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Hanging on for the ride: Adhesion to the extracellular matrix mediates cellular responses in skeletal muscle morphogenesis and disease

Q1 Michelle F. Goody [a], Roger B. Sher [b,c], Clarissa A. Henry [a,c,d,*]

[a] School of Biology and Ecology, University of Maine, Orono, ME 04469, United States
[b] Department of Molecular and Biomedical Sciences, University of Maine, Orono, ME 04469, United States
[c] Graduate School of Biomedical Sciences and Engineering, University of Maine, Orono, ME 04469, United States
[d] Institute for Molecular Biophysics, University of Maine, Orono, ME 04469, United States

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ABSTRACT

Skeletal muscle specification and morphogenesis during early development are critical for normal physiology. In addition to mediating locomotion, skeletal muscle is a secretory organ that contributes to metabolic homeostasis. Muscle is a highly adaptable tissue, as evidenced by the ability to increase muscle cell size and/or number in response to weight bearing exercise. Conversely, muscle wasting can occur during aging (sarcopenia), cancer (cancer cachexia), extended hospital stays (disuse atrophy), and in many genetic diseases collectively known as the muscular dystrophies and myopathies. It is therefore of great interest to understand the cellular and molecular mechanisms that mediate skeletal muscle development and adaptation. Muscle morphogenesis transforms short muscle precursor cells into long, multinucleate myotubes that anchor to tendons via the myotendinous junction. This process requires carefully orchestrated interactions between cells and their extracellular matrix microenvironment. These interactions are dynamic, allowing muscle cells to sense biophysical, structural, organizational, and/or signaling changes within their microenvironment and respond appropriately. In many musculoskeletal diseases, these cell adhesion interactions are disrupted to such a degree that normal cellular adaptive responses are not sufficient to compensate for accumulating damage. Thus, one major focus of current research is to identify the cell adhesion mechanisms that drive muscle morphogenesis, with the hope that understanding how muscle cell adhesion promotes the intrinsic adaptability of muscle tissue during development may provide insight into potential therapeutic approaches for muscle diseases. Our objectives in this review are to highlight recent studies suggesting conserved roles for cell–extracellular matrix adhesion in vertebrate muscle morphogenesis and cellular adaptive responses in animal models of muscle diseases.

Introduction

Proper muscle specification and morphogenesis during development are critical for adult muscle physiology. In addition, active homeostasis maintains muscle function despite the normal wear and tear that occurs with activity. Skeletal muscle is a remarkably regenerative and adaptable tissue, with muscle hypertrophy (increase in cell size) and/or hyperplasia (increase in cell number), occurring in response to exercise or injury. These adaptive cellular behaviors can be triggered by stimuli (physical or chemical) both inside the cell and in the microenvironment surrounding cells. A key fundamental question is how do cells detect changes in their microenvironment, integrate and transduce these inputs, and respond with discrete outputs? It is likely that that cell–extracellular matrix (ECM) adhesion complexes play a major role in this process because: (1) cell–ECM adhesion complexes provide a physical link between the cytoskeleton and the microenvironment, (2) bi-directional signaling between cells and their microenvironment occurs through cell–ECM adhesion complexes, and (3) cell–ECM adhesion complexes are dynamic. As cellular morphogenetic or adaptive responses require the perception and integration of multiple signaling inputs, cell–ECM adhesions may function as a link between signaling inputs and cellular behaviors.

Abbreviations: ECM, extracellular matrix; Fn, Fibronectin; BM, basement membrane; DGC, Dystrophin-glycoprotein complex; UGC, Utrophin-glycoprotein complex; NMJ, Neuromuscular junction; MTJ, myotendinous junction; HSPG, heparin sulfate proteoglycan; EMT, epithelial to mesenchymal transition; ECL, external cell layer; Hh, Hedgehog; SSF, superficial slow-twitch fiber; MP, muscle pioneer fiber; MFF, medial fast-twitch fiber; FAK, focal adhesion kinase; Dag1, dystroglycan; Nrk2b, nicotinamide riboside kinase 2b; CMD, congenital muscular dystrophy; DMD, Duchenne muscular dystrophy; MDC1A, Merosin-deficient congenital muscular dystrophy; UCMD, Ullrich congenital muscular dystrophy; hpf, hours post-fertilization

* Corresponding author at: School of Biology and Ecology, University of Maine, Q2 Orono, ME 04469, United States.
E-mail address: Clarissa.Henry@maine.edu (C.A. Henry).

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Here, we will focus on recent progress in understanding how cell–ECM adhesion mediates cellular responses during muscle morphogenesis and disease.

To highlight dynamic roles for cell–ECM adhesions in physiological and pathological processes in skeletal muscle tissue, we will focus on two major themes – connecting signaling/specification to normal muscle morphogenesis via cell–ECM adhesion, and connecting cell–ECM adhesion to cellular adaptation in muscle diseases. Excellent recent reviews have extensively documented what is known about cell–ECM and cell–cell adhesion during muscle development and disease (Borycki, 2013; Lund and Cornelison, 2013; Thorsteinsdóttir et al., 2011); thus, we will mainly focus on newer information through the lens of the innate adaptability of muscle tissue. We will begin by providing a brief introduction to proteins involved in muscle cell–ECM adhesion and then discuss roles for cell–ECM adhesion components in multiple stages of muscle morphogenesis, homeostasis, and disease.

Cell adhesion and the muscle extracellular matrix

Tissue morphogenesis and homeostasis require carefully orchestrated interactions between cells and their ECM microenvironment. A tissue's characteristics result from the properties and proportions of its ECM proteins. Thus, the stiffness of bones and the elasticity of (young) skin result from the biophysical properties of their constituent ECMs. Within the last two decades it has become clear that the ECM also modulates cellular signaling by multiple mechanisms. One way that the ECM modulates cellular signaling is by sequestering signaling molecules within the matrix (Droguett et al., 2006). Cell–ECM interactions can also modify cellular responses to signaling. For example, ECM receptors act as non-canonical co-receptors that impart specificity to FGF signaling (Polanska et al., 2009). ECM receptors are also both modulated and activated by Notch and MAP-kinase signaling (Karsan, 2008; Yee et al., 2008). Thus, the "ECM interactome" is ubiquitous and may play a central role in integrating cellular responses to multiple signaling pathways as well as mechanical stimuli. As morphogenesis and adaptation require the perception and integration of multiple signaling inputs, cell–ECM adhesions may function to 'translate' signaling inputs into discrete cellular responses.

The muscle extracellular matrix

The structure of mature mammalian muscle ECM has recently been described in detail (Gillies and Lieber, 2011). In brief, ECM is found at all spatial levels of muscle: muscle fibers are surrounded by *basement membranes* (*BMs*), ECM surrounds bundles of fibers, and whole muscles are encased in ECM (Fig. 1). The bridges between muscle and other tissues, the NMJs and the MTJs, are also rich in ECM.

Why is it important to understand how the muscle ECM develops and is maintained? One dramatic demonstration of muscle ECM function comes from comparing natural fiber bundles

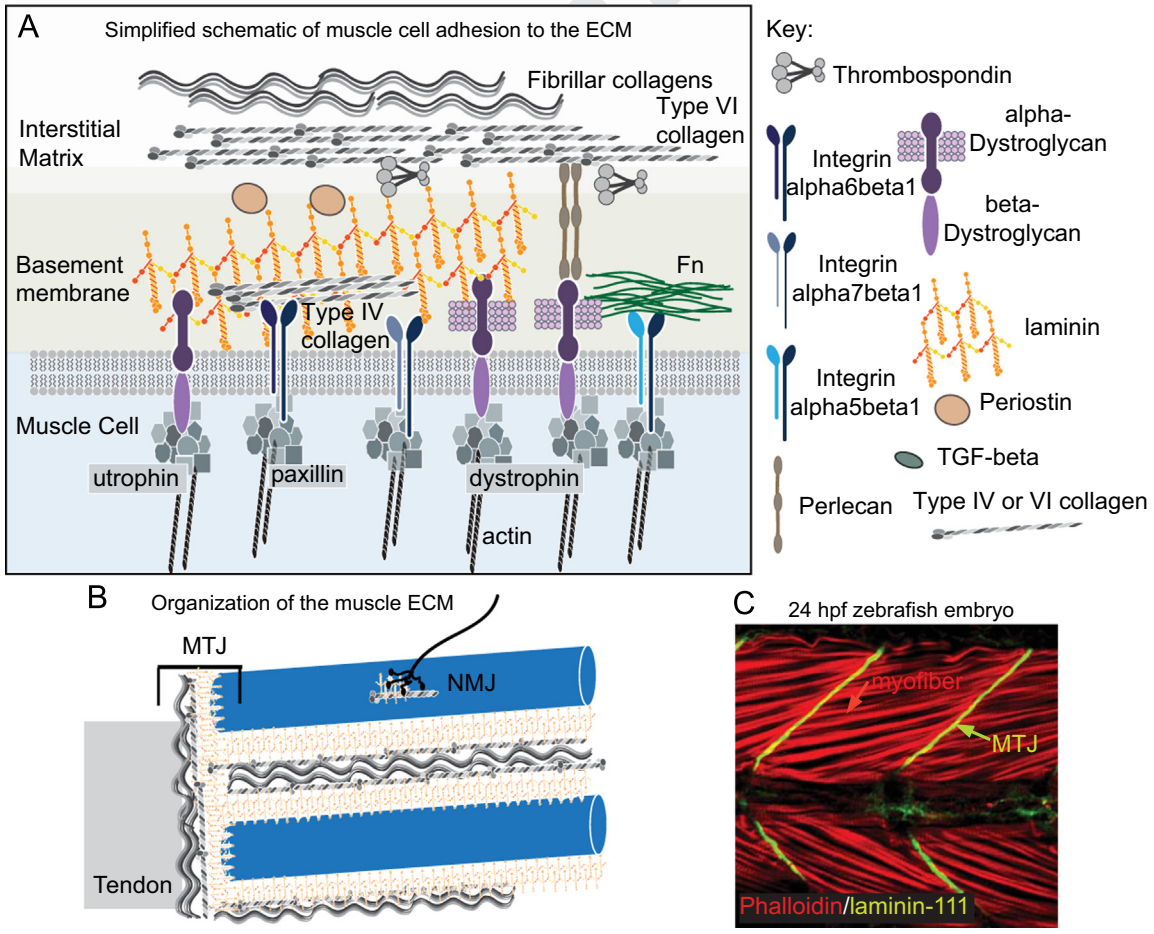

Fig. 1. The muscle ECM. (A) Simplified cartoon of proteins involved in muscle cell adhesion to the ECM. Multiple transmembrane receptor complexes indirectly link the intracellular cytoskeleton to the ECM. The BM attaches to the collagen-rich interstitial matrix. (B) Larger size scale view of the organization of muscle ECM. Not only are individual muscle fibers encased by ECM, but there are also specialized matrices that define the neuromuscular and myotendinous junctions (NMJ and MTJ, respectively). (C) A 24 hpf zebrafish embryo stained with phalloidin (red) to visualize actin and an antibody against laminin-111 (green). Side view, anterior left, dorsal top. Note the long muscle cells (red arrow) that connect to laminin-111 at the myotome boundaries (green arrow). These boundaries will generate the MTJ.

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