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Cell Adhesion and Myogenesis

The dictionary offers several synonyms for adhesion including unwavering attachment, fidelity, devotion, of being sticky and holding fast. These terms are easily applied to an epithelium consisting of a sheet of tightly packed cells that serves as a barrier to unrestricted diffusion. All cells of an organism must adhere to other cells or to molecules of the extracellular matrix. Without such adhesions, the integrity of tissues and organs is lost and survival is compromised. The classic example of cell adhesion gone awry is the process of metastasis during which a transformed cell loosens its attachments with its neighbors and begins to migrate to distant sites.

The development of cardiac and skeletal muscle, as well as the maintenance and functioning of adult muscle, are dependent on the interactions of cell adhesion molecules. Adhesion proteins are found in both types of muscle during all stages of their development. These include the integrins, cadherins and a member of the immunoglobulin superfamily NCAM. Cadherins and NCAM function in cell-cell adhesions whereas the integrins mediate both the adhesion of cells to each other and to the extracellular matrix. Besides their obvious roles in maintaining the organization of cardiac and skeletal muscle tissues, engagement of adhesion molecules with their ligands on adjacent cells or within the extracellular matrix results in the transmission of signals intracellularly. Adhesion related signaling events regulate cell motility, proliferation, gene expression, myoblast fusion and contractile function.

The cadherins, NCAM and integrins are developmentally regulated in response to external and internal signals. The progression of myogenic cells- towards differentiation and maturation is accompanied by alterations in the class of adhesion protein that is expressed by the cell, isoforms within a class, post-translational modifications and/or their amount and distribution on the cell surface. Post-translational modifications can be particularly important in regulating the strength of cell adhesion. For example, as myoblasts migrate from the somite to their appropriate locations throughout the embryo, N-cadherin mediated adhesions must be repressed to avoid premature differentiation, and integrins must bind to the extracellular matrix, but not too tightly that they become stuck in place. The following papers review the structure and function of adhesion molecules in developing and adult cardiac and skeletal muscle. During the formation of the heart, NCAM appears to function in regulating epithelial to mesenchymal transitions, aligning myocytes, gap junction communication and innervation (Watanabe). N-cadherin may be important for defining boundaries and coordinating differentiation within a compartment of cells (Linask). N-cadherin plays a similar role in the earliest stages in the development of skeletal muscle precursors as epiblast cells undergo gastrulation and during the formation of the somite, the source of most of the skeletal muscle of the body (George-Weinstein et al.; Linask). Although a small number of cells from the somite, the presomitic segmental plate mesoderm and epiblast can spontaneously undergo skeletal myogenesis ;'// *vitro,* most require interactions with other cells via N-cadherin in order to differentiate. Epiblast cells cultured in the presence of the Wnt-1 protein fail to switch from E- to N-cadherin and the expression of sarcomeric myosin is inhibited (George-Weinstein et al.).

Another member of this family of adhesion molecules, M-cadherin, is expressed somewhat later than N-cadherin in skeletal muscle precursors (Link et al.). M-cadherin appears to function after the initiation of differentiation, during the alignment of myoblasts in preparation for fusion. M-cadherin also may mediate the adhesion of mononucleated myocytes on myofibers within the embryo and in adult muscle (Link et al.).

A third class of adhesion molecules, the integrins, play multiple roles during myogenesis (DiLullo et al.). Different alpha and beta subunits of the integrin

heterodimer are expressed during various stages of skeletal muscle development. The particular alpha/beta combination dictates which molecule within the extracellular matrix or on the surface of an adjacent cell the integrin will bind, thereby generating tremendous functional versatility. Integrins regulate the replication, migration, differentiation and fusion of skeletal myoblasts and mediate adhesion within the neuromuscular and myotendinous junctions. In addition, integrins appear to be important for maintaining the structural integrity of muscle during contraction. The alpha/beta 1 integrin is present as a doublet within the I band, colocalizing with Ca^{2+} ATPase of the sarcoplasmic reticulum (DiLullo et al.). Thus, integrins may not only serve as a transmembrane link of the cytoskeleton to the extracellular matrix, but also may anchor the sarcoplasmic reticulum or T-tubule membrane systems to myofibrils.

A great deal of information has been obtained regarding the expression of different classes of adhesion proteins during all stages of myogenesis. Recombinant gene technology and antibody perturbation studies have yielded insights into the functions of various adhesion molecules in both cardiac and skeletal muscle cells. It is becoming increasingly clear that these proteins are not only cellular glue, but they transmit signals intracellularly to affect cytoplasmic and nuclear events. Although some of the downstream targets of these signaling systems have been determined, many remain a mystery, especially those genes that are sensitive to adhesive interactions. Another phenomenon that requires further analysis is the mechanisms by which different classes of adhesion molecules influence each others' activities. Cross-talk between proteins engaged in cell-cell and cell-extracellular matrix adhesion occurs in transformed cells (Leppa et al., 1998. J. Cell Sci. 109, 1393-1403; Miyanki et al., 1998. Oncogene 11, 2547-2552) and myoblasts (Huttenlocher et al., 1998. J. Cell Biol. 141, 515-526). The molecular linkages between adhesion systems and the result of such communication on gene expression in myogenic cells is one of the most exciting areas for discovery in the field of muscle biology.

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