

Review Article

Septopremaxillary ligament traction system: a review

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ABSTRACT

Over the years, several animal studies have been conducted concerning the role of cartilaginous nasal septum, septopremaxillary ligament in midfacial growth. Most of the studies utilized non primate animal models at first and then more recently in primates such as chimpanzee. Proper choice of animal model to extrapolate from is critical for successful experimental design. Although nonhuman primates are phylogenetically closer to humans than other mammalian groups for better extrapolation to human condition, not all the craniofacial experiments require primate models. Renewed interests in understanding the influence of septopremaxillary ligament resection on midfacial growth led to many in vitro experiments on animal models. Recently systematic review of relevant animal experiment is regarded as a prerequisite for the conduct of the new clinical trials. Despite this fact, the literature addressing this topic in humans and systematic review on the effect of the septopremaxillary ligament is scarce. The more recent studies show that the maxillary labial frenum encloses the septopremaxillary ligament and forms an important constituent of septopremaxillary traction system. The biomechanical force mediating through the septopremaxillary ligament, maxillary labial frenum and nasolabial muscles results in stimulating their effects on sagittal growth of the maxilla. The main purpose of this review is to update and extend the knowledge of the role of septopremaxillary traction system on the midfacial growth by synthesizing the available literature involving the septopremaxillary ligament resection in experimental models. If this review could synthesize the results of relevant research, a change in the therapeutic notions can also be expected.

Keywords: Labioseptopremaxillary region, Maxillary labial frenum, Nasal septum, Nasolabial muscles, Premaxillary/maxillary growth

INTRODUCTION

Systematic reviews are considered to be the highest level of medical evidence and improve the interpretation of already published scientific results. This will optimize patient safety and prevents unnecessary duplication of animal studies. It is rather difficult to perform high quality literature review in laboratory animal studies due to poor scientific quality and most papers do not report necessary details.¹

Systematic review of animal experimentation includes a wide range of various animal species. Consistent results across several species provide some reassurance that human beings might respond in a similar manner and that the results can be generalised. Recently systematic review of relevant animal experiments is regarded as a prerequisite for the conduct of the new clinical trials. Although performing systematic reviews is a standard practice in clinical studies, this is not the yet the case for animal studies.²

Several theories of craniofacial growth have been evolved over the years. One of the most leading theories is the cartilaginous (nasal septal) theory. Though German anatomist, Fick seems to be the originator of this theory, it has been closely connected with Scott.^{3,4} Later on it was modified by Latham by his septal traction hypothesis involving septal cartilage and the septopremaxillary ligament (SPL).⁵ It is a fibrous perichondral attachment which Precious and Delaire described it as “cellulose septum of the upper lip.”^{6,7}

For a better understanding of early midfacial growth due attention should be paid to the interaction of cartilaginous nasal septum and its related functional matrices.⁸ Recent studies suggest the existence of a relationship between hypoplasia of the anterior midfacial growth and both the disruption of the SPL attachment and the labioseptopremaxillary (LSP) region in cleft lip and palate individuals.^{9,10} This view is further supported by the complete reconstruction of the facial and muscular components of the nasolabial complex in cleft individuals.¹¹ Despite various designs of animal studies in different species were performed in this regard, the literature addressing this topic in humans and systematic review on the effect of the SPL in the animal models is scarce.¹²⁻¹⁴ The value of these studies that throws light upon the midfacial growth is usually undermined by the decisive influence of primary surgery which is known to interfere with subsequent growth and obscure the observations to a certain extent.^{15,16}

So, does the normal interaction of various components of nasomaxillary complex require maintenance of normal spatial relationships in the individual units in the complex?. In particular of the SPL, was the disruption of the ligament, its associated mucoperichondrium and musculature of the LSP region a determining factor in the midfacial advancement?. Does re-establishing the integrity of LSP region facilitate the anteroposterior midfacial growth?. To answer these questions various experimental studies were conducted at first in non-primates (rabbits, rats, pigs, dogs) and then more recently in primate subjects (Chimpanzee) for better extrapolation to human condition.¹⁷⁻²³

The main purpose of this review is to update and extend the knowledge of the role of septopremaxillary traction system on the midfacial growth by synthesizing the available literature that involves resection of the SPL in experimental animal models. If this review could systematically synthesize the results of relevant animal research, a change in the therapeutic notions can also be expected. This systematic review was reported using the ARRIVE checklist as a template.²⁴

Protocol and registration

No review protocol or systematic review registration was considered.

Information sources

With the assistance of a health science librarian, a computerized systematic search was conducted in the electronic databases such as PubMed, EBSCO and Google Scholar. In addition, a limited gray literature search was also conducted. The references of the selected articles were also hand searched for additional relevant studies that might have been missed out. Only published articles in English/translated to English were selected. Articles relating to the resection of the SPL, septal traction hypothesis and the growth of the nasomaxillary complex/ midface are considered.

Searches

When performing the above searches, specific medical subject headings and keywords were used first in PubMed (Table 1). The additional searches were modified appropriately.

Table 1: Search strategy for EBSCO (1935 up to December 2018).

S.No	Searches
1	Craniofacial morphology / maxillofacial/ maxilla/premaxilla/maxillary growth and development
2	Upper jawbone/ midfacial growth/growth and development of nasomaxillary complex/ hypoplasia/ post-natal growth
3	Malocclusion
4	Resection of septopremaxillary ligament, nasolabial muscles, nasal septum

Study design

In vitro animal experiments and observational animal studies.

Study selection

The selection of articles at each stage is presented in Figure 1. In step 1, only the titles and abstracts collected from the earliest records till March 2019 were considered.

In step 2, copies of full articles were reviewed from those selected in step 1, some were excluded if they did not specifically evaluate the growth and development of the nasomaxillary complex. In both steps of the review process, 2 reviewers independently reviewed the titles and abstracts and disagreements were resolved through discussion until consensus was achieved. Seven articles which satisfied the selection criteria were included in the present study.

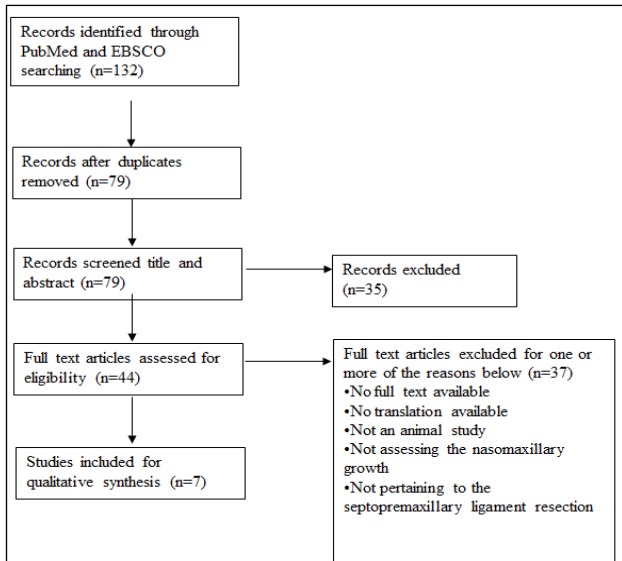


Figure 1: Systematic review literature search results.

Data extraction

Data were extracted from selected articles by the two reviewers independently with respect to the study design, experimental procedures, sample size, details of animals used, randomization, blinding, methods used to analyze the data, results of the study and generalisability or translation of the reported findings.

Literature search

We identified forty-four potentially eligible articles, of which seven met our inclusion criteria. Figure 1 shows the number of studies identified at each stage of the selection process.

Inclusion criteria

The seven studies^{10,16-18,20,22,23} included in this review are pertaining to the midfacial growth, septopremaxillary traction system and the SPL resection in experimental animal models. The included studies comprises of two observational and five interventional studies.^{10,16-18,20-23}

Risk of bias assessment

The credibility of the causal relationship between the intervention studied and the effects observed is dependent upon how animal experimentation is designed, conducted and analyzed.

An appropriate animal model in any experimental studies is a fundamental for a successful experimental design. Systematic reviews contribute in optimizing the experimental design and ensure adherence of necessary conditions for making use of animals in these experiments is justified. In most of the experiments the animals were deliberately killed and the use and sufferings of the animals are not balanced by benefits in terms of scientific advancement or/and human health.

Henceforth we focused on quality assessment of the included studies which involve the following internal validity items such as randomized study design (selection bias), blinding of the investigator (performance bias), blinding of the outcome assessment (detection bias) and specification of drop-outs (attrition bias) by the two authors independently as illustrated in Table 2.

The earlier study conducted by Gange RJ, 201 newborn Sprague-Dawley albino rats were obtained from thirty litters (Table 2). The study sample was divided into four groups such as those of controls, those underwent the surgical procedure at birth, those operated on at birth and at 8 days and a group that was operated on at birth, 8 days and 22 days. Thus, the part of the sample was subjected to series of additional lesions during the course of the study. All the animals were weaned at 21 days and fed with a diet of water and Purina laboratory chow in pellet form ad libitum. At the age of 43 days the animals were killed with an overdose of ether and prepared for cephalometric analysis.¹⁶

Experiment conducted by Bernstein in mongrel pups report that the mucoperichondrium enclosing the nasal septal cartilage probably plays a very important role in the nasal septal growth directly and in the growth of maxilla indirectly. The study was executed to determine the effect on midfacial growth following the submucous resection of the large section of the septal cartilage on 4 to 6-week-old canine pups (Table 2). Standard animal care was provided after the surgical procedure. Two weeks later, when the healing was deemed to have taken place the pups were transferred to special animal farm. The animals were examined 10 months postoperatively, for general configuration of the jaws and head, outline of the bony cartilaginous nasal dorsum and occlusion of the teeth. They were then killed by overdose of intravenous pentobarbital. The specimens were fixed immediately and the sections were stained for histological examination.²⁰

A 5-year longitudinal study was designed by Siegel et al to investigate the traction potential of the SPL and midfacial growth in a sample of 17 chimpanzee animal model (Pan troglodytes). The sample was divided into 7 unoperated controls, 5 shams and 5 animals with early SPL resection balanced for sex. Surgical procedure was performed at an average of 139 days and all the animals were housed and maintained under standard laboratory conditions. The lateral cephalograms and dental study models were collected quarterly through 1200 days of age, while the animals were tranquilized. The films and models were randomly selected blindly from the three groups and measurements were repeated for intra-examiner reliability. He demonstrated significant anterior midface or premaxillary growth deficits by 1200 days of age following early SPL resection in chimpanzee animal model, the most humanlike animal.¹⁰ The data from his another study using the chimpanzee animal model also support the concept of early reestablishment of SPL and labioseptopremaxillary region to facilitate normal midfacial and nasal capsule growth (Table 2).²²

Table 2: Summary of characteristics of included articles.

Article	Study design	Sample size	Species used	Age	Out-come measured	Statistical method used	Outcome estimation	Random-ization/blinding	Generalisability/translation
Gange R, Johnston LE (1974)	Interventional	201	Sprague Dawley albino rats	Followed up from at birth to 43 days of age	The animals were killed at the 43 days of age; size and position of nasomaxillary complex were measured using cephalometric landmark	F statistics was applied	Mean, variance and P value were estimate	Not reported	The study evaluate the role of SPL in the midfacial growth and study results conform closely to the predictions generated by the septal traction hypothesis
Bernstein L (1973)	Interventional	29	Mongrel pups	4 - 6 weeks of age	The autopsy specimen of nasal septum which is fixed and decalcified is stained with hematoxylin-eosin/Koneff stain	Not applied	Not applied	Not applied	The mucoperichondrium plays a more important role than the septal cartilage in the growth of the nasal septum and midface
Article	Study design	Sample size	Species used	Age	Out-come measured	Statistical method used	Outcome estimation	Randomization/blinding	Generalisability/translation
Siegel et al (1990)	Interventional	17	Pan troglodytes	3-5 months of age and followed up till 5 years of age	Lateral head x-rays and dental study models were collected quarterly through 1200 days of age.	Test of homogeneity of regression line slopes was applied	P value was estimated found to be < 0.05	Randomization applied	Premaxillary and maxillary growth rates were significantly reduced following SPL resection, independent of surgical trauma. It supports the concept of early reestablishment of SPL in primary nasolabial cleft repair
Siegel et al (1992)	Interventional	17	Pan troglodytes	3 - 5 months of age and followed up till 5 years	Dental casts and lateral cephalograms were taken preoperatively and 4.5, 9 months postoperatively and every 6 months thereafter. Measurements were made from the xeroxed copies of study models using the computer assisted digitization method	Two-way ANOVA, Least square regression equation calculated	Mean nasal capsule area with SEM and p value were estimated (p<0.05). Intraexaminer reliability was also estimate	Randomly assigned	Early septal mediate traction model of anterior midfacial growth may be responsible in part for the normal growth of the nasal capsule as well
Mooney MP, Siegel MI (1991)	Observational study	Skull from 55 chimpanzee (29 males & 26 females)	Protroglodytes	From infants to adults	Premaxillary - maxillary suture status and ANS status were assessed	Chi-square test and Phi coefficient were applied	P value (< 0.05) was estimate	Singles blinding applied. Intrarater reliability assessed	The results document the important role of SPL in anterior advancement of midface in the chimpanzee
Wealthall RJ, and Herring SW, 2006	Observational study	27 mice	CD-1 mice	0-15 days	Measured the cell division and mineralization rate at the septopresphenoidal and septoethmoidal junction using BrdU and double fluorochrome labeling	Appropriate statistical tests such as ANOVA, Tukey's HSD test, Levene's test, Welch ANOVA, least square regression were applied	Mean, SE, p value (p<0.0001) were estimate	Mice were randomly assigned to each of the four groups.	Interstitial expansion is the main contributor of septal growth which is consistent with the septopremaxillary traction hypothesis
Article	Study design	Sample size	Species used	Age	Out-come measured	Statistical method used	Outcome estimation	Randomization/blinding	Generalisability/translation
Al Dayeh AA, Herring SW (2014)	Interventional	6 Females - 4 Males - 2	Juvenile minipigs (Sus scrofa)	4.4±1 months	Proliferation and cellular density in different locations of the nasal septal cartilage was assessed	Kaleidograph and SPSS were used as appropriate.	Mean, confidence interval and p value for each of the variable were estimated. Intraexaminer reliability was performed.	Random numbers were assigned to the captured image to blind the examiner	The study emphasized that the anatomy of the septopremaxillary region in minipigs is conspicuous with that of the human embryo

Table 3: Table illustrating baseline data, animal husbandry, adverse events and limitations of the included studies.

Article	Baseline date	Housing and husbandry	Adverse events	Limitations of the study
Gange R, Johnston LE	Unclear	After recovering from anesthesia each animal was returned to its mother. They were weaned at 21 days of age and fed with diet of water and Purina laboratory chow in pellet form ad libitum	Not reported	All animals were anesthetized and initially subjected to surgical procedure within 24 hours after birth. On the 8th day, lesions were again created in two thirds of the experimental rats in each litter. At 22nd day additional lesion was created in half of the animals which had been operated on 8th day. At the age of 43 days they are killed with overdose of ether
Bernstein L (1973)	Animals used were of unknown parentage, weighing between 2 -2.5 kg.	Unclear	One pup has died several hours after surgery.	No intraexaminer reliability was estimated. No statistical techniques were applied. All the animals were killed after the observation period postoperatively.
Siegel et al (1990)	Normative data for the seven unoperated control animals were obtained from the previous growth study laboratory. The remaining ten animals were randomly assigned by sex to either of the other two groups at 3 to 5 months of age.	All animals were housed and maintained under standard laboratory conditions at the Southwest Foundation for Biomedical research, Texas.	Not reported	Experimental and sham control animals were subjected to the surgical procedure at an average of 139 days under general anesthesia
Article	Baseline date	Housing and husbandry	Adverse events	Limitations of the study
Siegel et al (1992)	Normative data for the seven unoperated control animals were obtained from the previous growth study laboratory	All animals were housed and maintained under standard laboratory conditions at the Southwest Foundation for Biomedical research, Texas.	Not reported	Experimental and sham control animals were subjected to the surgical procedure at an average of 139 days under general anesthesia
Mooney MP, Siegel MI (1991)	Sample was obtained from the primate collection housed at the Department of Mammals, Carnegie Musuem of Natural History, Pittsburgh, PA and Department of Mammals, Smithsonian Institute, Washington, DC.	The study sample was obtained from primate collections housed at the Deartment of Mammals, Carnegie Museum of gatural History, Pittsburgh, PA, and the Department of Mammals, Smithsonian Institute, Washington, DC	Not applicable	Not applicable
Wealthall RJ, Herring SW (2006)	Approved by institutional animal use and care committee, University of Washington. Sample was obtained from Charles River Labs, Wilmington, MA.	Housed under standard conditions with 12 hour light cycle, tap water supply and rodent chow from Picolab rodent diet20, Purina Mills, MO ad libitum	Not reported	Juvenile mice were sacrificed with intraperitoneal injection of pentobarbital and adult mice by Carbondioxide inhalation
Al Dayeh AA, Herring SW (2014)	Sample was obtained from Sinclair research farms, MO, USA, averaging 23±6 kg in weight	Not reported	Not reported	The animals were killed by intracardiac perfusion under isoflurane anaesthesia

The study sample of Mooney et al comprises of chimpanzee crania to document the presence of the anterior nasal tubercle (ANT) and the results are in agreement with the concept of septal traction model of midfacial growth (Table 2). The assessment of the suture status and the ANT were rated blindly. Intra-examiner reliability and appropriate statistical analysis were also performed.²³

Wealthall and Herring reported that endochondral ossification at the caudal and dorsal borders of the nasal septum when combined with the interstitial expansion displaces the facial skeleton away from the neurocranium and thereby enlarging the skull (Table 2).

In this study the juvenile mice (0-15 days postnatally) from three litters were divided into four groups. Bromodeoxyuridine labeling was used to compare cell division at the synchondroses, and double-fluorochrome labeling was used to measure mineralization rate. All the procedures undertaken in the study were approved by the institutional animal use and care committee. The animals were housed under standard conditions with a proper lighting and feeding. Appropriate statistical analysis was performed using SAS software.¹⁸ The study conducted by Al-Dayeh was carried out on six pre-pubertal minipigs (*Sus scrofa*). The choice of the study sample is based on the fact that it is the fast growing species with a long snout which enables to identify the sites of septal proliferation and to assess the uniformity of the growth of the septal cartilage (Table 2). The study sample was injected with 5'-bromo-2'-deoxyuridine (BrdU), 24 hour before death.¹⁷

In none of the selected studies, there was no mention about the detection bias. No report on drop outs could be found except for one of the included studies which stated that one of the experimental animals has died during the conduct of the study (Table 3).²⁰ Except for the study conducted by Wealthall et al., approval of the animal ethics committee is not specified in any of the studies.

The housing conditions of the included animal studies such as baseline characteristics, lighting, humidity and temperature which are known to influence the outcome of the study are tabulated in Table 3. Assessment of similarity in important baseline characteristics in experimental and control groups should be considered in all animal experimentation. The way the animals are housed (such as location of cage in a room) is a critical factor that may influence the outcome of the study. There can be four-fold differences in light intensity between the cages at the top and bottom of the rack. Small changes in light intensity are probably known to be associated with the reproductive and behavioral changes. Similarly small changes in temperature can also influence the metabolic rates and toxicity. The temperature of the cage varies with the group size, height of placement within the rack.

The top rack is 5°C warmer than that of the bottom. The presence of circadian rhythm or periodic variation in many biological processes such as the lipid metabolism, neurotransmitter levels, effects of pharmacokinetics etc might influence the direction and magnitude of the outcome measurement.²⁵

Evidence of the role of nasal septum on facial growth comes either from surgical extirpation of the septum or from in vitro growth experiments. The tissue separating force emanating from the expanding nasal septum is being transmitted to the premaxilla through the septopremaxillary ligament.^{5,6,9,26-28}

The influential role of cartilaginous nasal septum as the pacemaker of growth has received considerable attention in the literature. But the result of the experimental studies in laboratory animals has not led to universal results.^{15,17,19,29-33}

However, experimental resection of SPL in various animal models yields a consistent result of retardation of anteroposterior growth of the midface.^{10,16,22} The transmission of the growth force is of mechanical in nature³⁴ and the SPL, an apparently key structure, acts as a bridge of soft tissue between the nasal septum and the premaxilla.^{5,6,26,27}

DISCUSSION

Systematic reviews disclose inadequacies in the individual study design. It should take into account all relevant elements related to 3R credo of Russell and Burch-"Reduction, Refinement and Replacement".

The concept of 4th R, "Rehabilitation" of laboratory animals is befitting moral continuum incorporated by the amendment of the "Breeding of and Experiments on Animals (Control and Supervision) Rules 1998".^{35,36}

From the societal, ethical and scientific perspective laboratory animals must be used efficiently. This will help in improving the methodology of the future animal research and thereby assists in facilitating the translational process from "bench to bedside".¹ Risk of bias assessed by the systematic review of animal studies provides insight into the reliability of available evidence.^{25,37}

One of the advantages of animal studies is the ability to study a relatively homogenous group of animals. An extensive review of literature suggest that among the proposed theories of early midfacial growth, septal traction hypothesis involving septal cartilage and septopremaxillary ligament play a detrimental role in the midfacial advancement.

The labial frenum of the upper lip encloses the SPL that runs from the anteroinferior border of the nasal septum

above, traverses postero-inferiorly to the insertion on the anterior nasal spine, coursing to the mucosal part of the lip below and from the middle of the lip across the alveolar process to the tissues of interpremaxillary suture behind.^{5,6} As long as this bridging is disrupted with the hard tissue, the transmission of growth force is hardly conceivable leading to deformities.¹²

Studies report that microscopic examination of healing wound following resection of vomer in the beagle dog, showed the presence of elastin fibers, oxytalan and contractile fibroblast could serve to limit the premaxillary and maxillary growth leading to crossbite.²¹ The authors assume that the results of such studies could be extended to the labial frenum which encloses SPL and much of elastin fibers, few striated muscle fibers and fibroblasts and henceforth an aberrant frenum could restrict the sagittal growth of the maxilla.³⁸⁻⁴¹

Many authors have followed the dictum that any disturbances such as trauma or surgery in the LSP region could create a scar tissue. This leads to loss of normal soft tissue elasticity and disturbance of cartilage resilience.⁴² These experimental studies add direct support that re-establishing the integrity of the LSP region in the early stage of life facilitates the anteroposterior growth of the midface.⁴³

The upper lip forms the sagittal fascia of dense connective tissue that forms a partition from the inferior border of the nasal septum to the maxillary labial frenum which forms the inferior aspect of this fascia. Delaire had explained anatomic and neurophysiologic correlations existing between the labial frenum, septopremaxillary ligament and interincisal suture which are important determinants of vertical and anteroposterior relationship of mandible and nasomaxillary complex. He further stated that inadequate muscular reconstruction and mutilation of the labial frenum could result in growth abnormalities.⁴⁴ This was further emphasized in the subperichondrial dissection of cleft lip repair which permits reconstruction of nasolabial muscles and preserves the integrity of the maxillary labial frenum, an important constituent of the septopremaxillary traction system.⁶

Petrovic assumes that the displacement of maxilla occurs through the direct thrust of the nasal septal growth in conjunction with the forward traction of the nasolabial muscles through the maxillary labial frenum and the septopremaxillary ligament.^{40,41,45} Postnatal midfacial growth deficiencies are noted even after the successful repair of the cleft lip and palate individuals, which would suggest an early etiology.⁴⁶ Infant chimpanzee animal model is ideally suited for investigating the perinatal influence of SPL traction mechanisms. The results of which suggest a longer perinatal influence of SPL traction on midfacial growth in humans. The experimental findings in chimpanzee animal model support the fact that re-establishing the integrity of the LSP region early would facilitate anteroposterior growth

of the midface in infants with maxillofacial deformities.^{7,9} However, additional longitudinal data with extensive labioseptopremaxillary reconstruction is needed in cleft patient, which would be focus of ongoing research.

Several challenges exist in translating the outcomes of animal studies to humans in a clinical setting. Assimilation of results from animal studies to human growth is disputable and the conclusions should warrant further experimental and clinical testing through future research. Biological differences between the animals and humans and also within the animal species are often disregarded in the study design.

Methodological issues such as allocation concealment, randomization, blinding of outcome assessment were often neglected in many of the animal experiments. Other characteristics of animal study design such as gender, weight, housing conditions of the animals used which are known to influence the study results are not clearly reported in most of the studies. The statistical methods to analyze the results are flawed or unclear in some studies. Publication bias is also believed to be more problematic in animal studies than in clinical trials.

CONCLUSION

Systematic review on animal studies ought to become a standard practice before a new project is going to be executed. This would result in making better evidence based decisions and optimal experimental conditions for both scientific advancement and animal welfare. It is worthwhile to improve the translation of animal research into clinical practice.

Craniofacial biology is the scientific crossroad for understanding the basic mechanism of musculoskeletal physiology. This review addresses the coordinated effects and influential role of regional superficial musculoaponeurotic systems in the growth of the nasomaxillary complex. Apart from animal research involving partial or complete resection of nasal septum and its mucoperichondrium and septopremaxillary ligament, future research should be directed towards the role of maxillary labial frenum, a constituent of septopremaxillary traction system on the growth of the midface.

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