Table S1. Animal models of mechanoregulation in dentofacial development and remodeling: models, transduction pathways, key evidence, and study limitations

Category	Animal model	Method	Mechanotransduction pathway	Main finding	Limitations
Dental epithelial invagination	Mouse (E11–E13) molar placode/bud stage [1,2]	Live time-lapse imaging; suprabasal tissue incision–recoil; Shh inhibition; cell-mechanics analysis	Actomyosin tension–Shh axis; FGF-driven asymmetric division	Suprabasal cells assemble actin bundles to generate tension that bends the epithelium into the mesenchyme; Shh blockade prevents contraction/intercalation, yielding shallow, widened tooth germs; "vertical telescoping" proposed as a new early-invagination mechanism.	No in vivo force quantification; embryo sex mostly unspecified; mechanics inferred indirectly from recoil.
Dental epithelial invagination	Mouse (E11–E15) molar epithelial invagination; ex vivo live imaging [3]	4D live imaging; fluorescent cell tracking; Myosin II inhibition; Shh conditional knockout	Myosin II–Shh coordination axis; non-muscle myosin II drives cell adhesion and movement	Myosin II mediates cell adhesion and directed movement and acts with Shh to coordinate epithelial intercalation; Myosin II inhibition or Shh loss disrupts epithelial folding, integrating mechanical and morphogen signaling.	Possible off-target effects of Myosin II inhibitors; embryo sex unspecified; window limited to E11–E15.
Dental epithelial invagination	Mouse (E12–E15) molar bud/cap stage; ex vivo organ culture [4]	Organ culture; live fluorescence imaging; cell-trajectory tracking; cytoskeletal dynamics	Coordinated cell movement–tissue deformation axis (proliferation/migration/apoptosis coordination)	Epithelial deformation is driven by the coordinated interplay of proliferation, migration and apoptosis rather than a single factor; the coordination of cellular dynamics via actin remodeling plays an important role in tooth epithelial morphogenesis; trajectory analysis reveals collective tissue-scale mechanical behavior.	Ex vivo organ culture, largely descriptive; embryo sex unspecified; no direct force quantification; mechanism mostly correlative.
Dental epithelial invagination	Mouse (E11–E13) dental/salivary ectodermal placode [5]	In vivo suprabasal cell labeling; laser ablation; quantification of cell intercalation	Suprabasal contraction–cell intercalation–tissue invagination axis	Invagination is driven by active suprabasal contraction; suprabasal intercalation generates an inward mechanical push; the mechanism is conserved between tooth and salivary gland; laser ablation confirms suprabasal prestress.	Ex vivo ectodermal placode model (cross-organ inference, tooth/salivary gland); embryo sex unspecified; mechanics inferred from laser-ablation recoil only.
Mesenchymal condensation & crown morphogenesis	Mouse (E13–E15) molar mesenchyme; in vivo knockout [6]	In vivo Collagen VI knockout; IHC (Pax9, Msx1); quantification of mesenchymal condensation	LOX–collagen VI–ECM stiffening–RhoA–stem-cell fate axis	In vivo LOX cross-linking of collagen VI stabilizes the condensed mesenchyme; collagen VI loss destabilizes condensation and reduces Pax9/Msx1, showing ECM stiffening governs mesenchymal progenitor fate via RhoA.	Sex unspecified; ECM mechanics inferred from condensation phenotype; no direct force measurement.
Mesenchymal	Rodent (incisor/molar, E13–	Direct tissue-pressure	Proliferation-driven compressive	Proliferation generates an anisotropic stress	Mechanics captured at single time

condensation & crown morphogenesis	E15) proliferation-driven compression [7]	quantification; proliferation inhibition; exogenous pressure rescue; IHC (nuclear YAP, Shh)	stress–Hippo/YAP/TAZ–Shh signaling-center formation	field; the high-pressure center shows reduced nuclear YAP, suppressed proliferation and Shh expression, specifying the enamel knot (EK); inhibition abolishes EK, rescued by exogenous pressure.	points; sex unspecified; exogenous pressure may not match native magnitude.
Mesenchymal condensation & crown morphogenesis	Mouse (E13–E15) molar cap stage; αE-catenin/Yap/Taz cKO [8]	Conditional knockout (αE-catenin, Yap, Taz); YAP overexpression; histology/IF (Shh, Fgf4)	αE-catenin–cytoskeletal coupling–YAP/TAZ cytoplasmic retention–EK non-proliferative state	αE-catenin links neighboring cytoskeletons to resist proliferation-driven pressure; its loss causes aberrant nuclear YAP and EK defects, rescued by combined Yap/Taz deletion; YAP overexpression mislocates EK and arrests cap stage.	Single cap-stage window; sex unspecified; lacks direct in vivo tension readout.
Mesenchymal condensation & crown morphogenesis	Mouse (PN0–PN14) molar; YAP-overexpression transgenic [9]	YAP-overexpression transgenic mouse; histology; IF (EK markers Shh); crown morphometry	YAP nuclear activity–EK specification–Hippo dose-effect axis	YAP overexpression causes abnormal crown morphology, altered EK number/position and cusp defects, confirming YAP level is a key dose-dependent determinant of EK specification and crown shaping.	Sex unspecified; endogenous YAP dynamics unresolved.
Mesenchymal condensation & crown morphogenesis	Mouse (E13–PN0) molar; Yap cKO (K14-Cre) [10]	Yap conditional knockout (K14-Cre); histology; EK-marker analysis; cusp morphometry	YAP–primary/secondary EK specification–cusp number axis	Yap loss impairs primary EK specification and produces abnormal secondary EKs and fewer cusps, showing YAP/Hippo controls stage-specific EK appearance and multi-cusp patterning.	Sex unspecified; TAZ compensation not fully excluded.
Mesenchymal condensation & crown morphogenesis	Mouse molar; epithelial YAP1 cKO (Pitx2-Cre) [11]	Epithelium-specific YAP1 cKO; RNA-seq; IF (Shh, FGF4)	Epithelial YAP1–Shh/FGF signaling–ameloblast differentiation axis	Epithelial YAP1 promotes ameloblast terminal differentiation via Shh/FGF; YAP1 loss causes enamel defects and reduced ameloblastin, revealing YAP1's role in mechanics–differentiation coupling.	Sex unspecified; single time point for RNA-seq.
Mesenchymal condensation & crown morphogenesis	Mouse × bank vole molars; ex vivo organ culture + computation [12]	Ex vivo culture (jaw constraint removed); artificial braces mimicking lateral compression; finite-element modeling	Jaw lateral compression–cusp offset (physical constraint)	Vole molars lose species-specific cusp offset without jaw support; mouse molars gain offset cusps with artificial braces; lateral compression is sufficient to induce offset, defining jaw constraint as essential for tooth morphology.	Ex vivo culture and computational assumptions; donor-embryo sex/age unspecified; species comparison limited to two rodents.
Mesenchymal condensation & crown morphogenesis	Rodent ever-growing incisor; incisor-truncation model [13]	Unilateral/bilateral incisor clipping; BrdU; growth-rate assay	Occlusal unloading–mesenchymal stem-cell proliferation axis	Bilateral clipping increases mesenchymal stem-cell proliferation and eruption rate, implying occlusal load regulates stem-cell activity; unilateral clipping shows no change, so simple unloading is insufficient;	Contradictory unilateral vs bilateral outcomes; receptor unresolved; sex/age unspecified.

				integrin–YAP may mediate macro-force.	
Mandibular arch & muscle force	Mouse (E10–E12) mandibular arch mesenchyme [14]	Live imaging; vinculin FRET tension sensor; Wnt5a/Piezo1/Yap/Taz KO; oscillatory cortical-force analysis	Wnt5a–YAP/TAZ–Piezo1–Ca^{2+} transients–actomyosin ordering	Oscillatory cortical forces drive 3D mesenchymal intercalations that shape the mandibular arch; Wnt5a coordinates polarity and actomyosin dynamics; YAP/TAZ and Piezo1 orient intercalations via Ca^{2+} and actomyosin.	Early embryonic arch only (E10–E12); sex unspecified; force-sensing hard to separate from downstream transcription; no postnatal validation.
Mandibular arch & muscle force	Mouse (E12–E17) embryonic tendon/muscle–bone coordination [15]	Scx-Cre tendon lineage tracing; muscle paralysis; 3D skeletal reconstruction; craniofacial morphometry	Muscle contraction–tendon transmission–skeletal strain–bone morphological adaptation axis	Muscle-derived force transmitted via tendons is required for skeletal morphological adaptation; muscle paralysis yields characteristic craniofacial anomalies; tendon-lineage cells sense mechanical cues to coordinate the muscle–bone interface.	Sex unspecified; downstream force sensor unidentified.
Mandibular arch & muscle force	Mouse muscular dystrophy / tendon-deletion [16,17]	Dystrophy mutants; conditional deletion of masseter tenogenic/myogenic components; μCT; mandibular morphometry	Tendon-transmitted force–bone mechanosensing–mandibular shape axis	Chronically reduced muscle force in dystrophy yields characteristic craniofacial anomalies; loss of masseter tendon/myogenic components causes micrognathia, masseter degeneration and reduced mandibular mechanosensing, proving masseter-tendon force is essential for mandibular shape.	Downstream molecular pathway unspecified; species/sex varied and inconsistently reported.
Tooth root development	Mouse (PN3.5–PN21) molar root; trigeminal ganglion [18]	Sensory-neuron-specific KO; Ca^{2+} imaging; PDGF-A gain/loss-of-function	Piezo2 (trigeminal sensory neuron)–Ca^{2+} influx–PDGF-A paracrine axis	$Piezo2^{+}$ trigeminal neurons sense root-associated force and secrete PDGF-A in a Ca^{2+}-dependent manner to coordinate mesenchymal behavior; Piezo2 loss disrupts root morphogenesis, revealing a neuro-mechanical transduction mechanism.	In vivo functional contribution of the human homolog and dose–response limited; sex unspecified.
Tooth root development	Mouse (PN3.5–PN21); Gli1-CreER;Fgfr1(fl/fl) cKO [19]	Tamoxifen-inducible cKO; histology; IF (Piezo2, WNT/β-catenin); WNT-inhibitor rescue	FGFR1 ($Gli1^{+}$ progenitors)–Piezo2–β-catenin/WNT cascade	Fgfr1 loss in $Gli1^{+}$ progenitors aberrantly activates Piezo2 and WNT, narrowing the PDL space, ectopic cementum/bone and tooth ankylosis; WNT downregulation rescues ankylosis.	Sex unspecified; outcome assessed at limited time points.
Tooth root development	Rat (PN21) maxillary molar; sustained orthodontic force (7 d) [20]	Continuous force delivery (7 d); histology (H&E); Ki67 IHC; HERS morphology	Sustained force–apical proliferation–HERS integrity axis	Prolonged 7-day loading shortens roots, causes apical bending, reduces apical proliferation and disrupts HERS; damage is irreversible after force removal, defining a mechanically sensitive apical window.	Single sex/age cohort; molecular pathway unresolved; clinical extrapolation limited.
Tooth root	Rat (PN21 or 28) maxillary first	Light orthodontic force (3 d);	Light force–odontoblast	Three-day light force deforms dentin,	Short-term, single-dose study; sex

development	molar; light force (3 d) [21]	µCT; histology; dentin/odontoblast analysis	function–dentin formation axis	disorganizes odontoblasts, reduces apical proliferation and shortens roots, showing the developing root apex is highly sensitive even to short-term light force.	unspecified; no molecular mechanism.
Tooth eruption & replacement	Dog (deciduous/permanent); follicle removal/replacement [22]	Follicle removal; metal/silicone germ replacement; radiology/histology	Bite-force sensing–follicle–polarized osteoclast/osteoblast recruitment–RANKL/OPG remodeling axis	Replacing the germ with a replica still erupts if the follicle is intact; removing the follicle arrests eruption; the root is not required, polarized osteoclast/osteoblast recruitment is the core mechanism.	Modern molecular validation limited; sex/age inconsistently reported across species.
Tooth eruption & Replacement	American alligator (lifelong tooth renewal) [23]	BrdU/EdU multi-mitotic labeling; histology; artificial extraction; IF (β-catenin, sFRP1, Sox2)	Wnt/β-catenin activation–sFRP1 loss–quiescent progenitor activation axis	Quiescent odontogenic progenitors at the distal dental lamina are activated by physiological exfoliation or extraction; cycling correlates with β-catenin activation and sFRP1 loss, revealing a reptilian renewal niche.	Limited relevance to single-generation mammalian dentition; sex/age unspecified; in vivo lineage tracing restricted.
Tooth eruption & Replacement	Miniature pig (E50–PN10) tooth-replacement model [24]	Serial H&E 3D reconstruction; µCT; FEA (ANSYS); Flexcell compression; IF (integrin β1, ERK1, RUNX2, Wnt)	Integrin β1–ERK1–RUNX2–mesenchymal-to-epithelial Wnt conversion	Faster deciduous growth than the alveolus accumulates compressive stress that suppresses the SDL via integrin β1-ERK1-RUNX2; eruption releases stress, RUNX2 falls and Wnt shifts to the permanent epithelium, initiating succession.	Large-animal study with limited sample size; single breed; narrow sex/age window; FEA assumptions on tissue properties.
Tooth eruption & Replacement	Miniature pig; Fbln1 KO; SDL quiescence [25]	Conditional Fbln1 KO; RUNX2 overexpression; ChIP (RUNX2–Fbln1 enhancer); IF	RUNX2–Fibulin-1 (Fbln1)–SDL niche homeostasis axis (force→transcription→matrix)	RUNX2 binds the Fbln1 enhancer; the biomechanical RUNX2–Fibulin-1 axis maintains SDL niche quiescence; Fbln1 loss causes premature SDL activation, gating replacement timing.	Sex/age unspecified; niche mechanics inferred, not directly measured.
Jaw bone development	Rat ; soft- vs hard-diet [26-28]	Dietary intervention; µCT; histology; IHC (IGF-1r, PTHrP, Col2a1); mandibular morphometry	PTHrP–Ihh endochondral ossification axis; IGF-1r–chondroblast proliferation	Soft diet reduces masticatory load, lowering condylar bone volume, ramus growth and cartilage thickness with reduced IGF-1r, suppressing endochondral ossification and confirming load is required for growing-jaw development.	Single species/sex (often male) and age cohort; strain not quantified.
Jaw bone development	Rat (adult male); incisal bite-plane TMJ overload [29]	Bite-plane loading; µCT; histology (cartilage layers); mandibular length/ramus height	Overload–endochondral ossification suppression–condylar homeostasis axis	Increased TMJ load thins condylar cartilage, suppresses endochondral ossification and reduces total mandibular length and ramus height, inversely mirroring the soft-diet model.	Single species and sex (adult male rat only); one loading magnitude/duration; molecular pathway presumed.
Jaw bone	Mouse (Osterix-Cre;	Osteoblast/chondrocyte	BMP/BMPR1A	Bmpr1a loss shortens the anterior mandible	Single sex/age; interaction effects

development	Bmpr1a(fl/fl)); soft-diet × KO [30,31]	Bmpr1a cKO; soft diet; treadmill loading; µCT; superimposed imaging	mechanosensitivity (posterior vs anterior condyle)	and posteriorly inclines the ramus; BMP governs the posterior condyle while masticatory load governs the anterior part; KO osteoblasts become hypersensitive to load, gaining trabecular bone with exercise.	hard to disentangle; load quantification limited.
Jaw bone development	Zebrafish (craniofacial cartilage); muscle paralysis/Pthlha overexpression [32]	Muscle paralysis (tricaine); Pthlha overexpression; ISH (Col10a1 hypertrophic markers); IHC	Pthlha–muscle contraction–hypertrophic zone–endochondral ossification axis	Pthlha restricts the hypertrophic zone; muscle-derived force is required for normal hypertrophic-marker expression and ossification; paralysis abolishes this, showing muscle input is necessary for craniofacial cartilage ossification.	Zebrafish cartilage biology differs from mammalian bone; paralysis is global; sex/stage inconsistently reported; translation to mammals indirect.
Jaw bone development	Mouse Yap/Taz skeletal-cell cKO [33]	Yap/Taz osteoblast/skeletal cKO; bone histomorphometry; collagen analysis; TRAP	YAP/TAZ–osteoblast activation–matrix collagen organization–osteoclast suppression axis	Combined YAP/TAZ loss yields an osteogenesis-imperfecta-like phenotype with spontaneous fractures; YAP/TAZ synergistically promote postnatal bone development and suppress osteoclasts.	Sex/age cohorts limited; phenotype may mask cell-type-specific roles.
Periodontal ligament & OTM	Mouse (Lepr-Cre lineage); periodontal homeostasis [34]	scRNA-seq; Lepr$^+$ PDLSC lineage tracing and ablation; Piezo1 agonist Yoda1 injection; morphometry	Lepr$^+$ perivascular PDLSC–Piezo1 mechanosensing–periodontal homeostasis axis	scRNA-seq identifies Lepr$^+$ perivascular cells as core PDL-homeostasis stem cells; their ablation disrupts homeostasis; Yoda1 markedly promotes periodontal growth, showing Piezo1-mediated occlusal-force sensing.	Sex/age unspecified; translation to human PDL uncertain.
Periodontal ligament & OTM	Mouse (Gli1-CreER lineage); periodontal homeostasis [35]	Gli1-CreER lineage tracing; occlusal-force removal (extraction control); in situ Gli1$^+$ PDLSC marking	Occlusal force–osteocyte sensing–Gli1$^+$ periodontal stem-cell activation axis	Occlusal force, sensed via osteocytes, regulates Gli1$^+$ PDLSC proliferation and differentiation; force removal reduces Gli1$^+$ proliferation; orthodontic force reactivates Gli1$^+$ cells to drive alveolar remodeling.	Sex/age cohort limited; human PDL translation uncertain.
Periodontal ligament & OTM	Mouse (Gli1-CreER); orthodontic-force-induced alveolar remodeling [36]	Gli1-CreER lineage tracing; orthodontic spring; Gli1$^+$ proliferation/differentiation kinetics; µCT	Orthodontic force–Gli1$^+$ progenitor activation–osteoblast recruitment–alveolar remodeling axis	Orthodontic stimulation activates Gli1$^+$ PDL progenitors and drives osteoblast differentiation; Gli1$^+$ cells are the main source of tension-side bone formation during OTM.	Sex/age unspecified.
Periodontal ligament & OTM	Rat (orthodontic tooth movement); PDL proteomics [37]	Orthodontic appliance loading; PDL tissue proteomics (LC-MS/MS); ECM-protein quantification	Mechanical stress–ECM-remodeling protein expression–PDL structural adaptation axis (specific pathway unresolved)	Orthodontic force markedly alters ECM-remodeling proteins (collagen, fibronectin) in the PDL; proteomics reveals a stress-induced matrix-adaptation program underlying OTM.	Sex/age unspecified; pathway inference correlative.
Periodontal ligament	Rat (orthodontic tooth	In vivo MGF injection/gene	MGF–Fyn-FAK axis–	Occlusal force induces MGF; MGF drives	Sex/age unspecified; regenerative

& OTM	movement); PDL regeneration [38]	delivery; FAK/ERK/p38 inhibitors; histology (PDL collagen remodeling)	ERK1/2/p38 MAPK–PDLSC fibroblastic differentiation	PDLSC fibroblastic differentiation and in vivo PDL regeneration via Fyn-FAK-ERK1/2/p38; ERK1/2 is a rapid convergent node across mechanical stimuli.	outcome short-term.
Periodontal ligament & OTM	Mouse (orthodontic tooth movement, in vivo) [39]	ATG7 siRNA knockdown; in vivo OTM rate; RANKL/OPG; autophagic-flux assay	ATG7-dependent autophagy–RANKL/OPG–osteoclast 'brake' mechanism	ATG7 knockdown blocks autophagy, raises RANKL/OPG and accelerates OTM in vivo, showing ATG7-dependent autophagy restrains movement rate by limiting osteoclast activity.	Mixed mouse in vivo / human in vitro design; sex/age unspecified; single force magnitude.
Periodontal ligament & OTM	Mouse (orthodontic tooth movement); PDL fibroblasts × sensory neurons, in vivo [40]	In vivo compressive force; TAC1/SP IF; neuron-activation assay; TRAP	Compression–TAC1/SP secretion–sensory-neuron activation–pro-inflammatory/osteoclast loop (neuro-immune axis)	Compression induces TAC1 expression and SP secretion in PDL fibroblasts, activating sensory neurons that in turn drive inflammation and osteoclastogenesis; this neuro-immune loop underlies orthodontic pain.	Co-culture simplifies in vivo neuro-immune complexity; sex/age unspecified; pain readout indirect.
Periodontal ligament & OTM	Rat (orthodontic tooth movement); CD109/PDL alveolar remodeling [41]	CD109 conditional KO and overexpression; orthodontic spring; TRAP; osteoblast markers; μCT	Orthodontic force–CD109 (PDLSC surface receptor)–osteogenesis/osteoclastogenesis balance axis	Mechanical force activates CD109 on PDLSCs, balancing osteogenesis and osteoclastogenesis via TGFβ signaling; CD109 loss increases resorption and accelerates tooth movement.	Mixed in vivo rat OTM and in vitro PDLSC; CD109 role outside PDL unclear; sex/age unspecified; single force paradigm.
Periodontal ligament & OTM	Mouse; occlusal-force alveolar homeostasis / occlusion-loss control [42]	Tooth extraction/occlusal removal; μCT; endothelial markers (CD31, Endomucin); type-H vessel quantification	Occlusal force–type-H angiogenesis–bone formation coupling axis	Occlusal force maintains bone by promoting type-H vessels (CD31hiEndomucinhi) in alveolar bone; occlusion loss reduces type-H vessels and bone mass; pro-type-H signals partially rescue bone loss.	Vessel–bone causality partly correlative; sex/age unspecified.
Temporomandibular joint (TMJ)	Gli1Cre- mouse, Piezo 1 KO, temporomandibular joint osteoarthritis model [43]	Histological and immunohistochemical analyses; assessing the effects of Piezo1 deletion on condylar development and homeostasis	Piezo1 in fibrocartilage stem cells	Piezo1 is a key mechanosensitive ion channel in the cartilage, regulating condylar development and homeostasis. Its deletion in Gli1+ cells disrupts FCSC differentiation and endochondral ossification, leading to developmental deficiencies.	Sex/age effects not fully separated.
Temporomandibular joint (TMJ)	Mouse (TMJ attachment–condyle interface); Gli1^{+} TMJ progenitors [44]	Gli1-CreER lineage tracing; multi-timepoint labeling (BrdU/EdU); scRNA-seq	Gli1^{+} slow-cycling progenitor–fibrocartilage homeostasis–mechanoresponsive potential axis	Gli1^{+} cells enrich at the TMJ attachment–condyle interface, show slow-cycling clonal expansion and constitute the core fibrocartilage progenitor pool; scRNA-seq reveals multipotency and	Lineage tracing largely descriptive; sex/age unspecified; functional contribution inferred.

				mechanoresponsive transcription.	
Temporomandibular joint (TMJ)	Mouse (TMJ osteoarthritis); Gli1⁺/YAP-Hhip axis [45]	Surgically induced TMJ OA; Gli1-CreER lineage tracing; YAP cKO; Hhip functional analysis; subchondral μCT	Gli1⁺ osteochondral progenitor–YAP–Hhip–aberrant subchondral remodeling axis	In TMJ OA, Gli1⁺ osteochondral progenitors show elevated YAP activity, driving Hhip expression and aberrant subchondral remodeling; YAP loss or Hhip inhibition attenuates the OA phenotype.	Sex/age unspecified; cell-type specificity within Gli1⁺ pool unclear.
Temporomandibular joint (TMJ)	Porcine TMJ disc; in vitro mechanical loading [46,47]	In vitro disc loading; conductivity measurement; glucose diffusion coefficient; cell viability	Mechanical strain–reduced water/porosity–nutrient diffusion limit–cell metabolic stress axis	Strain lowers disc water content and porosity, reducing glucose diffusion; abnormal loading causes metabolic dysfunction and stem-pool exhaustion, driving TMJ OA, implicating disc biomechanics in degeneration.	Sex/age unspecified; does not capture chronic in vivo degeneration.

E, embryonic day; PN, postnatal day; PDL/PDLSC, periodontal ligament (stem cells); EK, enamel knot; SDL, successional dental lamina; HERS, Hertwig's epithelial root sheath; OTM, orthodontic tooth movement; TMJ, temporomandibular joint; cKO, conditional knockout; KO, knockout; FEA, finite-element analysis; HH, Hamburger–Hamilton stage.

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