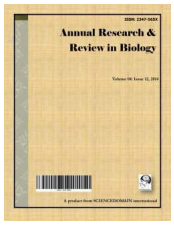

Annual Research & Review in Biology
9(6): 1-9, 2016, Article no.ARRB.24329
ISSN: 2347-565X, NLM ID: 101632869

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Craniofacial Muscles-differentiation and Morphogenesis

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Authors' contributions

This work was carried out in collaboration between all authors. Authors AAM and UVK downloaded the literature and helped in the introduction whereas authors VDS and SVD gathered the initial draft whereas the idea the formatting the final draft was designed by author ASP. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/ARRB/2016/24329
Editor(s):
(1) George Perry, Dean and Professor of Biology, University of Texas at San Antonio, USA.
Reviewers:
(1) Ayhan Goktepe, Selcuk University, Konya, Turkey.
(2) Parveen Akhter Lone, Indira Gandhi Government Dental College, Jammu, India.
(3) Rafael Denadai, Institute of Plastic and Craniofacial Surgery, Sobrapar Hospital, Campinas, Sao Paulo, Brazil.
Complete Peer review History: http://sciencedomain.org/review-history/13556

Review Article

Received 14th January 2016
Accepted 23rd February 2016
Published 4th March 2016

ABSTRACT

Unraveling the complex nature of tissue interactions is essential to generate structural and functional diversity present among craniofacial muscles. There are various distinct skeletal muscles in craniofacial region, the development of which are closely co-ordinated with other craniofacial tissues. The head musculature is known to originate from the cranial paraxial mesoderm (CPM) located anterior to the somites, and lacks any overt signs of segmentation. A consortium of transducting signals is required for the differentiation of skeletal muscle establishing spatially and temporally diverse myogenic populations. The induction, differentiation, and morpho-differentiation of these muscles is a relatively untouched area for experimentation with a cascades of signaling molecules, growth factors and genes. Various regulatory factors like Myf5, MyoD, Pax3, Pax7, Pitx2, Tbx1, Musculin and Tcf21 play a vital role in craniofacial muscle embryogenesis and morphogenesis. The relationship between craniofacial muscles and craniofacial morphology would seem to confirm the functional matrix theory of form and function. This review has been to highlight the classification, embryonic origin, differentiation and myogenesis, as well as the role of craniofacial muscles in growth of the craniofacial skeleton.

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Keywords: Embryogenesis; differentiation; craniofacial muscles.

1. INTRODUCTION

Understanding the intrinsic tissue interactions and its various pathways for morphogenesis of craniofacial muscles is very challenging. There are 60 distinct skeletal muscles in craniofacial region the head that control food intake, facial expression and eye movement. The development of these muscles is closely coordinated with other craniofacial tissues. The head musculature is known to originate from the cranial paraxial mesoderm (CPM) located anterior to the somites, and lacks any overt signs of segmentation. The CPM cells move into the branchial arches which eventually give rise to the facial structures. The regulation of head muscle patterning and differentiation by signals from adjacent tissues has been extensively explored in recent past [1]. The organization of craniofacial muscles is highly conserved, yet they are the most diverse musculoskeletal structures present in vertebrates. Skeletal muscles originate from the paraxial mesoderm which is a mesenchymal population. Surface ectoderm lies above the cephalic paraxial mesoderm with the pharyngeal endoderm under it with the migration of neural crest cells on its surface. The cell types generated within head paraxial mesoderm are similar to the cells present in trunk somite. At various axial levels, the morphogenesis and subsequent differentiation of skeletal muscle are under the interplay of various signaling molecules, growth factors and genes which control the myogenic cell populations [2]. Various tissues adjacent to craniofacial myogenic mesoderm are unique to the head (neural crest–derived mesenchymal cells and pharyngeal endoderm) and segment-specific which play a role myoblast differentiation and morphogenesis. Various craniofacial muscle primordial move from their sites of differentiation within the paraxial mesoderm into peripheral locations e.g., muscles that rotate or elevate the skull. Movements of the craniofacial complex results in differentiation of myocytes, with infusion of neural crest cells around the head muscles. The elongation and alignment of myocytes and angiogenesis of the muscular network coincides with the segregation of the neural crest cells and myogenic cell network. Our goal in preparing this review has been to highlight the classification, embryonic origin, differentiation and myogenesis, as well as the role of craniofacial muscles in growth of the craniofacial skeleton. The relationship of various craniofacial muscles in different growth patterns and it effect on orthodontic treatment has also been discussed.

2. CLASSIFICATION OF CRANIOFACIAL MUSCLES

The head muscles are generally classified according to their anatomical location within the head: They can also be classified as four distinct populations i.e. i) extra-ocular, ii) branchial, iii) laryngoglossal, and iv) axial. [3].

Axial muscles include muscles that cause various movements of the head. Terrestrial vertebrates unlike mammals have superficial facial muscles that are part of a constrictor colli system which help in swallowing and provide ventral muscle tone whereas in the mammals, there is a set of superficial facial muscles that permit fine motor movements of lips, eyelids, cheek, nose and specialized pharyngeal constrictors.

2.1 Extra-Ocular Muscles (EOMs)

The function of EOMs is to move and maintain the rotational stability of the eye in birds. The basic pattern of the six EOMs is common among all vertebrate classes, with various evolutionary adaptations. In early gnathosomes, vertical orientation of the lateral rectus is seen as compared to the horizontal alignment in most vertebrates. Various EOMs have been modified to form an appendage called the tentacle which results in reduction of the eye size in caecilian amphibians. Marlins, sailfish, and swordfish show a functional EOM adaptation. EOMs are compartmentalized into superficial as well as global orbital domains, allowing the global domain to initiate eye movements, whereas the orbital domain acts via the connective tissue pulleys as an elastic loading system, maintaining the rotational stability [3,4].

2.2 Branchial Arch Muscles

Branchial muscles are those associated with the first and second pharyngeal arches related to the craniofacial region which have evolved from an set of homologous gill muscles and skeletal elements [5]. Recent studies contradict the hypothesis that the first branchial arch have evolved from gill-supporting ancestor [3,5]. Axons innervating branchial muscles areise in lateral regions of the brainstem, which is distinct

from EOM and somatic motor nuclei [6]. As the terrestrial vertebrates evolved and there was loss of gill-supporting skeletal elements and the muscles within each arch underwent substantial modifications. The embryonic origins of suprahyoid muscles are diverse, including mylohyoid arch and digastricus, stylohyoid, and geniohyoid. Muscles derived from the second branchial arch myoblasts whic segregate to periauricular, periorbital, and perioral regions are associated with facial expression and ear movement are unique to mammals [3].

2.3 Intrinsic Laryngeal Muscles and Tongue

Glossal and laryngeal Muscles have a more extended ancestry and are relatively a part of evolutionary adaptations of the craniofacial musculoskeleton [7]. Hypobranchial myoblasts originate from the rostral somites and migrate underneath the pharyngeal structures in lamprey embryos [8] where in fishes these myoblasts attach gill elements to the coracoids bone [9]. It is surprising to see that in amphibians the same myoblasts arising from occipital somites forms the hypoglossal cord which elongates and allows myoblasts migrate ventral to pharynx, where they help in morphogenesis os the intrinsic tongue an dlayngeal muscles as well as extrinsic tongue muscles [10].

Initial hypotheses of the tongue muscles arising from the gills have much been discarded after identifying that they are innervated from neurons located in somatic instead of the branchial motor nuclei [11]. Where as in transgenic mice null for Tbx1 some tongue muscles are intact thus classifying them as hybrids [12].

2.4 Axial Muscles

Muscles for craniofacial stabilization are arising from the medio-dorsal and latero-ventral domains of occipital as well as cervical somites and are multi-segmental [13]. These muscles are classified as (i) hypaxial .i,e. muscles that are ventral to the transverse process and (ii) as epaxial i.e. muscles that are dorsal to the transverse process. Among the hypaxial are the infrahyoid muscles which assist in lowering of the root of the tongue and larynx [13].

3. EMBRYONIC ORIGINS AND FORMATION OF HEAD MESODERM

The cascade of events will be explained according to following sequence:

i) Head Cavities and Pre-Otic Somites
ii) Prechordal Mesoderm
iii) Paraxial Mesoderm
iv) Regionalization of the head mesoderm

3.1 Head Cavities and Pre-Otic Somites

In shark embryos a series of epithelial-lined condensations rostral to the otic vesicle retain connections with the coelomic cavity [14,15] which inturn become isolated during lateral expansion of pharyngeal pouches and visceral clefts. Gilbert [16] identified mesenchymal condensations in early cat and human embryos that included primordia of extraocular muscles and within which myotome-like epithelium cluster are formed that becomes associated with an EOM-innervating cranial nerve, [17]. They also identified paired premandibular cavities which were small in size in chick embryos [17].

3.2 Prechordal Mesoderm

Head mesoderm is developed and is in its position by mid gastrulation stages. The head mesoderm includes prechordal mesoderm n the median plane. Paraxial mesoderm is contineous laterally with prechordal mesoderm which arises from progenitors cells in the rostral margin of the elongating primitive streak (avian) and finally extends to the first somite [18]. The prechordal mesoderm is often indistinguishable from the neuroepithelial and endodermal layers [19]. Homeobox signaling i.e. Hedgehog and nodal signals from these cells are essential for the regional specification of the neural crest cells and also for the bifercation of the prosencephalic structures [3,20].

Retroviral mapping studies and transplantation studies have shown that the prechordal mesoderm contributes to the formation of the medial, ventral, dorsal rectus as well as the ventral oblique muscles, which are innervated by the III cranial nerve i.e. oculomotor nerve [21,22].

3.3 Paraxial Mesoderm

Paraxial mesoderm which helps in formation of the craniofacial structures is formed by the time the streak reaches its maximum length. Normally the paraaxial mesoderm is generated from the primitive node and streak beginning at the onset of gastrulation, and most of the head mesoderm. The head paraxial mesoderm appears as a rapidly generated population without spatially separable progenitors [23].

3.4 Regionalization of the Head Mesoderm

The exact molecular nature of the CPM and SpM, remains unclear. Recent gene expression analyses in avian models have begun to reveal the molecular milieu of head muscle progenitors in St. 8, St. 10, St. 16 and St. 20 and 24 chick embryos [24-27]. Pitx2, Tcf21 (capsulin), Msc (MyoR), Twist, Alx4, and Tbx1 genes are shown to be expressed in the head mesoderm: Alx4, Tbx1, Cyp26C1, and Twist are expressed in the CPM In St. 8 chick embryos, the SpM is found to express, Isl1, Nkx2.5, Fgf10, and Tbx20, a set of second heart field markers in agreement with the cardiogenic potential of these cells [24]. There is considerable overlap in the expression of head muscle markers e.g., Myf5, Tcf21 (capsulin), Msc (MyoR), Tbx1, Pitx2 and cardiac lineage markers (e.g., Islet1 and Nkx2.5) in the CPM and SpM [24]. Taken together, these studies have begun to delineate the molecular regionalization of the headmesoderm continuum in these fields along the medial lateral/dorsal–ventral axes.

Craniofacial paraxial mesoderm is mesenchymal in nature and appears homogeneous in nature from the optic vesicles to the hindbrain, site of somite formation which is co-ordinated by growth factors, genes and various pathways like Fgf8, retinoic acid, Wnt signaling, Notch pathway related genes such as hairy1 and 2.

In a series of SEM examinations in amphibians, reptiles, chicks and mammals; shallow transverse grooves demarcates he superficial and deep surfaces of head mesoderm, wherein the cells attained a circular orientation named somitomeres which represent vestiges of an evolutionarily condition which proves that the head mesoderm was fully segmented [28-30]. But the earlier has been proved wrong as they arrest before epithelialization and thus lack any separations.

Pattern of movement is the distinguishing factor for each of these lineages i.e. certain chondrogenic cells are stationary and differential expansion helps in change in location [31]. Osteogenic precursors of intramembranous bone which arise medial to the head paraxial mesoderm, move dorsally around the brain settling at the superior surface of the future frontal and the parietal bones. The initial locations of many myogenic condensations within branchial arches led to the conclusion that myoblasts mesoderm originates in this lateral mesoderm [32]. All head myoblasts especially in avian and murine embryos arise in paraxial mesoderm [22,33].

Progenitors of craniofacial skeletal muscles are organized as individual muscle primordia and later segregate into several muscles which occupy specific locations in branchial arch. Branchial muscle primordia, located superficially within head paraxial mesoderm, are initially in contact with overlying surface ectoderm. EOM primordia tend to be closer to the midbrain and hindbrain than are branchial myoblasts [34].

4. MOLECULAR ASPECT OF AXIAL MUSCLE DIFFERENTIATION

The core myogenic network are recruited during evolution to create the craniofacial muscles determine muscle identity and promote muscle differentiation. They consists of the myogenic regulatory factors Mrf4, Myf5, Myf6, Myod and myogenin [35,36].

4.1 Myf5

Myf5 expression in the cervical and occipital somites is an effect of loss of gene function of pax3 and shh. [37], which are a result of the variable Hox code along the body axis along with the variation in Notch signaling in the mesoderm [38]. Distinct enhancers regulate myf5 expression both temporally and spatially within the developing embryo in a combinatorial and co-operative fashion. Myf5 expression within the craniofacial musculature is also variabily controlled at differential locations and these sites operate as part of an integrated modular controlling network [36,39].

4.2 MyoD

MyoD expression in differentiating myoblasts is controlled by the myoD enhancer [40]. MyoD expression in the somites is regulated differentially indicative that the signaling pathways controlling the onset of myogenesis are not mimicked in the entire embryo.

4.3 Pax3 and Pax7

Pax3, which is absent in craniofacial muscle progenitors and Pax7; activate Myod expression by binding to its regulatory sequences [41-43]. Furthermore, embryos in which embryonic Mrf4 expression is perturbed in cis by disruption of the Myf5 locus, craniofacial muscle morphogenesis

is seen where as trunk muscles do not develop. Some head muscles have shown to up-regulate various genes like capsulin, engrailed and tbx1 which are not usually part of the axial myogenic repertoire. Tbx1 null mice results in agenesis of branchial arch muscles sparing only a few muscles of the mandibular prominence indicating heterogeneity within the branchial arches in the myogenic populations or the phenotype [12] MyoR upregulation help in this muscle survival which is linked to the first branchial arch myogenic defects in the tbx1 null mice [36].

4.4 Pitx2 and Tbx1

Pituitary homeobox 2 (Pitx2) expressed in the head of mouse embryos plays a key role in specifying EOMs where as Pitx2 which is expressed in trunk muscle progenitors plays a role in downstream of Pax3 in somitic myogenesis [44,45]. Pitx2 acts by binding to the promoters of Myf5 and Myod [45]. The T-box gene Tbx1 is a transcription factor which specifies PA, but not EOM, muscle founder cells [43]. A monolateral ablation of skeletal muscles is observed in Tbx1-null mutants whereas Tbx1 and Pitx2 cross-regulate each other and activate the same target genes [43,46].

In humans, Pitx2 mutations cause Rieger syndrome whereas, TBX1 mutations causes DiGeorge syndrome suggesting that both these genes act autonomously, as well as non autonomously, to influence muscle development [47].

4.5 Musculin and Capsulin

Musculin (expressed in head and body muscles) and Capsulin (Tcf21) act as repressors in morphogenesis. These transcription factors play a key role in the PA, but are not upregulated or down regulated in the EOM founder cells. Musculin and Capsulin mutant mice embryos result in agenesis of a subset of first branchial arch-derived jaw muscles [48]. The linkage and pathway between these transcription factors and MRFs has still not been explained and understood.

4.6 Others

Barx2, myoR, meox1, six1 and -4, pitx2, and the c- Met ligand HGF are other regulatory genes common to both head and trunk muscles. But there expressibility of these differ in different regions which is seen by less severe disruption of head myogenesis in null mutant mice [49]. Six1 inactivation causes little effect on the epaxial and other head muscles but affects the trunk muscles like the diaphragm, muscles of abdominal wall, limb and tongue muscles. An exacerbated version was seen in the double Six1/Six4 knockouts with defects extending to the head muscles delaying extraocular myogenesis [37]. Myogenic lesions following loss of pitx2 function in mice were found only in the extraocular muscles whereas on the contrary gene-inactivation of pitx2 in the periocular cranial neural crest cell has not shown to the early differentiation of ocular muscles [36].

5. MECHANISMS OF CRANIOFACIAL MYOGENESIS

Developing craniofacial muscles require a consortium of molecular signals and gene expressions to produce a plethora of transduction and transcription pathways. Cranial myogenic mesoderm has localized commitments to different lineages due to its proximity with a number of tissues. Signaling of the Wnt, Fgf, and Bmp families determine specification of these placodal fields [3,50]. Additional region-specific signaling of Fgf3, Fgf19 and Tbx1 have been identified within the paraxial mesoderm below the otic placode [51]. Neural crest population migrates over the precursors of 1st branchial arch muscles and express the Wnt antagonist Frzb, and the Bmp antagonists noggin as well as gremlin. Wnt1 exhibits a dynamic expression pattern in the midbrain and areas of decreased Wnt expression correspond to myogenic focal areas within the paraxial mesoderm. Shh play a major role in the maintenance of epaxial trunk muscles but does not play any role in the initial regulation of myogenic differentiation [52]. Co-expression of Bmp7 from the midbrain, diencephalon and the notochord augments Shh un responsiveness [53].

6. MORPHOGENESIS OF HEAD MUSCLES

Muscle morphogenesis consists of relocation of muscle precursors from their site of origin to the site of terminal differentiation and the process of arrangement of the primary myotubes as well as the accumulation of individual muscle fibres to adjacent connective tissues. Myoblasts express regulatory factors like lbx1, paraxis and six1 which help in migration of these cells from the lateral myotomes [54,55]. These migrators are essential for the formation of all intrinsic and

extrinsic tongue muscles. The neural crest cells and the differentiating myoblasts reach the future branchial muscle primordial shifting ventrally in concert with each other. No sooner they shft ventrally the motor axons contact and enter the myogenic cord [56].

The final locations of the EOM primordia are achieved by various processes like population expansion, as well as multidirectional movements, synchronous with the changes in the orientation and position of the eye [57]. Regulatory interactions arising between the EOMs and eye are absolutely essential for formation of secondary motubes and differentiation of the retina [3,58].

Borue and Noden, [59] have proposed "mesoderm interface" which is a passive displacement model which is based on changes in the contour of the neural crest. It has been proved beyond doubt that the dorsal oblique is not a moving island but is at the extreme end of a straight projection of mesoderm that intermingles with projections of neural crest cells. Ectopic trunk mesoderm cells block the periocular crest cells which would encircle the myogenic tip.

The surrounding connective tissues provide positional cues for the formation of attachments of muscles with branchial skeletal and connective tissues. Altered patterned in the organization of craniofacial muscles is seen in experiments with manipulation of branchial arch crest populations which helps us to conclude that there must be extensive interplay in the consortium of signals which control muscle morphogenesis in the head and trunk [60-62].

Direct evidence is lacking that periocular neural crest cells play a major role in EOM morphogenesis. The intimate cellular, molecular, biochemical and genetic co-relationship between the head, face and heart manifested in various cardiac and craniofacial birth defects is termed as cardio-craniofacial morphogenetic field [3].

7. SUMMARY

Morphogenesis of craniofacial muscles is seen with a plethora of complex cellular, biochemical, molecular and genetic cascades. Various regulatory factors like Myf5, MyoD, Pax3, Pax7, Pitx2, Tbx1, Musculin and Tcf21 play a vital role in craniofacial muscle embryogenesis and morphogenesis. The challenges that lie ahead will be to precisely the signals that regulate the dynamic developmental processes underlying the specification, migration and differentiation of the different myogenic lineages in the head.

Form and function theory still seems to dominate the inter-relationship between morphology and muscle which has been proved by studies showing brachyfacial individuals having thick mandibular muscles where as dolichofacial patients have relatively weak mandibular muscles. Developing craniofacial muscles require a consortium of molecular signals and gene expressions to produce a plethora of transduction and transcription pathways. Myogenic regulatory factors Mrf4, Myf5, Myf6, Myod and myogenin as well as Pax3, Pax7, Barx2, myoR, meox1, six1 and -4, pitx2, Musculin and Capsulin play a major role in morpho-differentiation of craniofacial muscles.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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