SYMPOSIUM

Grand Challenges in Comparative Tooth Biology

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Synopsis Teeth are a model system for integrating developmental genomics, functional morphology, and evolution. We are at the cusp of being able to address many open issues in comparative tooth biology and we outline several of these newly tractable and exciting research directions. Like never before, technological advances and methodological approaches are allowing us to investigate the developmental machinery of vertebrates and discover both conserved and excitingly novel mechanisms of diversification. Additionally, studies of the great diversity of soft tissues, replacement teeth, and non-trophic functions of teeth are providing new insights into dental diversity. Finally, we highlight several emerging model groups of organisms that are at the forefront of increasing our appreciation of the mechanisms underlying tooth diversification.

Introduction

Teeth provide an important phenotype for integrating across biological disciplines ranging from ecology to genomics. For instance, teeth are used to make inferences about ancient as well as recent ecologies (Purnell et al. 2007; Cuozzo et al. 2014), to understand how highly conserved structures are biomechanically modified to generate novel organismal functions (Silverman and Dunbar 1980; Parmentier et al. 2017), as well as to understand tissue development (Mitsiadis et al. 1998; Tucker and Sharpe 2004), cell (Sharpe 2001), and gene interactions (Thesleff and Sharpe 1997; Jernvall and Thesleff 2012; Jackman et al. 2013). Because all vertebrate teeth are homologous and derived from mineralized tooth-like structures present in a common early ancestor (Smith and Coates 1998; Smith 2003; Fraser and Smith 2011; Rasch et al. 2016), they are an excellent organ system for determining how multiple levels of biological complexity have comparatively contributed to vertebrate diversification. Serially homologous teeth with different phenotypes also frequently co-occur in the same trophic apparatus (Liem 1973; Herring 1993; Vonk et al. 2008; Fraser et al. 2009; Hulsey et al. 2016; Karagic et al. Forthcoming 2020a). We can leverage these replicated structures to investigate mechanisms of tooth formation that contribute to differentiation in a single organism. Well-studied mammalian dentitions represent only a small subset of vertebrate dental diversity, so comparative studies of teeth in non-mammalian vertebrate models will likely provide the next generation of transformative insights concerning tooth diversification.

In this review, we identify research areas in comparative tooth biology that represent important challenges for the field and provide possibilities for significant future scientific advances (Table 1).

Table 1 Grand challenges in comparative vertebrate tooth biology

Developmental genomic challenges
Deep homology of teeth
Conserved genetic basis of tooth development
Evolutionary developmental networks and modules
Novel genes deployed during tooth development
Functional morphological challenges
Interacting functions of soft and hard dental tissues
Polyphyodont dentitions
Non-trophic roles and multifunctionality
Emerging models
Bats
Non-mammalian amniotes
Teleost fishes
Chondrichthyans

The broad categories of challenges discussed and particularly compelling topics within those categories that are highlighted in the text are listed. Additionally, we highlight several emerging model groups where addressing these challenges is likely to be highly tractable.

Furthermore, we emphasize how these synthetic areas are becoming increasingly tractable because of recent advances in technology, analytical approaches, and the comparative study of dentitions in emerging model groups. Each of these grand challenges is a call for collaborative and interdisciplinary work that integrates knowledge across fields, levels of biological organization, and incorporates studies on new lineages of vertebrates (Fig. 1). The grand challenges we outline in developmental genomics and functional morphology of dentitions should also provide insight into the need for training and educating future comparative tooth biologists. Because teeth and human health are inextricably linked (Nesse et al. 2006; Gibbons 2012; Boughner and Rolian 2015; Hovorakova et al. 2020), each challenge holds real potential for translational interactions with the field of dentistry.
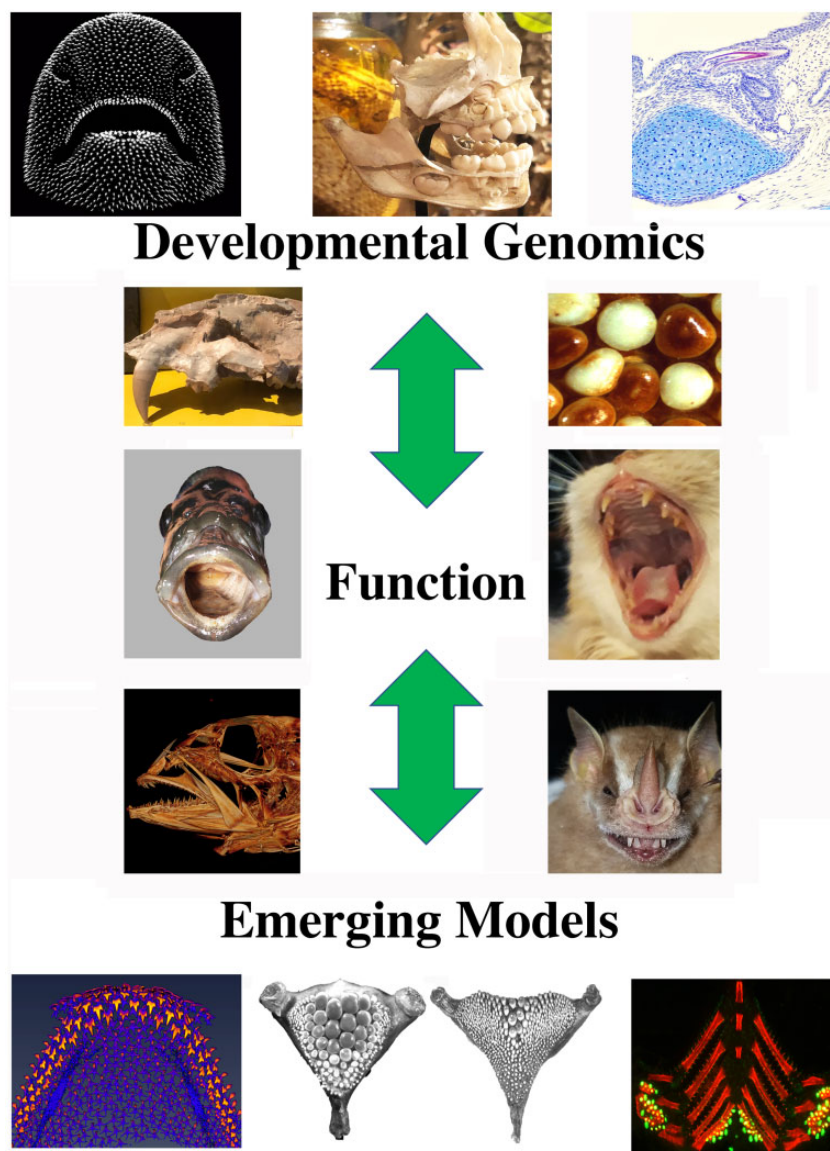
Developmental genomic challenges

Developmental genomics is undergoing a revolution as technological advances make the integration of genomic and gene expression data tractable like never before. These new technologies and methodological approaches are allowing us to peel back the developmental machinery of vertebrates and expose new and exciting generalizable patterns. It is clear that many structures like teeth often share highly conserved developmental pathways with other organs, and that all vertebrate teeth are generated

using some of the same genes (Fraser et al. 2010). But, a comprehensive understanding of developmental genetics will require an appreciation of how genes interact in networks as well as determining if genes that are unique to particular lineages of vertebrates play an important role in the evolutionary development of teeth (Hulsey et al. 2016).

Deep homology

Teeth have long been recognized as being homologous to other vertebrate integumentary organs. Remarkably, Darwin (1875), long before any understanding of developmental genetics, but after encountering humans and dogs lacking both teeth and hair, wrote "The skin and the appendages of hair, feathers, hoofs, horns, and teeth, are homologous over the whole body . . .". Over a century later, work based on comparative histology and subsequent developmental genetics has supported different levels of homology for teeth and other epithelial appendages, including scales, feathers, mammary glands, and hair (Pispa and Thesleff 2003; Dhouailly et al. 2019). On a morphological level, homology of these structures rests on early development when they all first arise via placodes, local thickened epithelial swellings overlying a mesenchymal condensate (Ørvig 1967). Genetic data showing that the same genes pattern diverse epithelial appendages further supported the hypothesis of homology. For example, ectodermal dysplasia, the phenotype that likely inspired Darwin to propose homology between teeth and hair, affects teeth and hair in humans, mice, and dogs. This condition was found to result from single gene mutations (e.g., in *Ectodysplasin* [*Eda*] and its receptor [*Edar*]) (Sadier et al. 2014). Furthermore, the finding that mutations in the orthologs of these genes in distant vertebrates including reptiles and fish show that this gene regulatory network involving *Eda* and *Edar* has regulated these appendages for several hundred million years of vertebrate evolution (Kondo et al. 2001; Harris et al. 2008; Di-Poï and Milinkovitch 2016).

This homology of the different epithelial appendages raises the question of at what level of biological organization are these different vertebrate organs homologous (Abouheif et al. 1997). One favored model has involved co-option, that the gene regulatory network that evolved first to make a scale or a tooth, was subsequently repurposed at other anatomical sites (Mindell and Meyer 2001). For example, the initial observation that *Edar* in medaka fish is required for scale formation led to the proposal that this circuit was likely co-opted into reptilian

Fig. 1 The scientific interplay between developmental genomics, dental function, and emerging models of tooth diversification is highlighted visually.

scales that then evolved into mammalian hair (Sharpe 2001).

To date most developmental genetic studies of epithelial appendages have focused on the development of the initial primary organs. However, the ancestral state of tooth development is polyphyodonty (the constant regeneration of teeth throughout the lifetime of the adult animal), a condition retained in extant sharks, fish, and reptiles (Handrigan and Richman 2010; Martin et al. 2016; Rasch et al. 2016; Thiery et al. 2017; Bertin et al. 2018; Salomies et al. 2019). Since many other epithelial appendages also regenerate, one outstanding question is whether the genetic regulatory networks regulating epithelial appendage regeneration are also shared across diverse epithelial appendages. Recently, developmental genetic studies have begun to focus on the genetic pathways regulating epithelial appendage regeneration (Wu et al. 2013; Hsu et al. 2014; Tucker and Fraser 2014; Ellis et al. 2015; Rasch et al. 2016; Aman et al. 2018). The most intensely studied regenerating epithelial appendage is mammalian hair, and decades of elegant genetic studies have revealed deep insights into the gene networks that regulate hair regeneration. This work has supported a model where organ regeneration is negatively regulated by the bone morphogenetic protein (BMP) pathway and positively regulated by the Wingless (Wnt) signaling pathway (Kobielak et al. 2007; Kandyba et al. 2013). Genetic studies in fish have

yielded some support for a model where teeth and hair regenerate using a shared genetic circuit, as the *Bmp6* gene has been implicated in negatively regulating fish tooth regeneration (Cleves et al. 2018), perhaps similar to the role of mammalian *Bmp6* in negatively regulating hair regeneration (Wu et al. 2019). Whether or not these genetic similarities extend to a larger gene regulatory network and support homologous networks governing the regeneration of teeth and other epithelial appendages remains a grand challenge for future work.

The conserved genetic basis for tooth development

Despite the incredible diversity in form, arrangement, and regenerative capacity of vertebrate dentitions, tooth development across all vertebrates is in many ways surprisingly highly conserved (Jernvall and Thesleff 2012; Tucker and Fraser 2014). Essentially, the same cells express a highly similar network of genes to coordinate the construction of vastly different teeth from fish to mammals. Conservation of this system is a rigid developmental foundation, whereby evolution has routinely modified from but retained the developmental and overall functional veracity of the vertebrate dentition (Fraser et al. 2009). Recently, genomic and developmental advances in the study of odontogenesis have led to new perspectives focused on the implications of this conservation and the discovery of novel genetic markers involved in the development and renewal process (Salomies et al. 2019; Seidel et al. 2017; Sharir et al. 2019). One such implication of this conservation is that knowledge of how distant groups, such as elasmobranchs, reptiles, and rodents, are able to maintain continuous or perpetual tooth production could highlight essential elements (i.e., cellular or genetic) that have disappeared in other groups that have reduced or have completely lost tooth regeneration and/or renewal.

The ability to make and then replace teeth is highly dependent on the activity and maintenance of the dental lamina, an epithelial sheet from where teeth originate (Smith et al. 2009; Martin et al. 2016; Rasch et al. 2016). This dynamic layer of epithelial cells is diverse in its form and function, with some vertebrate groups only able to produce a single generation of teeth, whereas others (e.g., sharks) have a near infinite supply of developing teeth (Huysseune and Sire 1998; Rasch et al. 2016). Thus, the assumption is that integrity of this cell layer is vital to further tooth production and that its degradation is related to the inability to develop further tooth generations (Popa et al. 2019). As our knowledge of the dental lamina and its persistence among lineages improves, we can further test the role of the dental lamina in tooth replacement. For instance, sharks exhibit perpetual regeneration of the dentition and this is linked to the constant proliferative activity, growth, and maintenance of stem/progenitor sites within the entirety of the dental lamina (Smith et al. 2009; Martin et al. 2016; Rasch et al. 2016). However, in mammals that exhibit a restricted number of tooth generations, typically two (Diphyodonty), it is thought that the breakdown of the dental lamina is responsible for the restricted and limited productivity of the dentition (Buchtová et al. 2012). Additionally, several recent studies have emerged that shed a different light on the ultimate fate of the dental lamina in mammals. Even though the typical mammalian dental lamina degrades via apoptosis, some cell clusters are retained in the oral epithelium/gingiva (Buchtová et al. 2012). These clusters of remnant dental lamina, or dental rests, that have no clear function are maintained into adulthood and contain cells that share a similar stem/progenitor cell signature to the active shark dental lamina, albeit with a lower number of proliferative cells (Fraser et al. 2019).

Biologists are now taking advantage of the availability, not only of new organismal model systems (see below), but also taking note of the comparative value of these species toward a more directed understanding of the human dentition (Fraser et al. 2019). This utility of animal models in understanding the human dentition is generally based on the concept of genetic and developmental conservation. Interestingly, new evidence suggests that human tissue may have a greater regenerative capacity than previously thought, at least with some form of stimulation. The dental lamina in humans for example degrades after two generations of tooth formation and sequential molar formation, but pockets of these rested lamina cells, either stay rested, disintegrate, or become tumorigenic (Buchtová et al. 2012; Fraser et al. 2019). The trigger for dental pathologies emerging from rested epithelia is complex; however, in some cases these tumors can produce characteristic dental tissues suggesting that the fate of these cells has always been dental, i.e., of dental lamina origin (Heikinheimo et al. 2015). With knowledge of active and controlled proliferation for new teeth, i.e., in the shark model, combined with genomic information from rested and aberrant dental lamina in mammals, a grand challenge of comparative tooth biology will be to piece together the necessary ingredients for natural tooth formation in humans for future tooth generations.

Evolution of gene expression networks and modules

Tooth development has been intensively studied using morphological comparative analyses, *in vivo* and *in vitro* methods, as well as through mathematical modeling. Because of this, the developmental network giving rise to teeth is one of the best described and best understood gene regulatory networks for the development of any organ (Jernvall and Thesleff 2012; Salazar-Ciudad 2012). Importantly, these studies have demonstrated that the diversity observed in tooth morphology among mammals is shaped by the conserved developmental mechanisms that control tooth development. As a result, dental organs represent an ideal case to study how the structure of gene regulatory networks influence the evolution of phenotypes (Salazar-Ciudad and Jernvall 2010; Uller et al. 2018). Among the developmental processes proposed to influence the direction of phenotypic evolution, the modular organization of gene regulatory networks shows particular promise. This theory suggests that the arrangement of gene regulatory networks into sub-units, also sometimes called sub-modules, can influence the direction of evolution by facilitating or constraining the appearance of new phenotypes (Lipson et al. 2002; Kouvaris et al. 2017; Uller et al. 2018).

In a modular organization, some units can be more conserved than others, with conserved core units realizing essential function of the phenotype while less-conserved, peripheral sub-units being more susceptible to variation. Some recent work (reviewed in Uller et al. 2018) has theorized about the importance of developmental network topology in biasing evolution based on inferences from empirical examples. Studies mixing developmental and computational experiments have shown that teeth are patterned by semi-autonomous sub-units of gene regulatory networks or modules (Salazar-Ciudad and Jernvall 2010; Jernvall and Thesleff 2012; Lacquaniti et al. 2013). This patterning lies at the root of tooth diversity. However, there is little direct experimentally-based knowledge of how the topology of gene regulatory networks (i.e., in sub-networks) are modified in response to environmental selection (Dumont et al. 2012; Usui and Tokita 2018).

Teeth are serially homologous structures that vary greatly in number and shape across mammals. Evolutionary changes in molar size, shape, and in the presence, size, and shape of individual cusps (Fig. 2) are all critical for increasing feeding performance within particular food types or enabling dietary transitions across food sources (Hunter and
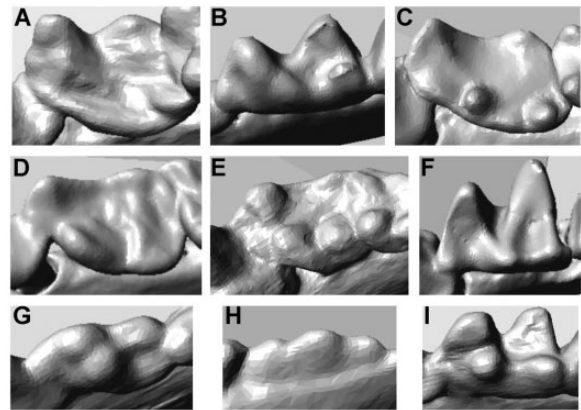
Fig. 2 Bat first molar diversity: from left to right, up to bottom; CT scan reconstructions of molars in the bats **A)** *Uroderma bilobatum*, **B)** *Macrotus waterhousii*, **C)** *Artibeus phaeotis*, **D)** *Brachyphylla pumila*, **E)** *Centurio senex*, **F)** *Noctilio leporinus*, **G)** *Sturnira lilium*, **H)** *Desmodus rotundus*, and **I)** *Trachops cirrhosus*.

Jernvall 1995; Santana et al. 2011a). For instance, comparative studies have demonstrated that the evolution of specific molar morphologies, including their size and shape, can be highly labile and evolve independently of other tooth traits. However, experiments regarding the influence of the modular structure of gene regulatory networks on phenotypic evolution have remained limited to model species such as mice and to computational predictions for other species (Häärä et al. 2012; O'Connell et al. 2012; Salazar-Ciudad 2012; Harjunmaa et al. 2014). As teeth in general and mammalian molars in particular exhibit a modular organization, both phenotypically and in their gene regulatory networks, teeth constitute a powerful model to study these questions. With increasing access to new species thanks to next-generation sequencing and reverse genetic techniques such as CRISPR/Cas9, we have arrived at an exciting time when we can test hypotheses about network modularity in a comparative framework. Teeth represent an excellent model system to study how the inherent structure of gene regulatory networks influence variation and the evolution of actual and potential morphospaces. Studies of the evolution and development of teeth will help to advance the extended evolutionary synthesis by potentially finding new paradigms for the mechanisms underlying trait evolution in general.

Novel genes deployed during tooth development

As discussed above, extensive knowledge exists concerning the developmental mechanisms involved in odontogenesis in mammalian model systems especially in mice (Tucker and Sharpe 2004; Thesleff 2006). It has become axiomatic that many

developmental programs involved in tooth development are conserved across all vertebrates. Even highly derived phenotypes such as constantly growing mouse incisors (Wang et al. 2007), pufferfish beaks (Fraser et al. 2012), the crushing dentition of rays (Underwood et al. 2015), or venom-delivering fangs in snakes all follow the same developmental bauplan (Vonk et al. 2008; Landova et al. 2020). However, what could differ extensively during the development of teeth in disparate vertebrates are genes further downstream of signaling pathways such as genes involved in tooth mineralization that can be very lineage specific (Kawasaki et al. 2004; Kawasaki and Weiss 2008; Kawasaki 2009). Studies on non-model organisms have begun to show evidence that there could be substantial developmental divergence among vertebrates during tooth formation (Kawasaki et al. 2004). Additionally, there is great diversity regarding dental phenotypes in vertebrate lineages, especially in teleost fish (Liem 1973; Mehta and Wainwright 2007; Fraser et al. 2012; Berkovitz and Shellis 2018). To understand the source of this incredible diversity, a more complete approach to the genomics of tooth formation will be required and genes, other than those that have been shown to have highly conserved roles like Wnts or Fgfs, will need to be studied in more detail.

For instance, investigations into the secretory calcium-binding phosphoprotein (*scpp*) gene family illustrate how divergent genetic mechanisms involving novel genes can generate diversity during tooth formation (Kawasaki et al. 2005). *Scpp*s are genes present in all vertebrates and are involved in processes such as tooth mineralization (Kawasaki and Weiss 2008). All members of the *scpp*-family, including prominent tooth genes like *amelogenin* or *enamelin*, evolved from *sparc* which was present in the common ancestor of vertebrates and have since diverged independently in various lineages (Kawasaki 2009). Comparing teleosts and mammals, considerable differences in terms of gene family size, homolog sequences, and potentially their respective functions have been reported (Van de Peer et al. 2003; Hoegg and Meyer 2005). The *scpp* gene family illustrates how conserved structures and processes can have considerable variation in their developmental genetic basis and comparable variation could potentially underlie much odontogenetic diversity across vertebrates. Considering the immense diversity of trophic adaptations exhibited by teleosts and other vertebrates (Liem 1973; Eastman 1977; Hulsey 2006; Wang et al. 2007; Vonk et al 2008; Mehta and Wainwright 2007; Fraser et al. 2009,

2012;), it is very likely that a large number of genes involved in odontogenesis remain unknown.

Novel tooth genes, here defined as genes not present in or not known from mammalian odontogenesis, could readily have contributed to the dental diversity seen in groups like teleost fishes. Following the whole genome duplication shared by most teleosts, many novel genes with divergent functions likely arose by sub- or neofunctionalization (Ohno 1970; Van de Peer et al. 2003), as illustrated by the *SCPP* gene family. Additionally, there has likely been the birth of additional novel genes from non-coding regions that have evolved to produce functional proteins. This type of gene birth was once regarded as likely to be a rare event, but its frequency and potential role in adaptation has recently been appreciated to be more common and evolutionarily important (Chen et al. 2010; Wu et al. 2011; Wu and Zhang 2013; McLysaght and Guerzoni 2015). Although the identification of such novel tooth genes remains challenging, novel genes associated with the repeated evolution of larger teeth have for instance been identified in cichlid fishes (Karagic et al. 2020a). Now that whole genomes are rapidly becoming available for many species, comparative genomic approaches will allow us to shed light on the presence of many previously unknown paralogs or orthologs as well as completely novel genes (Kawasaki et al. 2005). In general, these genes will need to be further validated regarding their role during tooth formation and for recently evolved genes, it will often be exceptionally difficult to infer gene functions due to the lack of comparative approaches. However, high-throughput transcriptomic approaches that facilitate examinations of the expression of all genes in a certain tissue, e.g., tooth buds, odontoblasts, or even single cells, could provide a much more detailed picture of what genes are active during odontogenesis and facilitate rigorous comparisons among taxa. Powerful new sequencing technologies coupled with the increased use of non-model organisms will allow us to rise to the challenge of unraveling how important previously undocumented and novel genes are to the diversity of vertebrate tooth formation.

Functional challenges

Teeth bear the stamp of their primary function in capturing and processing prey however, our understanding of the extensive functional diversity of dental structures is far from complete. Dentitions are more than a battery of hard structures and the

function of soft tissues in vertebrate dentitions are receiving greater appreciation. The extensive focus on mammalian dentitions has come at the expense of understanding the role that frequent tooth replacement likely plays in the dentition of most vertebrates, but this is changing. Additionally, there is often a match between perceived tooth function in feeding and shape, but this is not always true. For instance, because teeth are often sexually dimorphic and used for many non-trophic tasks, feeding should not remain the only possible *de facto* explanation for dental adaptation and diversity.

Interacting functions of soft and hard dental tissues

Teeth are the hardest part of the dental battery and have driven research on dentition for 200 years (Owen 1845; Green et al. 2019). However, the dental papilla, dental ligament, and to a lesser extent the tooth pulp have all been shown to play crucial roles in the development and evolution of teeth (Huysseune and Witten 2008; Denes et al. 2019). However, a grand challenge remains in understanding the function of dental soft tissues, particularly as they relate to polyphyodont dentitions.

The periodontal ligament provides an example of a multifunctional soft tissue that in mammals serves to dampen transient impacts, facilitates post-eruptive tooth movement, and plays an essential role during chewing (McCormack et al. 2014; Underwood et al. 2016). This ligament is also present in crocodilians, that are polyphyodont, providing the potential for comparative analyses to understand the functional importance of this structure (Bertin et al. 2018). This might be especially valuable as it is unclear if transient loads matter in the context of a polyphyodont dentition outside of mammals. Also, in the absence of a periodontal ligament, it is unclear how polyphyodont teeth manage variable loading conditions while simultaneously maximizing tooth performance. Polyphyodont teeth can be attached to the bone by collagen (e.g., *Iguana* and *Salmo*) (Huysseune and Witten 2008) or through ankylosis (e.g., *Chameleo* and *Pomatomus*) (Bemis et al. 2005), a process in which the tooth fuses to the jaw and loses it connection to surrounding soft tissue. Flexibility of attachment modalities in the evolution of polyphyodont dentitions may have commonly released functional constraints imposed by the periodontal ligament.

Not only do polyphyodont dentitions vary in their attachment to the jaw, they also vary in another way that has functional implications—the developmental trajectory from a germ to a fully mature tooth

(Fraser et al. 2013; Tucker and Fraser 2014). Tooth replacement patterns vary from completely extraosseous replacement in which the teeth develop in the oral epithelium adjacent the jaw to intraosseous patterns in which the tooth germ migrates into the bone to complete development (Trapani 2001; Bertin et al. 2018). The migration of a tooth into the jaw bone results in substantial remodeling that affects not only the structural integrity of the jaw, but also the replacement tooth size and shape (Bemis et al. 2005; Witten and Huysseune 2009; Bertin et al. 2018). These biological realities raise many questions such as: are replacement modalities contingent on the structural mechanics of the jaw? How does the dental battery change functionally as teeth of different shapes are ankylosed in new positions? Can a tooth that develops outside of the jaw be as robust as one that develops inside a bony crypt? We need histological and functional studies of tooth development from a diversity of species to answer these questions.

Teeth are characterized by having a center of vascularized pulp and the proportion of the pulp cavity relative to the dentine and enamel is highly variable across species (e.g., Huysseune and Sire 1998). The biomechanics of teeth, like any organ, are governed by structural and material properties (Anderson and LaBarbera 2008). But, how much of tooth function is determined by the pulp cavity? Take for example two cases of "fang-like" teeth in fishes: the hollow fangs of *Alepisaurus ferox* and robust fangs of *Ophiodon elongatus*. Both have small conical teeth interspersed with larger fangs (Gallo and Levin 2016). The diets are different: *A. ferox* consumes gelatinous prey (Kubota and Uyeno 1970) while *O. elongatus* is a piscivore. This is one of many examples where anatomical descriptors such as "fang" or "conical" provide limited information to link tooth form and function. Perhaps the structure and/or material of the teeth of *A. ferox* are incapable of resisting abrasive forces generated during puncture. Quantifying proportions of pulp, dentine, and enamel is one simple way that could be used to separate these and other dentitions. A better understanding of the performance of soft tissue will help us answer questions of tooth complexity within taxonomic and functional groups from new perspectives.

Soft tissue is likely as variable functionally and morphologically as the hard parts of the dental battery, and could be even more important in polyphyodont dentition when compared with vertebrates with diphyodont dentitions. Evaluating soft tissue with respect to function, instead of as an incidental necessity of tooth development, will reveal patterns in polyphyodont dentitions that

have otherwise been obscured by the focus on the hard elements of vertebrate dentitions.

Distinct functions of polyphyodont dentitions

The teeth of some fishes, when considered as a battery, are so unusual as to defy hypotheses of function (Fig. 3). The hard tissue of the dental battery has been a fertile ground for research, with particular attention to the physical and mathematical modeling of the relationship between form and function (Herring 1993; Evans and Sanson 2006; Crofts and Summers 2014; Freeman and Lemen 2007; Ramsay and Wilga 2007; Anderson and LaBarbera 2008; Anderson 2009; Whitenack and Motta 2010; Santana et al. 2011a; Evans 2013; Smits and Evans 2012; Berthaume et al. 2014). The biomedically relevant and extensive focus on mammalian teeth gives us a biased view that now provides a grand opportunity for understanding the performance consequences of possessing a polyphyodont dentition rather than one with a single replacement cycle (Huysseune and Sire 1998). We have substantial gaps in our understanding of polyphyodont dentitions including unexplained patterns of tooth size, a variety of tooth replacement modes, and tooth shapes that have no intuitive function.

For instance, the diversity of dental batteries in fishes leads to speculation that continuous replacement of teeth makes possible tooth shapes, positions, and orientations that seem precarious (Fig. 3A). For example, in some deep-sea fishes (e.g., *Anoplogaster*, Fig. 3B) the teeth are so slender and tall that it is hard to imagine that they can be used to penetrate anything of substance. Another species (e.g., *Omosudis*) has alternating groups of large and small blade-like teeth. Yet another (e.g., *Anotopterus*) has blade-like teeth pointing anteriorly. What drives this diversity? Could it be driven by the lack of constraint inherent in continuous, cheap replacement teeth?

In diphyodont animals, replacement teeth default to a homologous position, but in many polyphyodont dentitions replacement teeth are not homologous to the functional tooth they replace (i.e., a bigger tooth may replace a small tooth). Gaengler (2000) proposed the question "can a canine be incisiform"? Highlighting the deeper question: is the function of a tooth more determined by shape or by position? If tooth shape dominates function, then an incisor in the place of a molar should still function as an incisor. This predicament is further muddied when we consider the functions of similarly shaped teeth (e.g., fang versus cones) (Olson 2017).
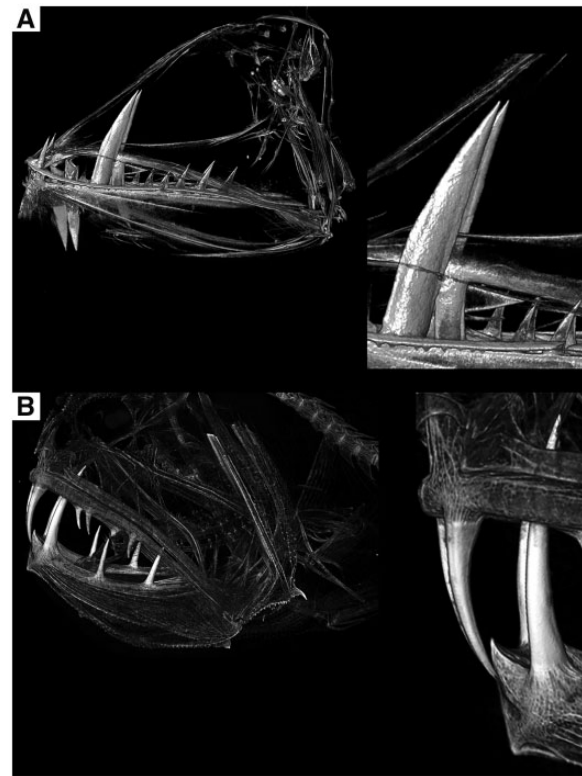

Fig. 3 A) CT image of *Omosudis lowii*. Note the enlarged fangs at the front of the dentary followed by smaller conical teeth posteriorly. **B**) CT image of *Anoplogaster cornuta* with large, curved fangs extending from both the upper and lower jaws.

Mihalitsis and Bellwood (2019) addressed the divergence in form and function by recognizing that position and orientation of conical teeth changes function. This is because similarly shaped teeth at opposite ends of the jaw will necessarily have different amounts of forces acting on them. Berthaume et al. (2013) showed that it took a combination of dull and sharp cusps to create an ideal grinding surface, rather than a single tooth or tooth type. Whitenack and Motta (2010) found that many different shark tooth morphologies were functionally equivalent. Much research has focused on geometric ways to create ideal puncturing, grinding, or slicing tools (Anderson 2009; Whitenack and Motta 2010; Berthaume et al. 2013; Crofts and Summers 2014; Anderson et al. 2016). But, the functional implications of a single tooth could also change when placed in the context of the entire dentition.

Homodonty and heterodonty only begin to describe the entire battery by associating the regionalization of tooth types with a regionalization in function (Keene 1991; Cohen et al. Forthcoming 2020). These terms are vague and provide little quantitative understanding of a tooth or dental function. Even when we incorporate phylogenetic,

developmental, or ontogenetic constraints, these diphyodont-centric terms provide no space for constraints, limitations, or plasticity provided by a polyphyodont dentition (Karagic et al. 2020b, in review). The enormous range in polyphyodonty asks us to reconsider what constraints the function of a tooth has in the context of a functioning dental battery. If polyphyodonty is an ancestral trait, then what does heterodonty and homodonty truly represent? Is a homodont dentition one where all of the teeth, despite shape or size variation, perform in the same way? Quantifying tooth shape in terms of function allows us to explore teeth relative to how they interact with a prey item. By incorporating geometric constraints back into our understanding of the dental battery, we can begin to quantify tooth complexity, integration, and morphology of polyphyodonts in new functional and evolutionarily meaningful ways.

Non-trophic roles and multifunctionality

Teeth provide an exceptionally interesting phenotype for examining the interplay between natural and sexual selection (Darwin 1871; Katsikaros and Shine 1997; Gorman and Hulsey 2020, in review). For instance, many tooth sexual dimorphisms have been shown to be associated with divergent male and female feeding ecologies (Dayan et al. 1989). Yet, although tooth sexual dimorphism could often foster trophic differences, it might also commonly reflect other functions of teeth that have diverged between males and females that are not related to subduing or processing prey (Randau et al. 2013). For instance, teeth are often used in aggressive displays related to dominance hierarchies in groups such as primates and carnivores (Harvey et al. 2009). Many groups such as elephants, vampire deer, and the narwhal also use their teeth specifically for intraspecific contests often involving male–male combat (Silverman and Dunbar 1980). Teeth could also commonly be used for marking territories in ungulates and other territorial organisms. Defense against predators, especially when one sex is more susceptible to predation, could likewise be a cause of tooth dimorphism (Cowlisha 1994; Ovsyanikov 1995). Teeth could often promote ecological divergence and specialization that extends beyond the direct functional consequences of trophic needs.

The extensive sexual dimorphism in teeth also highlights the multi-functionality of teeth (Gorman and Hulsey 2020, in review). For instance, the grinding or scraping of teeth that are otherwise specialized for certain foods can be used for intraspecific vocalizations and mating calls. Mammals such as guinea pigs can engage in teeth chattering and many teleost fish species putatively use their pharyngeal teeth for inter- and intra-specific communication (Parmentier et al. 2017). Additionally, the morphology of teeth in the front of the oral cavity likely influences non-tooth vocalizations of many mammals such as dolphins and bats (Perrin et al. 2011). Additionally, teeth could commonly be used for grasping mates during copulation. This is likely the case for the sexually dimorphic teeth found in groups such as stingrays and other elasmobranchs (Kajiura and Tricas 1996). Many teeth have also been modified into sexual ornaments for attracting the opposite sex (Hendrie and Brewer 2012). Groups of primates and other mammals also likely use teeth during grooming (Rose et al. 1981). A number of groups such as crocodilians, cardinal fishes, and cichlid fishes also brood their offspring in their mouths (Hulsey 2009). Teeth could therefore be modified to enhance this mouth brooding or maternal care. There could commonly be substantial interactions between natural and sexual selection in structuring the evolution of teeth, and as we increase our ability to evaluate multiple functionality, teeth will continue to be an excellent trait to highlight the relative importance of these two forces.

Because teeth do generally have extensive roles in trophic ecology, understanding the mechanisms related to the switch to using teeth for novel functional tasks associated with sexual dimorphism might also be especially tractable (Gorman and Hulsey 2020, in review). There are several vertebrate groups for which sex-specific tooth modifications have been suggested to confer highly novel functions. For instance, male narwhals are thought to use their enlarged single tusks as salinity gauges (Nweeia et al. 2014). Many vertebrates can also use their teeth for novel locomotory functions. For instance, walruses use their tusks for hauling themselves onto ice-shelves (Fay 1982). Many fishes such as gobies and catfishes also use their sucker mouths for holding station in flow or moving through torrential environments such as waterfalls and teeth could be critical here (Geerinckx and De Kegel 2014). Groups such as elephants and rodents also use enlarged teeth for forcing or digging their way through complex environments (McIntosh and Cox 2019). In light of our extensive understanding of the developmental genetics and evolutionary history of teeth, non-trophic dental functions could provide challenging but highly tractable systems for examining the integrative origin of novel evolutionary abilities.

Emerging animal models

To better understand the developmental genomics and function of all vertebrate tooth diversity, we obviously need to incorporate studies of many vertebrate groups. But, comparative biologists have honed in on a few groups such as bats, reptiles, rapidly diversifying teleosts, and chondrichthyans that show particular promise in shedding new light onto the fundamental mechanisms governing the developmental genomic, functional divergence, and evolution of vertebrate tooth diversity.

Bats as eco–evo–devo models

Thanks to the rise of non-model systems, it is now possible to investigate evolutionary morphological variation at the genomic, developmental, and phenotypic levels *in situ*. In this respect, bats (Chiroptera) represent an iconic example: currently with 1411 described species (https://batnames.org), and an incredible craniofacial diversity (Usui and Tokita 2018), bats are now considered a key evo–devo group to study craniofacial variation. Following the acquisition of powered flight, bats underwent a major adaptive radiation into a range of dietary niches that encompass nearly all possible mammalian diets, (i.e., fruit, nectar and pollen, leaves, seeds, arthropods, small vertebrates, fish, and even blood) (Dumont et al. 2012). To be able to exploit this extensive range of diets, bats have evolved a wide diversity of tooth morphologies, including variation in width, length, height, and (in the case of molars) cusps, that has been intensively studied in the last 30 years (Freeman 1988, 1992; Santana and Dumont 2009; Santana et al. 2011a, 2011b; Dumont et al. 2012; Santana and Cheung 2016). Bats exhibit a classic mammalian tribosphenic molar design (Freeman 1992): a first molar (m1) with five cusps that is derived from the ancestral mammal condition by loss of the hypoconulid. Additionally, some mechanisms have been proposed to explain their craniofacial variation in relationship to diet (Arbour et al. 2019; Camacho et al. 2019). Moreover, they represent a good model to study the evolution and the developmental differences between tooth classes, as some species exhibit molariform premolars or reduced canines (Crompton and Hiiemae 1969; Freeman 1992) as well as other important variations of their dental formula between species (Freeman 1992; Giannini and Simmons 2007). Finally, because they are diphyodonts, bats are also a very good model for the study of tooth replacement (Popa et al. 2016). To date, the developmental mechanisms governing the dental morphology in non-model, wild mammal species have been only partially understood, due to difficulties in obtaining embryonic materials for analyses or having genomes available. Thanks to new techniques, access to museum specimens (Hedrick et al. 2018), field caught pregnant bats, possibilities offered by *in vitro* culture for teeth, and the bat1K genome consortium, we now have access to unparalleled eco–evo–devo resources to study dental evolution in this most species-rich lineage of mammals. Together, these characteristics make bats an outstanding model to study tooth evolution in a comparative framework and to address other big questions involving such topics as tooth replacement and bioengineering *in vitro* synthesis of teeth.

Non-mammalian amniotes

Several lineages of what are generally referred to as reptiles including crocodilians, lizards, and snakes also provide exciting emerging models for tooth biology. Dental developmental genetics and functional morphology in these non-mammalian amniotes will continue to provide critical insight into the evolution of mammalian dentitions. Mammalian traits such as extensive morphological heterodonty, enlarged tooth cusps, occlusion, and reduction of tooth replacement can all be placed in a more robust historical context as we learn more about reptilian teeth (Berkovitz and Shellis 2018). For instance, a number of lineages like snakes and agamid lizards have highly heterodont dentitions with extensive shape diversity of individual teeth that form their dental arcades (Cooper et al. 2009; Landova et al. 2020). This within individual variability in teeth likely has facilitated a high degree of feeding specialization (Dumont et al. 2012). Tooth replacement has also likely been convergently reduced in some of these amniote lineages facilitating comparative studies (Buchtová et al. 2013). Likewise, crocodilians share several aspects of tooth attachment and replacement with mammals that could be functionally and genetically investigated (Wu et al. 2013; Bertin et al. 2018). An enhanced understanding of the functional morphology of extant amniotes will also provide greater insight into fossil groups especially those unique to the extinct ancestral lineages leading to mammals (Berkovitz and Shellis 2018). Further examinations of the diversity of tooth attachment, implantation, and replacement in extant and extinct reptiles will also continue to provide understanding into the ancestral condition of these fundamental dental traits in mammals and other amniote trends in tooth diversification (Bertin et al. 2018).

Reptile dentitions will also continue to shed light on the genetic mechanisms generating dental complexity. The deep homology of epithelial appendages, including teeth, will continue to benefit from studies of reptiles (Di-Poï and Milinkovitch 2016). Additionally, the degree to which developmental processes such as morphogenesis and replacement are genetically decoupled can be readily explored in reptiles (Handrigan and Richman 2010; Salomies et al. 2019). What developmental pathways are responsible for the continued maintenance of the dental lamina and polyphyodont replacement patterns will continue to provide evolutionarily relevant comparisons to the mammalian condition (Whitlock and Richman 2013). The genes recruited in the formation of highly novel tooth types such as snake fangs will further provide insight into the origin of dental novelty (Vonk et al. 2008; Landova et al. 2020). As developmental genomic tools become increasingly available in non-model reptiles that can be investigated experimentally, we will gain a greater understanding of all amniote dentitions including our own.

Teleost fishes

Teleost fishes provide a rich evolutionary context for the investigation of the mechanisms generating dental divergence because of the numerous axes along which their teeth have diverged phenotypically and presumably developmentally (Hulsey et al. 2016). In emerging model groups like sticklebacks, pufferfish, and cichlids, the study of how vertebrate teeth can diverge among species into phenotypically novel traits is especially evolutionarily and experimentally tractable. These species can often be brought into the lab, hybridized to study the genetic basis of tooth divergence, and now can frequently be readily manipulated using reverse genetic techniques such as CRISPR (Hulsey et al. 2017; Cleves et al. 2018; Kratochwil et al. 2018).

Research on these fishes also address another problem with using more traditional models like the mouse and its dental developmental network as a standard for all vertebrate teeth which is that unlike both humans and cichlid fishes, mice do not replace their teeth (Fraser et al. 2004). Therefore, we know relatively little about whether the genes responsible for phenotypic differentiation of vertebrate replacement teeth are generally the same genes utilized in the formation of the initial dentition (Fraser et al. 2004, 2012, 2013; Handrigan and Richman 2010). Thus, there could be substantial differences in the genes generating replacement teeth

(Streelman et al. 2003; Schneider and Meyer 2017). Importantly, unlike mammals that replace their teeth at most a single time, cichlids and most teleost fishes can replace their teeth once approximately every 100 days repeatedly throughout their life (Huysseune and Sire 1998; Streelman et al. 2003).Much of the phenotypic diversity in the teleost dentition is also set up during the time between when tooth replacement begins and the onset of reproductive activity (Ellis et al. 2015). Therefore, teleost fish offer a system that could be used to determine what genes are conserved not only during initial vertebrate tooth formation but also what genes are expressed as these structures are replaced and differentiate phenotypically into adult dentitions.

The ever-increasing availability of genomic resources is now making it feasible to conduct comparative genomic analyses, extensively manipulate gene expression and to perform functional assays of gene networks in structures such as the toothed oral and pharyngeal jaws of cichlids and sticklebacks (Hulsey et al. 2016). The exploration of regulatory mechanisms like 3′-UTRs and microRNAs that govern important aspects of all vertebrate tooth development are also receiving increased focus in teleost fishes (Xiong et al 2018, 2019; Franchini et al. 2019). Coupling these comparative analyses with experimental approaches and modeling of the potential interactions among genes will further allow us to test the distinctiveness of individual dental modules. Teleost dentitions will continue to provide a potent system in which to examine tooth function, development, and evolution.

Chondrichthyans

The evolution of teeth was a key event in vertebrate evolution and was linked to a greater capacity for feeding as different tooth morphologies were able to facilitate distinct feeding strategies. In fact, the predatory lifestyle that arose early in gnathostome evolution depended not only on the evolution of the jaw, but also of hard tissues such as bones and teeth (Owen 1845). Along with this, patterning or organization of teeth on the jaw sets up the functional dentition, while tooth replacement ensures new teeth are readily available at the oral surface. Coordinating all these factors across the jaw requires precise positioning of new teeth and is perhaps most apparent in the vertebrate group Chondrichthyes (sharks, rays, and chimaeroids). For example, even in the very different dentitions of sharks and rays, there are similar patterns of tooth addition,
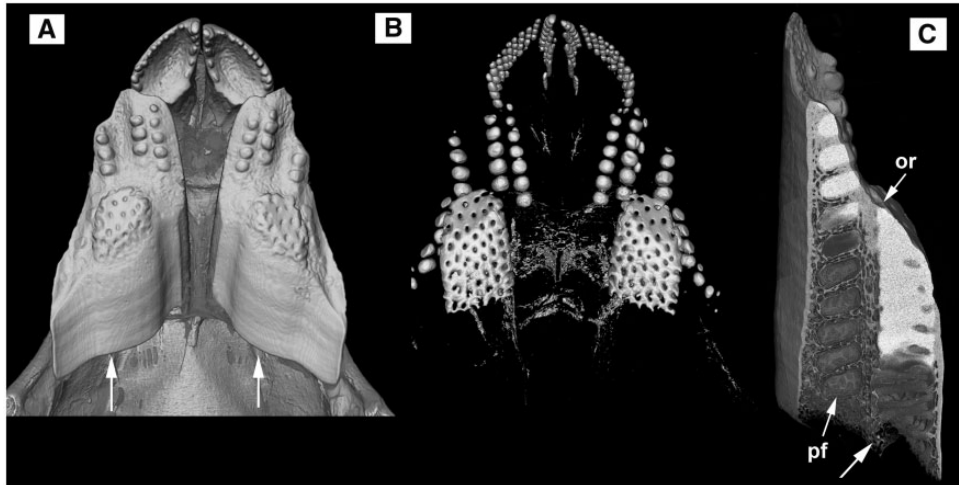
Fig. 4 *Harriotta raleighana* (Chimaeridae; Chimaeroidei; Holocephali), upper dentition, micro-CT scan. **A**) Skull and anterior and posterior upper jaw dental plate. **B**) Rendered scan to show mineralized dentine structures, including columns of ovoids and tritors. **C**) Virtual section through lower jaw dental plate showing mineralized ovoids and tritors, and surrounding trabecular dentine of lower mineral density. Tissue growth occurs at the aboral surface (opposite to the oral surface, or), including organized, preformed spaces within the trabecular dentine for ovoids and tritors. From Smith et al. (2019, figs. 2D and 16G and H).

positioning along the jaw, and replacement such that commonalities in these groups (known as Elasmobranchii) can be identified (Underwood et al. 2015, 2016).

By comparison, the third major group of chondrichthyans, the chimaeroids (=holocephalans), shows a very different type of dentition (Patterson 1965; Didier et al. 1994; Stahl 1999) involving broad dental plates in the upper and lower jaws. There is no indication of replacement teeth forming at any time during the development of these plates (e.g., Smith et al. 2019), in any of the holocephalan families (Callorhinchidae, Chimaeridae, Rhinochimaeridae). However, some researchers have suggested that different parts of these plates represent original tooth germs (Schauinsland 1903; Kemp 1984; Didier et al. 1994). There are nevertheless some intriguing similarities to replacing and patterning chondrichthyan dentitions in the holocephalans. For example, dental plate tissues are clearly replaced at the postero-lingual margin of the plate, in close association with the base of the cartilage jaw (Smith et al. 2019; Fig. 4A, C), in a position similar to the dental lamina in elasmobranchs, and the tooth-producing tissues located there (Smith et al. 2009; Underwood et al. 2015; Martin et al. 2016). Also, multiple mineralized dentine elements that form part of the dental plate in the family Chimaeridae show patterning within the dental plate (Fig. 4B), including preformed spaces within the surrounding less mineralized dentine (Fig. 4C). How these spaces are organized and involve gene regulatory networks related to tooth development in

chondrichthyans and bony fishes (e.g., Fraser et al. 2009; Rasch et al. 2016) will be an interesting area for future research.

How these plates evolved is also uncertain because most fossil relatives are very similar to the living families (Patterson 1965; Stahl 1999; Johanson et al. Forthcoming 2020a). However, more distantly related taxa and new phylogenetic analyses (Coates et al. 2017, 2018) are providing a clearer picture, along with computed tomography (CT) scanning, which allows us to investigate the patterning, organization on the jaw, and histology of these dentitions in greater detail. One of the most interesting of these fossil relatives is *Helodus simplex*. *Helodus* was first described in the mid-1800s (Agassiz 1833–1843), and like many chondrichthyan fossils, was known from isolated teeth that had fallen apart after death. Rarer, more complete specimens (Moy-Thomas 1939) demonstrate that these teeth were joined to form a whorl-like structure (a common feature of fossil chondrichthyans), and that substantial fusion has occurred among the dental elements. This fusion creates a more plate-like structure, but later in development—initially these teeth are more separated in the tooth whorl (Johanson et al. Forthcoming 2020b). *Helodus* therefore provides a mechanism for holocephalan plate development, while new phylogenies resolve a range of fossil taxa with broadly similar tooth whorls as holocephalan relatives (e.g., Cladoselache; Johanson et al. Forthcoming 2020b), suggesting that a progressive loss of tooth identity was characteristic of the evolution of this group and led to the formation of a

novel dental morphology. The combination of fossil material with extant diversity will continue to be an important challenge that helps us to better understand not only what vertebrate dental diversity has existed but also how it originated.

Conclusion

In this article, we have highlighted the importance of grand challenges in tooth biology. It is clear that it will take interdisciplinary research to make real advances in this critical area of organismal biology. This process needs to include the training of new scientists in interdisciplinary fields that are likely to provide important insights and possible solutions to major problems. We also need to identify the tools that we require to make these advances. We must stimulate, encourage, and train comparative biologist who will provide us with the novel approaches necessary to open future horizons in tooth biology. Importantly, the grand challenges that we have identified are not intended to be exhaustive or to limit the focus on other important issues within comparative tooth biology. Nevertheless, frequent reassessment of our grand challenges with a focus on the future will allow us to highlight the advantages of comparative knowledge for those examining the different levels of biological organization that contribute to tooth diversity.

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