Int. J. Morphol.,
42(2):341-347, 2024.

Striated Musculature: Embryonic and Fetal Development

Musculatura Estriada: Desarrollo Embrionario y Fetal

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GARCÍA-OROZCO, L.; DUQUE-COLORADO, J.; ALARCÓN-APABLAZA, J.; ROA, I. & ROJAS, M. Striated musculature: Embryonic and fetal development. *Int. J. Morphol., 42(2)*:341-347, 2024.

SUMMARY: The different embryological origins of striated muscle tissue make it an interesting tissue but at the same time difficult to understand, this is how the musculature of the face comes from the first pharyngeal arch, on the other hand. The muscles of the tongue derive from the somites. The muscles of the larynx come from the pharyngeal arches. The muscles of the spine come from the medial or internal myotome of the somite, while the muscles of the limbs and body wall come from the external myotome. The cardiac musculature originates from the lateral splanchnic mesoderm. In this work, the development of myoblasts in human, mouse and chicken fetuses was studied in the facial region, tongue, and spine, limbs, body wall and cardiac muscles using histological histochemical techniques and immunohistochemical technique. The objective of the work is to compare the histogenesis of striated muscle (skeletal, visceral and cardiac), indicating the differences in origin, evolution of the morphological characteristics in each of them and the signaling routes that are involved in its development.

KEY WORDS: Skeletal striated muscles; Visceral striated muscles; Somites; Myoblasts, Mesoderm; Myotome; Myocytes; Cardiac muscle.

INTRODUCTION

Muscle tissue is made up of highly differentiated elongated cells, whose primary function is contraction, thanks to the presence of specialized organelles and the proteins actin and myosin. There are thus three varieties, smooth muscle and striated skeletal and cardiac muscles (Kierszenbaum & Tres, 2016).

Skeletal striated muscle tissue fulfills various bodily functions within which it is important to highlight the process of converting chemical energy to mechanical energy in order to generate strength and power, maintain posture and generate voluntary movements that contribute to functional independence. The origin of this tissue is determined by the paraxial mesoderm, also known as somitic mesoderm (Frontera & Ochala, 2014). It appears as a long multinucleated fiber, with transverse striations, peripherally related to the myosatellite cells (Fig. 1A).

The cardiac striated muscle tissue, for its part, is found making up the wall of the heart, specifically the myocardium. The type of movement of these tissues is involuntary and allows the distribution of nutrients and oxygen to cells throughout the body to fulfill various functions. This muscle originates from the visceral or splanchnic mesoderm (Sepúlveda & Soto, 2015).

Although both muscle fibers mentioned above are striated, they have significant morphological differences. Cardiac striated muscle cells are branched and join at their ends through intercalated discs that form the myocardial fibers (Welsch, 2007). Skeletal striated muscle cells are not branched and do not have junctions similar to intercalated discs. In cardiac muscle, the arrangement of the nuclei is central, while in skeletal muscle they are located peripherally (Roman & Gomes, 2017) (Fig. 1B).

The objective of this review is to describe the histogenesis of striated muscle (skeletal and cardiac), indicating its embryonic origin, development, morphological characteristics and the main signaling pathways that are involved in its development, in order to contribute to the teaching of Embryology. Finally, a description of the

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Received: 2023-12-10 Accepted: 2024-01-17

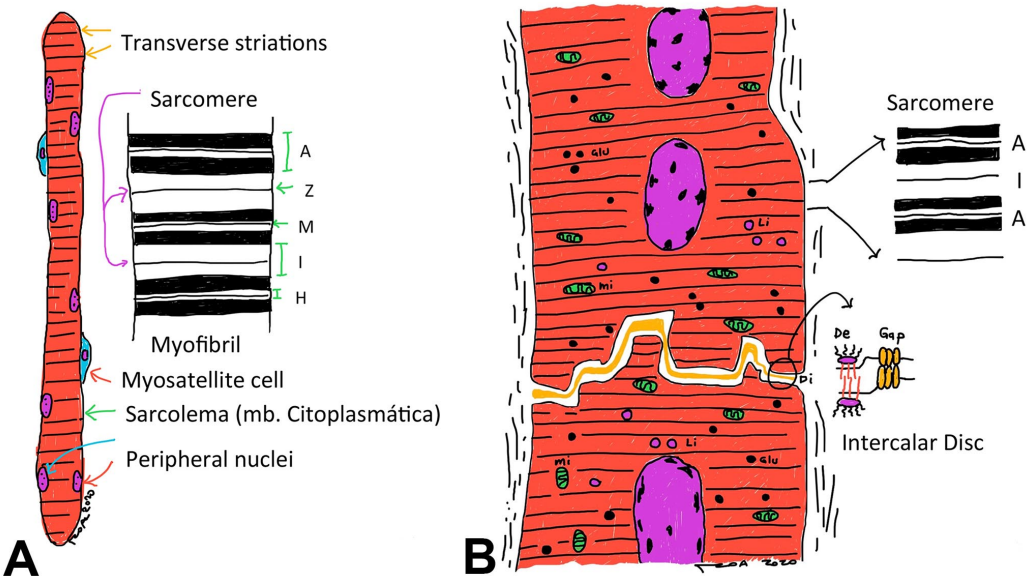

Fig. 1. A. Striated skeletal muscular tissue, histological structure. B. Striated cardiac muscular tissue, histological structure.

embryonic and fetal development of the striated muscle fibers of the different embryonic origins was made based on learning objectives and teaching purposes.

MATERIAL AND METHOD

80 histological sections of chicken (*Gallus gallus domesticus*) embryos of 24 and 48 h, mouse (*Mus musculus*) of 14 days and human fetuses of 9, 12 and 14 weeks, from the Laboratory of Comparative Embryology of the Faculty of Medicine of the University of Chile, Chile. All samples were processed with the H/E/Alcian Blue histochemical technique; for mouse samples, the anti-Sonic hedgehog antibody was also used. Histological slides were scanned and digitized using a NanoZoomer XR C12000 series microscope (Hamamatsu Photonics, Hamamatsu, Japan). obtaining files in WSI format. Finally, a description of the embryonic and fetal development of striated muscle fibers as well as their different embryonic origins was made.

RESULTS AND DISCUSSION

Embryonic formation of muscle fiber. During the course of the 4th week, the middle and ventral part of the somite proliferates forming the sclerotome, the dorsal part thus becomes the dermatome, which in its deepest segment gives rise to the myotome (Gómez Dumm, 2003). The cells that proliferate from the myotome initially have mesenchymal properties and characteristics; these become myoblasts, the result of multiple mitotic divisions mediated by growth factors (FGF and TGF-b) that cause them to continue within the cell cycle. Subsequently, with the accumulation of myogenic regulatory factors (MyoD and MyF5), cells synthesize cell cycle protein p21 which irreversibly removes them from this cycle. Through insulin-like growth factor (IGF), postmitotic myoblasts initiate the synthesis of myosin and actin. Once the myoblasts fuse, they give rise to myotubes, which through the synthesis of troponin and tropomyosin make it possible for these proteins to assemble with myofibrils, thus generating sarcomeres. As the myotubes are occupied by myofibrils, the nuclei migrate towards the periphery, at this point the myotube is considered to have differentiated into a muscle fiber (Carlson, 2019) (Fig. 2).

Myosatellite cells (myosatellitocyte). These cells present in skeletal striated muscle tissue represent a group of myoblasts that persist since muscle embryogenesis, located between the sarcolemma (cytoplasmic membrane) and the basal lamina that surrounds each skeletal striated muscle fiber. Satellite cells that have the ability to activate, re-enter the cell cycle, proliferate and give rise to myoblasts, which subsequently differentiate and withdraw from the cell cycle, subsequently fusing with the damaged myofibers for repair, or with each other for the formation of new myofibers. Quiescent satellite cells are activated by muscle damage or a growth stimulus, as in the embryo their entry into myogenesis depends on Myf5 and MyoD. A fraction of satellite cells self-renew and return to quiescence beneath the basal lamina for future muscle repair. After numerous investigations, it was suggested that Pax7 marks pre-fusion myoregenerative cells that participate in the repair of damaged muscle fibers (Kadi *et al*., 2005; Apponi *et al*., 2011).

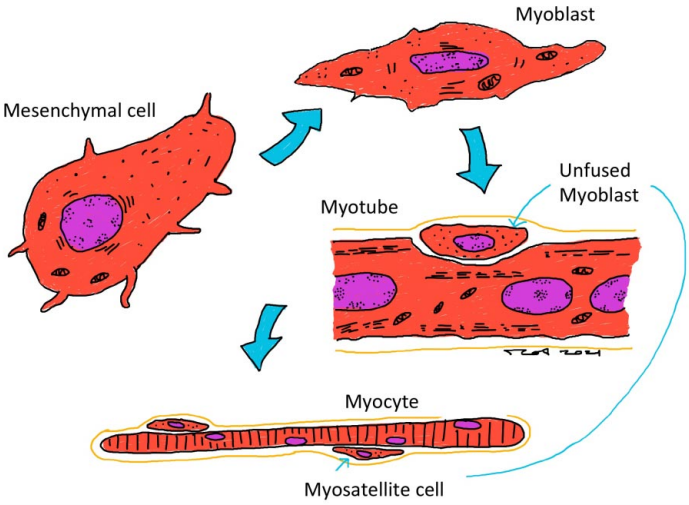

Fig. 2. Myocyte development and his relation with Satellite cells.

Molecular regulation of myogenesis. All the aforementioned embryological events that conclude with muscle development are specifically controlled by myogenic regulatory factors (MyoD, Mrf4, Myf5, Myog) and transcription factors (Pax3 and Pax7), in their absence. skeletal muscle is not formed (Buckingham & Rigby, 2014).

The specification and organization of myogenic cells in the somite depends on signals from the surrounding tissues, the secretion of Wnt6 by the dorsal ectoderm is relevant for the maintenance of the epithelial structure of the dermamyotome, an event necessary for the orderly progression of myogenesis. Wnt signaling, which in turn is modulated by SHH, is involved in the regulation of Myf5, the first regulatory gene that is activated first in the epaxial domain and subsequently in the hypoaxial domain. MyoD is transcribed after the expression of Myf5 and is activated in the opposite way, first in the hypoaxial domain and subsequently in the epaxial domain. Together, these two genes act to determine myogenic fate and regulate cell proliferation. The transcription factor Pax3 has been initially expressed in the presomitic mesoderm and with the process of somite differentiation its action is limited to the dermamyotome, the expression of Pax7 is induced in the central domain of the dermamyotome in the embryo, both Pax3 and Pax7 also respond to Wnt signaling, Pax3 plays an important role during skeletal muscle formation in the embryo, while Pax7 predominates during postnatal growth and muscle regeneration in the adult. Activation of the enhancer that directs Myf5 expression in the limbs and greater hypoxial somite depends on a Pax3 binding site. Both Myog and Mrf4 are activated at early stages, but act at later stages for differentiation, fusion and growth of muscle cells, Mrf4 is only expressed in differentiated muscle cells (Buckingham, 2006; Comai & Tajbakhsh, 2014; Buckingham & Rigby, 2014; Shi & Grifone, 2021).

Craniofacial myogenesis. The craniofacial muscles can be organized into several groups: (1) muscles that control eye movement (extraocular), (2) muscles in or associated with the head (tongue and neck muscles derived from the somites), and (3) branchiomeric muscles that are involved in chewing, facial expression, and function of the pharynx and larynx (Lescroart *et al*., 2010). The branchiomeric muscles originate from the mesodermal nucleus of the pharyngeal arches (FA), which consists of cells from both the cranial paraxial mesoderm (CMP) and the lateral splanchnic mesoderm (MLM).

Head Muscles. Most head muscles originate from the somitomeres; the masticatory (closing and opening of the jaw), and ocular muscles are derived from somitomeres 4, 6-7 and 1-3, respectively (Huang *et al*., 2000; Noden & Francis-West, 2006; Meruane *et al*., 2012), with the exception of the iris muscles that derive from the ectoderm (Sadler, 2019). The facial muscles corresponding to the maxillary and mandibular regions are formed from the derivatives of the first pharyngeal arch. At the 12th week of development, on the face of a human fetus it is possible to observe the formation of myoblasts, these appear as elongated multinucleated cells, with central nuclei, the cytoplasm is chromophobic and the cells are close to fusing with each other (Fig. 3A).

Activation of myogenesis in the craniofacial region depends on myogenic regulatory factors (Myf5, Mfr4 and MyoD). Muscle stem cell specification is driven by the basic helix-loop-helix (bHLH) transcription factors MyoR, Capsulin and the T-box factor Tbx1, Pax7 expression occurs after Myf5 and MyoD expression; Pax3 is not expressed in head muscle formation and it is Pitx2 and Pax7 that regulate myogenesis in this region (Buckingham, 2006). Sonic hedgehog (Shh) is a morphogen that also participates in the development of facial muscles (Straface *et al*., 2009), making it possible to observe myoblasts with positive immunostaining for the anti Shh morphogen (Fig. 3B).

Tongue muscles. Tongue myogenesis begins when Pax3-expressing myogenic progenitor cells detach from the ventrolateral edge of the occipital somites and migrate toward the lingual primordium via the hypoglossal cord. These muscles receive their innervation from the XII cranial nerve (hypoglossal nerve) except the palatoglossus, whose innervation comes from the vagus nerve. Cranial neural crest cells play an important role in tongue myogenesis, acting as a scaffolding structure for the organization of myoblasts that migrate toward the myogenic nucleus and operating as a source of molecular instruction to direct survival. proliferation and differentiation of myogenic progenitors. The close relationship between both cell types also plays an important role in the

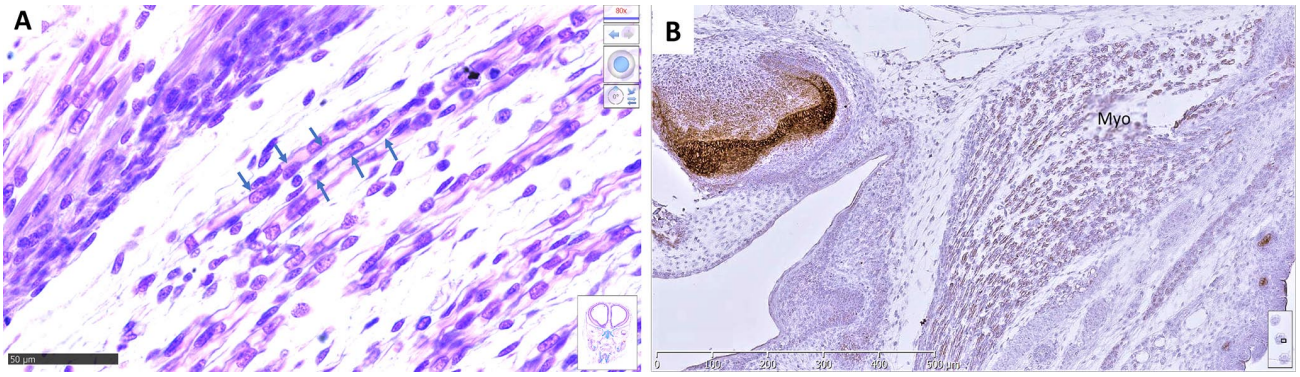

Fig. 3. A. Frontal section of the head of a human fetus, 12 weeks old. Multinucleated myoblasts are observed very close to each other (see arrows). The fibers are elongated and chromophobic. Endomysium formation can also be differentiated. H-E-Alcian blue, 800X. B. Frontal section of the head of a mouse embryo 14 days after fertilization. Immunostaining of the Shh morphogen is identified, with a brown color that slightly marks the myoblasts (MIO) of the mandible. A tooth germ is also observed that corresponds to the positive control. Anti Shh antibody immunohistochemical technique. 100X.

regulation of cell fate. The initial activation of the Pax3 gene induces the activation of the myogenic regulators MyoD, Myog and Myf5 leading to the formation of striated muscle (Parada *et al*., 2012; Comai & Tajbakhsh, 2014). In Figures 4A and 4B it is observed that the tongue presents myoblasts in a longitudinal direction alternating with other myoblasts arranged in a horizontal direction.

Myogenesis of the larynx. The larynx has striated muscles associated with the vocal folds that control the emission of sounds; these come from the mesenchyme of the fourth and sixth pharyngeal arches (Lungova & Thibeault, 2020). In Figure 3 we can see that in a 12-week human fetus there are fused myoblasts forming multinucleated cells, as well as satellite cells and cells of the future endomysium (Figs. 5A and 5B).

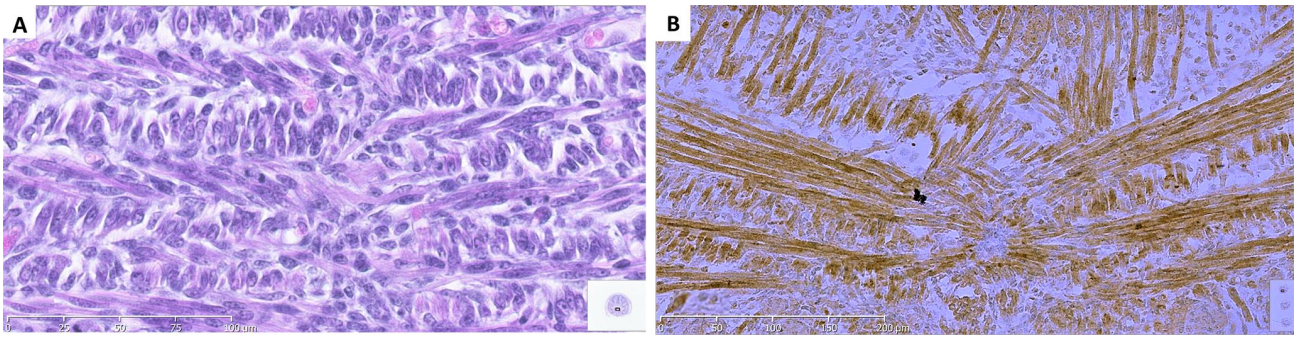

Fig. 4. A. Frontal section of mouse embryo. The tongue is observed with its myoblasts arranged alternately in an oblique and transverse direction. H-E 400X. B. Frontal section of mouse embryo. The tongue has myoblasts in a longitudinal direction alternating with other myoblasts arranged horizontally. Immunostaining is positive for myoblasts. Anti Shh antibody technique 200X.

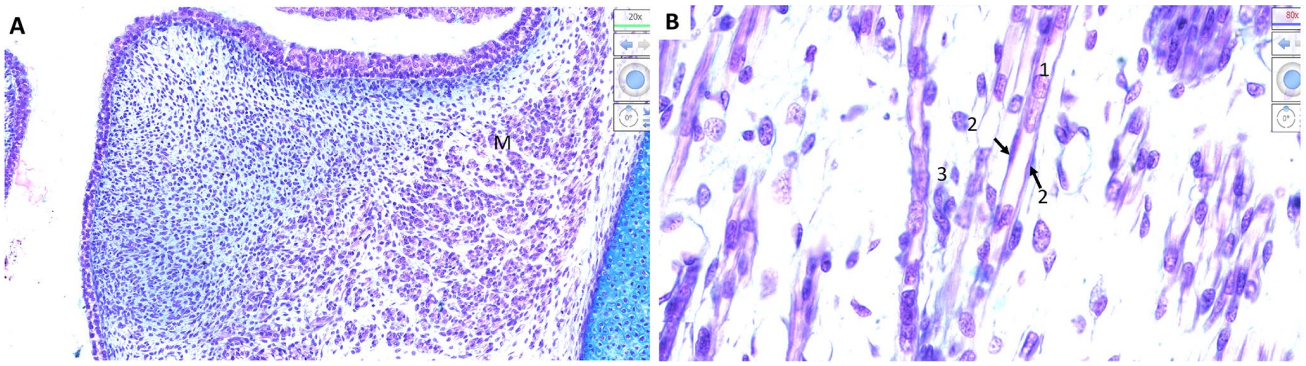

Fig. 5. A. Frontal section of the head of a 12-week human fetus. The true vocal cord of the larynx is observed, with stratified squamous epithelium, mesenchymal tissue, and the formation of myoblasts (M) H-E. Alcian blue 200X. B. Multinucleated myoblasts (1), satellite cells (2). endomysium formed by mesenchymal tissue (3). H-E. Alcian blue, 800X.

Myogenesis of the spinal column muscles. The cells of the ventrolateral region of the somite migrate towards the lateral somatic mesoderm crossing the incipient margin, defined as the limit between each somite and between the parietal layer of the mesoderm of the lateral plate, thus forming two domains, the primaxial domain and the abaxial domain (Shearman & Burke, 2009) (Figs. 6A and 6B). The migrating cells together with those of the somatic lateral mesoderm will thus make up the abaxial domain, which is the one that will form the muscles of the body wall, in addition to the musculature of the upper and lower limbs. On the other hand, the primaxial domain is that made up of a uniform population of somitic cells that surround the neural tube that will give rise to the muscles of the back, waist and intercostals (Burke & Nowicki, 2003). The domains mentioned above have great relevance in terms of the muscular innervation of the axial skeleton, since in the recent description of muscle development the embryonic origin of muscle cells is taken as a basis, taking into account two precursor populations of myocytes, the abaxial cells and primaxial, where the epaxial muscles (muscles of the back) are innervated by the dorsal primary branches and the hypaxial muscles (muscles of the body wall and limbs) are innervated by the ventral primary branches (Sadler, 2019). The innervation of the axial muscles is of great importance for locomotor function, since the striated muscle fibers are directly controlled by central neuronal activity where the motor nerves come in contact with the muscle fibers, which allows the voluntary action of the muscles. This is contrary to what happens with the cardiac muscle where spontaneous and involuntary activity occurs (Greger & Windhorst, 1996). In summary, a medial myotome that forms the intrinsic muscles of the back and from the lateral myotome, muscles of the limbs and body wall are formed.

Myogenesis of limb muscles. This process begins during the 7th week of development, where a condensation of mesenchyme derived from somites becomes evident on the dorsal and ventral sides of the limbs, cells that will later differentiate into myoblasts (Fig. 7A-B and 8). This process is regulated by connective tissue from the somatic lateral mesoderm (Moore & Persaud, 2020).

The development of limb muscles is determined by molecular signals from the neural tube and the notochord. These induce the expression of Pax3, MyoD and Myf5 in the somites, specifically in the ventrolateral region of the dermamyotome. Pax3 regulates the expression of MET (a migratory peptide growth factor) in the limb anlage, which regulates the migration of myogenic precursor cells (Comai & Tajbakhsh, 2014).

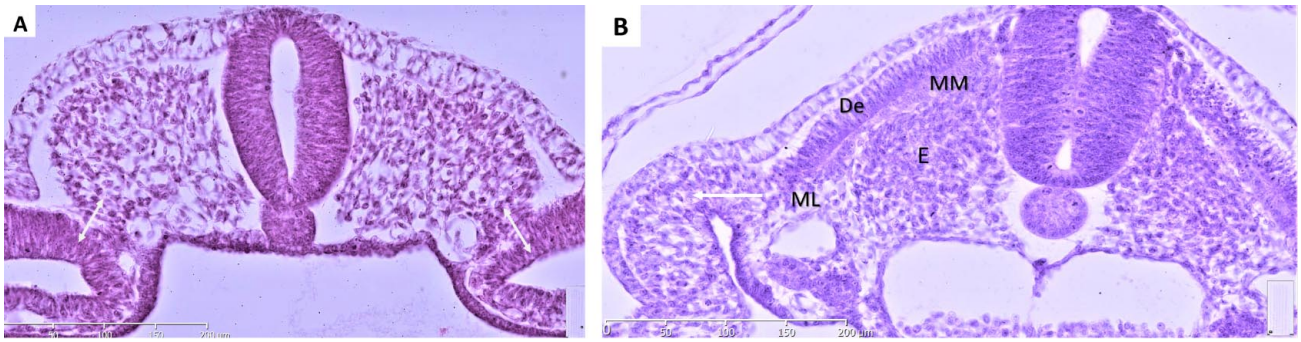

Fig. 6. A. Cross section of 24-hour chicken embryo. The somitic margin is observed (see arrows) the mesoderm that has not differentiated is very close to the somatic lateral mesoderm. H-E Alcian blue, 200X. 6B. 48-hour chicken embryo. Dermatome (De) has been differentiated from the somite (medial myotome (MM), lateral myotome (ML) and sclerotome (E). The somatic lateral mesoderm is adjacent to the myotome cells. 200X.

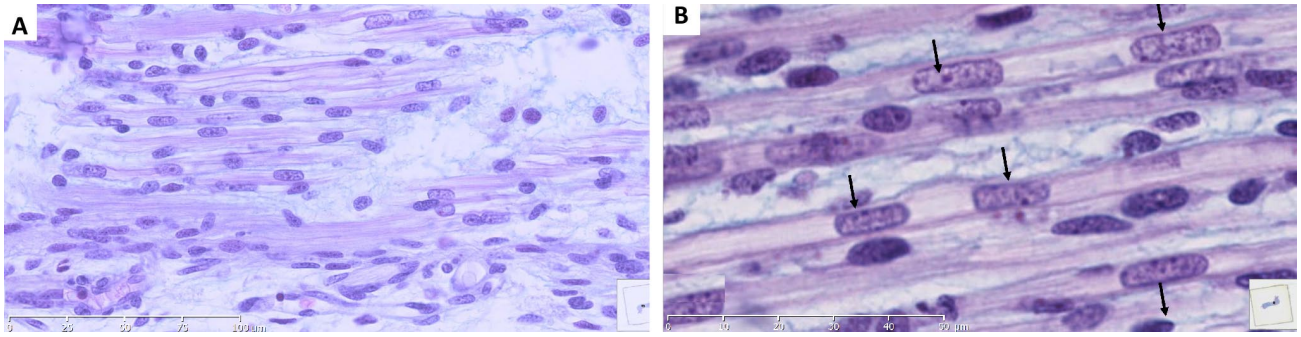

Fig. 7. A. Upper limb of a 9-week fetus Multinucleated myoblasts fuse with each other to form the muscle fiber. H-E Alcian blue 400X. B. Upper member. Higher magnification of the previous figure the myoblast nuclei are large and central (see arrows), very different from the nuclei of the endomysium. Alcian blue H.E 1000X.

Myogenesis of the cardiac muscle. Regarding the formation of cardiac muscle, it is important to consider that both it and skeletal muscle share certain characteristics; expression patterns become specific during postnatal development where the differentiated cardiac muscle does not express proteins that are specific to skeletal muscle (Clause *et al*., 2012).

The visceral or splanchnic mesoderm gives rise to cardiac myocytes that are in close contact both structurally and functionally, this through the intercalated discs that are responsible for joining adjacent cells together, which helps the contraction of multiple cardiomyocytes simultaneously as a unit for proper cardiac function (Carlson, 2019) (Fig. 9).

Specific signaling pathways involving fibroblast growth factors (FGF), bone morphogenetic protein (BMP), sonic hedgehog protein (SHH) and non-canonical Wnt ligands favor the specification of the cardiac mesoderm, subsequently through an activation cascade of transcription factors, cardiac specification and differentiation occurs (Paige *et al*., 2015).

Heart development begins when mesodermal progenitor cells within the primary cardiac field adopt a cardiac fate, in response to inducing signals from surrounding tissues to converge along the midline of the embryo to form a linear heart tube. Nkx2.5 is the first cardiac marker gene to be expressed, it occupies the center of the transcriptional circuit that confers the commitment and determination of the precursor cells of the cardiacfield to a myocardial destiny, this gene activates other transcription factors SRF, GATA4/6, Mef2c, Tbx5 and Hand1/2 involved in myocardial contractile function. Myocyte-specific factor (MEF) is expressed in cardiac cells and controls the timing and magnitude of muscle formation (Bassel-Duby & Olson, 2013).

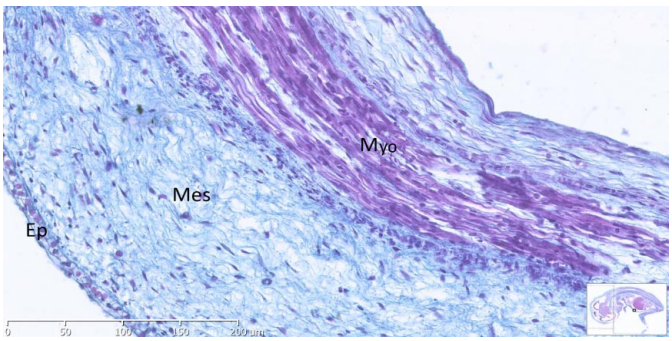

Fig. 8. Sagittal section of the ventral wall of a 14-week human fetus. The epidermis (Ep), mesenchymal tissue (Mes) and the myoblasts (Mio) in formation are observed to adopt an acidophilic coloration very different from the underlying mesenchyme. H-E Alcian Blue 200X.

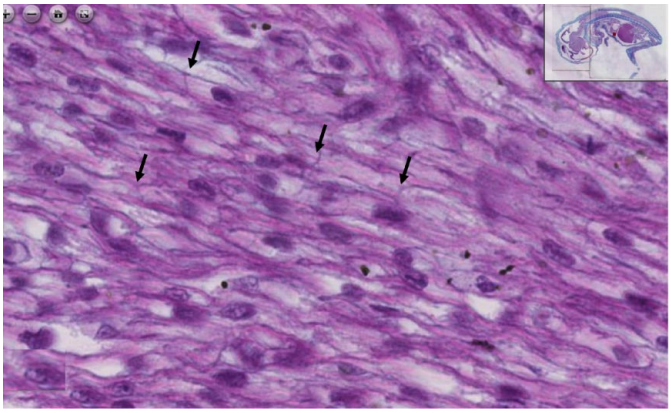

Fig. 9. Sagittal section of the heart of a 14-week human fetus. Cardiac musculature with intercalated discs is observed (see arrows). H-E 800X.

CONCLUSION

The formation of striated muscle is regulated by transcriptional factors that vary depending on the place where said tissue is formed. Myogenic regulation factors are expressed in all striated muscle except the tissue that corresponds to the heart since it has characteristics differences that make their development different from all others, analyzing the signaling pathways as well as the genes and factors that are involved, providing new elements to treat diseases of the skeletal and cardiac muscle.

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RESUMEN: Los distintos origenes embriológicos del tejido muscular estriado lo hace un tejido interesante, pero a la vez difícil de entender, es así como la musculatura de la cara proviene del primer arco faríngeo, en cambio, la musculatura de la lengua deriva de los somitos. La musculatura de la laringe proviene de los arcos faríngeos. La musculatura de la columna vertebral proviene del miotomo medial o interno del somito, en cambio la musculatura de los miembros y pared del cuerpo proviene del miotomo externo. La musculatura cardiaca se origina del mesoderma lateral esplácnico. En este trabajo se estudió el desarrollo de mioblastos en fetos humanos, de ratón y pollo, en la región facial, lengua, columna vertebral, miembros, pared del cuerpo y musculatura cardíaca mediante técnicas histológicas histoquímicas y técnica inmunohistoquímica. El objetivo del trabajo fue comparar la histogénesis del músculo estriado (esquelético, visceral y cardíaco), indicando las diferencias de origen, evolución de las características morfológicas en cada una de ellas y las rutas de señalización que se ven involucradas en el desarrollo del mismo.

PALABRAS CLAVE: Musculatura estriada esquelética; Musculatura estriada visceral; Somitas; Mioblastos; Mesodermo; Miotomo; Miocitos; Musculatura cardíaca.

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