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REVIEW ARTICLE

Signaling pathways in osteogenesis and osteoclastogenesis: Lessons from cranial sutures and applications to regenerative medicine

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Abstract One of the simplest models for examining the interplay between bone formation and resorption is the junction between the cranial bones. Although only roughly a quarter of patients diagnosed with craniosynostosis have been linked to known genetic disturbances, the molecular mechanisms elucidated from these studies have provided basic knowledge of bone homeostasis. This work has translated to methods and advances in bone tissue engineering. In this review, we examine the current knowledge of cranial suture biology derived from human craniosynostosis syndromes and discuss its application to regenerative medicine.

Introduction

Ideal model systems for studying biological processes require three components: simplicity, controllability, and physiologic relevance. In the investigation of bone homeostasis, few models have been more useful than the cranial suture. In terms of simplicity, there is no other model system that exists for bone that can be isolated down to the bare essentials for intramembranous ossification. Due to the limited number of cell types and minimal changes in mechanical forces that occur at cranial sutures, this system allows for direct evaluation of the interactions between osteoprogenitors, osteocytes, osteoclasts, the dura, and the extracellular matrix. Mechanical load on the calvarium is relatively limited considering that the skull is not a weight bearing entity. Muscular pull on the bones is minimal

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in that there are only two muscles directly attached to the cranial bones. In terms of control of the system, *in vitro*, *ex vivo*, *in vivo*, investigation using multiple species, and human syndromes with significant phenotypes can all be used to systematically evaluate single molecular mechanism. Finally, the significance of human phenotype based on single gene mutations cannot be underscored enough. The relevance of processes affecting osteogenesis in cranial sutures is clearly not just an artificial laboratory entity but an actual physiologic process with developmental consequences. These revelations also inspired significant avenues of investigation in bone tissue engineering. In this review, we discuss several major pathways governing bone homeostasis derived from craniosynostosis syndromes and describe its translation to skeletal regeneration.

Cranial suture development and fusion

The mammalian cranial vault contains five bones: paired frontal bones, paired parietal bones, and the occipital or interparietal bone (Fig. 1). Four cranial sutures separate the five bones: the sagittal suture exists between the two paired parietal bones, the coronal suture between the frontal and parietal bones, the metopic between the two frontal bones, and the lambdoid between the occipital and parietal bones. Malleability of the skull imparted by the cranial sutures is essential for the birthing process and subsequent growth of the brain. Growth of the calvarium is typically perpendicular to the direction of the sutures as the brain expands. In the event of a stenosed suture, the compensatory growth occurs parallel to the stenosed suture by expansion at the unaffected sutures. Ossification of the skull occurs via intramembranous ossification from the interplay between the suture mesenchyme and the dura. With the exception of the metopic suture which closes around 18 months of age, all other sutures close after completion of cranial growth well into adulthood. Similar to the human calvarium, the murine posterior frontal suture, analogous to the metopic suture, is the only suture in the mouse to fuse at about 40 days after birth.[1,2]

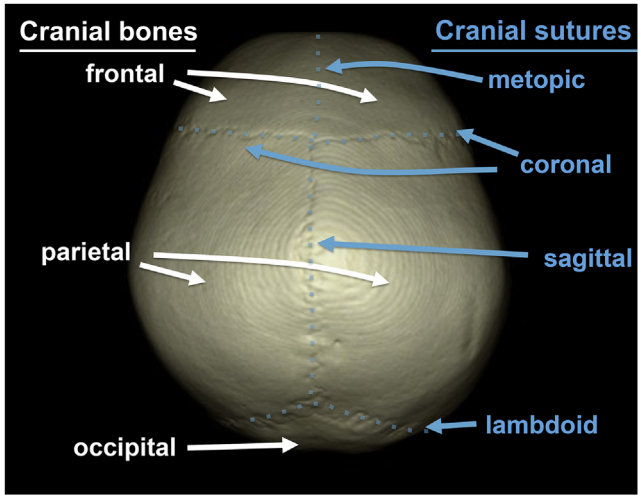

Figure 1 Cranial bones and cranial sutures.

Murine transgenic reporter gene models have now demonstrated that development of the skull is derived from a combination of neural crest and mesodermal lineages. Using two different transgenic mice that labeled cell types with galactosidase under either the Wnt-1 or Mesp-1 promotors, Morriss-Kay and colleagues were able to differentiate the origins of bony development of the skull between the neural crest or mesodermal lineages.[3,4] Their landmark studies definitively demonstrated that the frontal bone is neural crest in origin, the parietal bones are mesodermal, and the occipital bone is a combination of the two. During embryonic development, the coronal suture contains a boundary between the neural crest derived frontal bone on one side and the mesoderm-derived suture mesenchyme and parietal bone on the other side.[3,4] Similarly, at the sagittal suture, there is also a boundary between neural crest and mesodermal lineages. This boundary is likely important for the timing of suture patency versus fusion.

Craniosynostosis, or early fusion of cranial sutures, occurs in approximately 1 in 2000—2500 live births of which the majority are nonsyndromic in nature.[5,6] Single suture nonsyndromic craniosynostosis accounts for over 80% of all craniosynostosis. Sagittal synostosis is the most common form accounting for 40%—50% of all nonsyndromic craniosynostosis with a prevalence of about 1.5 in 10,000 live births and a male to female ratio of 2.5:1. Unicoronal craniosynostosis accounts for 0.7 in 10,000 live births with a male to female ratio of 1:2.3.[7] Metopic synostosis occurs in 0.8 in 10,000 live births with a male to female ratio of 3.3:1. Lastly, lambdoid synostosis occurs in about 0.7 in 10,000 live births with a male to female ratio of 2.2:1.

The consequences of early cranial suture fusion are both visible and functional. With the exception of mild cases, the majority of patients with craniosynostosis have characteristic head shapes depending on the type of synostoses that is present. This congenital anomaly is not only distressing to parents, but it may also harbor functional consequences. In multi-suture or syndromic cases, suture fusion has clearly been related to increased intracranial pressure with potential consequences in brain development.[8,9] In nonsyndromic cases, several landmark studies have now demonstrated that functional consequences also occur. Persing and colleagues have recently published their prospective, multi-center studies using a battery of neuropsychiatric testing to show that total cranial vault remodeling before 6 months of age improves outcomes. In addition, their work also showed that minimally invasive endoscopic strip craniectomies are definitively inferior to total cranial vault remodeling even when completed at an early age.[10—12] Although these studies do not consider intermediate surgical techniques such as the *pi* procedure in cranial vault reconstruction, their work is of great significance in surgical decision making and states that a minimally invasive correction for nonsyndromic sagittal synostosis adversely affects the future intelligence and neuropsychological function of a child with craniosynostosis.

The etiology of craniosynostosis is varied. A number of monogenetic alterations have been described, however, factors such as advanced maternal age, advanced paternal age, race, birth plurality, and gender have all been