). Correspondingly, in mouse models of SMA, deafferentation from sensory inputs onto motor neurone results in lower input from presynaptic activity, which can account for the impaired motor activity of SMA (Mentis et al., 2011; Murray et al., 2010a; Mikesh et al., 2011; Ling et al., 2010). In addition, SMN deprivation causes overlapping defects in both motor and sensory neurones, including reduced axonal hnRNP-R mRNA and growth cone size (Jablonka et al., 2006).

These studies raise the question whether any abnormal communication onto the motor neurone might aggravate motor neurone pathology. This hypothesis received some initial support from an SMA *Drosophila* model, which has an obligate requirement for SMN in cholinergic neurones, proprioceptive neurones and partial interneurones but not in motor neurones, for recovering motor behaviours (Imlach et al., 2012), suggesting that normal sensory or other inputs play an important role in regulating motor neurone impairment.