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Editorial

Intrinsic Laryngeal Muscles and Potential Treatments for Skeletal Muscle-Wasting Disorders

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Laryngeal muscles are groups of muscle pairs within (intrinsic laryngeal muscles) and outside (extrinsic laryngeal muscles) the larynx. They contribute to movement of the vocal folds inside the larynx and positioning of the whole larynx within the trachea. The intrinsic laryngeal muscles originate and insert on the larynx, move the arytenoid cartilage, and adjust the tension of the vocal folds and ligaments. Thus, these muscles play an important role in voice production, breathing, and vocal fold closure during swallowing. These intrinsic laryngeal muscles include the posterior cricoarytenoid (PCA), transverse arytenoid, oblique arytenoid, lateral cricoarytenoid, thyroarytenoid (TA), and cricothyroid (CT) muscles. They are innervated by the vagus nerve and share the internal branch of the superior laryngeal nerve as the sensory innervations. Most of these muscles share the recurrent laryngeal nerve as the source for motor innervation, except the CT muscle, which receives motor innervation via the external branch of superior laryngeal nerve.

The PCA, TA, and CT muscles are the most commonly studied intrinsic laryngeal muscles in terms of myosin heavy chain (MyHC) isoforms, function, innervation, neuromuscular junction morphology, and mitochondrial content [1-8]. These characteristics determine the differences in muscle force, velocity, and strength among the intrinsic laryngeal muscles and between them and limb muscles.

One fascinating aspect of the intrinsic laryngeal muscles is that some of them are spared from certain muscle wasting disorders. For example, the intrinsic laryngeal muscles, except for the CT muscle, are spared from myonecrosis in the mdx mouse model of Duchenne muscular dystrophy and congenital muscular dystrophy type 1A [9-12]. In this model, the CT muscle and extrinsic laryngeal muscle show myofibrillar damage and myopathy similar to the diaphragm and limb muscles [9,10]. In addition, the CT muscle is more severely affected by myasthenia gravis than the TA and PCA muscles, as determined by electromyography [13]. We have shown that the PCA, but not the CT muscle, is spared from muscle wasting in a murine model of the Acute Respiratory Distress Syndrome (ARDS) and Intensive Care Unit-Acquired Weakness (ICUAW) [14].

The mechanisms underlying the sparing of intrinsic laryngeal muscles from muscle wasting are incompletely understood. Elucidating these mechanisms is necessary to develop better treatments for a variety of muscle degenerative diseases.

Muscle functional and morphological characteristics depend on their fiber type and motor innervation, which are modulated by specific genes [15,16]. MyHC, the motor protein of muscle thick filaments, is predominantly expressed in each individual muscle fiber and defines specific muscle fiber properties and responses in various muscle diseases. In addition to the intrinsic laryngeal muscles, other craniofacial muscles, such as the extraocular muscles (EOM), are also spared from some muscle wasting disorders [17-20]. In addition, the masticatory muscles are spared from ICUAW in humans and experimental models [21]. Although the mechanisms are not fully understood, the distinctive gene expression profile in the EOM and masticatory versus limb muscles indicates a highly complex and muscle-specific/developmental response that may protect these muscles [21,22].

The intrinsic laryngeal muscles share some unique MyHC expression and innervation, and the mechanisms of muscle sparing between these groups may be similar. Specifically, both the PCA and EOM contain extraocular myosin heavy chain (MyHC-EO) protein [14,23], which is absent in the limb muscles and some intrinsic laryngeal muscles (e.g., the CT muscle). Second, these two muscles have multiple innervation patterns in a single muscle fiber [2,24-27] compared to other limb muscles, which have a single pattern. Third, utrophin mediates muscle protection from dystrophinopathy in both intrinsic laryngeal and EOM [28,29]. Utrophin, a protein expressed within skeletal muscle tissue, neuromuscular synapse and myotendinous junctions, is necessary for normal membrane maintenance, and for the stability and function of the acetylcholine receptors (see [30] for a review).

Given that the PCA muscle and the EOM share some structural characteristics, the mechanisms underlying their sparing from muscular diseases should be similar. In our mouse model of acute lung injury, the PCA (but not CT and limb muscle) is spared from the atrophy mediated by the E3 ubiquitin ligase muscle ring finger-1 protein (MuRF1) [14]. MuRF1 was first identified in transcript profiling in fasting and immobilization models of rodent muscle atrophy [31]. In our mouse model of acute lung injury, it is responsible for limb muscle atrophy in the early phase of muscle wasting [32]. We found that, compared to the CT and limb muscles, the PCA muscle has lower levels of MuRF1 and lacks MuRF1 upregulation following lung injury. In addition, MyHC-EO composition is higher in the PCA muscle (27%) versus the EOM (14%) (unpublished data).

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MyHC-EO, encoded by the MYH13 gene, is supposed to be the fastest MHC isoform but is functionally similar to the slower isoforms [33,34]. The PCA and CT muscles have similar MyHC composition in our mouse model except for the high expression of MyHC-EO in the PCA muscle. We hypothesize that MyHC-EO and its related cell signaling may play an important role in the protection of PCA muscle from atrophy in critical illness. Further exploration of the MyHC-EO and its relationship to MuRF1 may lead to a deeper understanding of how these muscles function, and thus may identify future therapeutic targets for muscle wasting disorders.

In summary, further studies to explore why intrinsic laryngeal muscles are spared from muscle wasting disorders may facilitate the development of novel strategies for the prevention and treatment of muscle wasting in a variety of clinical scenarios.

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