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RESEARCH ARTICLE

Comparative postnatal histomorphogenesis of the mandible in wild and laboratory mice

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ABSTRACT

The coordinated activity of bone cells (*i.e.*, osteoblasts and osteoclasts) during ontogeny underlies observed changes in bone growth rates (recorded in bone histology and bone microstructure) and bone remodeling patterns explaining the ontogenetic variation in bone size and shape. Histological cross-sections of the mandible in the C57BL/6J inbred mouse strain were recently examined in order to analyze the bone microstructure, as well as the directions and rates of bone growth according to the patterns of fluorescent labeling, with the aim of description of the early postnatal histomorphogenesis of this skeletal structure. Here we use the same approach to characterize the histomorphogenesis of the mandible in wild specimens of *Mus musculus domesticus*, from the second to the eighth week of postnatal life, for the first time. In addition, we assess the degree of similarity in this biological process between the wild specimens examined and the C57BL/6J laboratory strain. Bone microstructure data show that *M. musculus domesticus* and the C57BL/6J strain differ in the temporospatial pattern of histological maturation of the mandible, which particularly precludes the support of mandibular organization into the alveolar region and the ascending ramus modules at the histological level in *M. musculus domesticus*. The patterns of fluorescent labeling reveal that the mandible of the wild mice exhibits temporospatial differences in the remodeling pattern, as well as higher growth rates particularly after weaning, compared to the laboratory mice. Since the two mouse groups were reared under the same conditions, the dissimilarities found suggest the existence of differences between the groups in the genetic regulation of bone remodeling, probably as a result of their different genetic backgrounds. Despite the usual suitability of inbred mouse strains as model organisms, inferences from them to natural populations regarding bone growth should be made with caution.

1. Introduction

Bone remodeling refers to changes in size and shape of vertebrate skeletal elements during postnatal ontogeny (Enlow and Hans, 1996). This mechanism involves the coordinated activity of two types of bone cells: osteoblasts and osteoclasts (Enlow, 1963; Bloom and Fawcett, 1994; Baron and Kneissel, 2013). Osteoblasts secrete and mineralize the organic bone matrix, mainly composed of collagen fibers, and finally get trapped inside cavities within this matrix called osteocytic lacunae, where they differentiate into osteocytes (Robling and Turner, 2009). Osteoclasts demineralize and reabsorb the organic bone matrix, leaving concavities in the

Abbreviations: PW, postnatal week.

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resorption front of bones named Howship's lacunae (Gilbert, 2000). The realization of the final bone shape and size is determined by the genetic program of bone cells, either inherited (phylogenetic signal) or species-specific (autapomorphies); however, it is also influenced by epigenetic factors: mechanical loads exerted by muscles, as well as metabolic and hormonal factors (Atchley and Hall, 1991; Enlow and Hans, 1996; Cubo et al., 2005; Robling et al., 2006; Baron and Kneissel, 2013; Burr and Allen, 2013).

Bone growth by deposition of periosteal tissue slows down over postnatal ontogeny (Amprino, 1947). This is concomitant with a gradual transformation of the histological bone microstructure: fast bone deposition results in woven bone tissue, while parallel-fibered bone tissue and especially lamellar bone tissue result from slower bone deposition (Amprino, 1947; de Ricqlès, 1975; de Buffrénil and Pascal, 1984; Castanet et al., 2000; Currey, 2002; de Margerie et al., 2002). In addition to the analysis of bone microstructure, the labeling of bones with fluorochrome markers has long been applied to the histological study of the dynamics of bone growth in vertebrates (Harris, 1960; Frost, 1969; Rahn and Perren, 1971; Meunier, 1972, 1974; Pautke et al., 2005; van Gaalen et al., 2010). Shortly after their supply *in vivo*, these vital fluorescent dyes are naturally fixed to the active mineralization front of the growing bone tissue. As a result, fluorescent labels appear as lines in histological cross-sections under ultraviolet light, and these lines actually correspond to the outline of the bone tissue mineralizing front at the time of the fluorochrome fixation (Pautke et al., 2005; van Gaalen et al., 2010). This methodology allows for calculation of periosteal bone deposition rates, and can inform about the lack of net bone growth resulting from bone resting or osteoclastic bone resorption (van Gaalen et al., 2010). The examination of bone microstructure, but also of the directions and rates of periosteal bone deposition from histological cross-sections, has enabled the study of the postnatal histomorphogenesis and growth of several skeletal elements in different vertebrate species, like the long bones in humans and the mandible in mice (Bang and Enlow, 1967; de Buffrénil and Pascal, 1984; de Margerie et al., 2002; Martinez-Maza et al., 2012; Gosman et al., 2013; Cambra-Moo et al., 2015).

The mandible of the house mouse (*Mus musculus*) is a bony structure that originates from the assemblage of several neural-crest-derived morphogenetic units, and represents a key model system for research on the development, morphology, function, and evolution of complex morphological structures (Atchley and Hall, 1991; Hall, 2003; Klingenberg et al., 2004; Renaud et al., 2010; Muñoz-Muñoz et al., 2011; Klingenberg and Navarro, 2012). The early postnatal histomorphogenesis of the mouse mandible was recently characterized in the classical inbred mouse strain C57BL/6J (Martinez-Maza et al., 2012). The inbred laboratory mouse strains are indisputably very valuable and widely-used models in biological research; not only because mice have a shorter genetic distance with respect to humans than other model organisms, but also because these strains provide a wide range of different genotypes and phenotypes (Beck et al., 2000; Wade et al., 2002; Wade and Daly, 2005). However, the genomes of most classical inbred mouse strains, including C57BL/6J, consist of a mixture of segments from three house mouse subspecies found in nature and thus do not represent any of these subspecies, although *Mus musculus domesticus* is pointed out as having had a major role in the origin of these genetic mosaics (Bishop et al., 1985; Bonhomme et al., 1987; Boursot et al., 1993; Silver, 1995; Beck, 2000; Wade et al., 2002; Wade and Daly, 2005; Frazer et al., 2007; Yang et al., 2007, 2011; Didion and Pardo-Manuel de Villena, 2013).

To date, it has not been assessed whether or, if so, how the postnatal histomorphogenesis of the mandible differs between the C57BL/6J strain and *M. musculus domesticus*. The aim of the present study is to explore to what extent this biological process is similar between these two genetically different but closely related groups of mice. To this end, we first examine the histological characterization and growth dynamics of the mandible in an ontogenetic series from the 2nd to the 8th week of postnatal life of wild-derived specimens of *M. musculus domesticus*. Then, we compare our results with those obtained by Martinez-Maza et al. (2012) from the C57BL/6J mouse strain, since the two samples were reared under the same conditions.

2. Materials and methods

2.1. Sample

Ten pregnant wild females of the western European house mouse (*M. musculus domesticus* Schwarz and Schwarz, 1943) were captured alive with Sherman traps between 2009 and 2014 in Castellar del Vallès, Castellfollit del Boix, Nulles, and Santa Perpètua de Mogoda (Northeastern Iberian Peninsula). In these localities, only populations of *M. musculus domesticus* with the standard karyotype (2n = 40) have been recorded (Medarde et al., 2012). Animal collection permits were granted from the Departament d'Agricultura, Ramaderia, Pesca, Alimentació i Medi Natural of the Generalitat de Catalunya (Government of Catalonia; Catalonia, Spain). Each pregnant female was housed separately in a standard cage with environmental enrichment, and placed in an animal room under controlled conditions at Universitat Autònoma de Barcelona (Barcelona, Spain). Litters were born after a few days, and the day of birth of each one was noted. Animals were monitored daily, and supplied with water and food *ad libitum*.

To ensure their survival right after birth, the newborns were housed together with their biological mothers and were not manipulated during their first week of postnatal life. The sample used in this study consisted of 36 mouse pups that survived this critical period, and remained alive until euthanasia. The value of this sample is worth noting, since several critical points conditioned its acquisition. First, the live-trapping of evidently pregnant wild females; then, their accommodation to the laboratory conditions despite their high susceptibility to stress; finally, the birth of their pups and their survival during the entire process. After all, a sample size equivalent to that used by Martinez-Maza et al. (2012) was obtained.

In order to match the growth conditions between our mice and those analyzed by Martinez-Maza et al. (2012), each litter of wild mice was housed together with a foster mother of the C57BL/6J strain and her own pups from the 7th postnatal day. In each case, own and adoptive offspring of each wet-nurse female were about the same age. When the final litter sizes exceeded the average in normal conditions (6–8 pups), some of the biological pups were removed. The biological litters were not included in this study. In addition to being a standardizing measure, this fostering strategy was followed due to the better suitability of female mice from laboratory strains to breed in captivity; wild animals are more sensitive to stress in captive conditions and, therefore, stress affects more severely their breeding performance (Wallace, 1976). Water and the same diet supplied by Martinez-Maza et al. (2012) to their sample, consisting of standard rodent pellets, were supplied *ad libitum* in all cages. Thus, the two mouse groups under comparison were fed the same diet before and after weaning, a developmental milestone that typically occurs around the 21st postnatal day in the house mouse.

Mouse pups were allowed to grow until they were two to eight weeks old. Sample sizes were balanced according to weeks approximately as in Martinez-Maza et al. (2012): 2 weeks, n = 6; 3 weeks, n = 7; 4 weeks, n = 7; 5 weeks, n = 6; 6 weeks, n = 4; 7 weeks, n = 3; 8 weeks, n = 3. Specimens were euthanized by cervical dislocation. Due to the existence of populations of *M. musculus domesticus*