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REVIEW ARTICLE

Molecular basis of cranial suture biology and disease: Osteoblastic and osteoclastic perspectives

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Abstract The normal growth and development of the skull is a tightly regulated process that occurs along the osteogenic interfaces of the cranial sutures. Here, the borders of the calvarial bones and neighboring tissues above and below, function as a complex. Through coordinated remodeling efforts of bone deposition and resorption, the cranial sutures maintain a state of patency from infancy through early adulthood as the skull continues to grow and accommodate the developing brain's demands for expansion. However, when this delicate balance is disturbed, a number of pathologic conditions ensue; and if left uncorrected, may result in visual and neurocognitive impairments. A prime example includes craniosynostosis, or premature fusion of one or more cranial and/or facial suture(s). At the present time, the only therapeutic measure for craniosynostosis is surgical correction by cranial vault reconstruction. However, elegant studies performed over the past decade have identified several genes critical for the maintenance of suture patency and induction of suture fusion. Such deeper understandings of the pathogenesis and molecular mechanisms that regulate suture biology may provide necessary insights toward the development of non-surgical therapeutic alternatives for patients with cranial suture defects. In this review, we discuss the intricate cellular and molecular interplay that exists within the suture among its three major components: dura mater, osteoblastic related molecular pathways and osteoclastic related molecular pathways.

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Introduction

The human skull is formed from nine cranial bones, including two frontal bones, two parietal bones, two temporal bones, one ethmoid bone, one sphenoid bone, and one occipital bone. These bones articulate with one another at joints composed of fibrous tissue, also known as cranial sutures. The areas where several sutures come into contact are called fontanelles. The skull contains a number of sutures, including the sagittal suture, located between the two parietal bones, the coronal sutures, located between the two frontal and parietal bones, the metopic suture, located between the frontal bones, the lambdoid sutures, located between the supraoccipital and parietal bones, and the squamosal suture, located between the temporal, parietal, and sphenoid bones (Fig. 1A—C) During suture formation, the neighboring bone fronts of the calvarial bones come into close proximity to one another. The bones either abut at the suture site, as is the case at the sagittal and metopic sutures, or overlap, which occurs at the coronal and lambdoid sutures.[1] In addition to these cranial sutures, there are also a number of facial sutures present in the human craniofacial skeleton — however, the embryology, anatomy, and research pertaining to the facial sutures are outside the scope of this review.

The human skull begins to form between days 23—26 of gestation, from both mesoderm- and neural crest-derived tissues. During development, these sutures remain patent to allow for the expansion of the cranial vault and the underlying brain. The metopic suture is the first to undergo fusion at approximately 9 months of age, while the sagittal suture does not fully close until adolescence or later.[2,3] As the calvarial bones continue to grow, cranial sutures also act as important areas of new bone formation and bone turnover, and facilitate skull growth in the direction perpendicular to their suture orientation.

Bone can form in one of two ways: either through endochondral or intramembranous ossification. Most bones in the human body undergo endochondral ossification, whereby mesenchymal stem cells first differentiate into chondrocytes, which secrete a cartilage matrix that eventually undergoes osteoblast-driven ossification. The bones of the cranial vault, however, undergo intramembranous ossification, a process that does not have a cartilage intermediate. Instead, mesenchymal cells, located between the dermal mesenchyme and the meninges, differentiate directly into osteoblasts, which then form bone through the secretion of an osteoid matrix.

The cranial suture can be thought of as a complex, composed of the two osteogenic bone fronts on either side of the suture, the mesenchymal tissue of the suture, the underlying dura mater, and the overlying pericranium (Fig. 2).[4] The cells in the middle of the mesenchymal tissue of the suture remain undifferentiated during cranial vault development, while the cells near the two osteogenic bone fronts typically become bone through the process of intramembranous ossification.

The tissues of the cranial suture complex all interact with one another to allow for proper suture formation and patency throughout development. In functional terms, suture formation and development must be in tight synchronicity with underlying organ development to facilitate

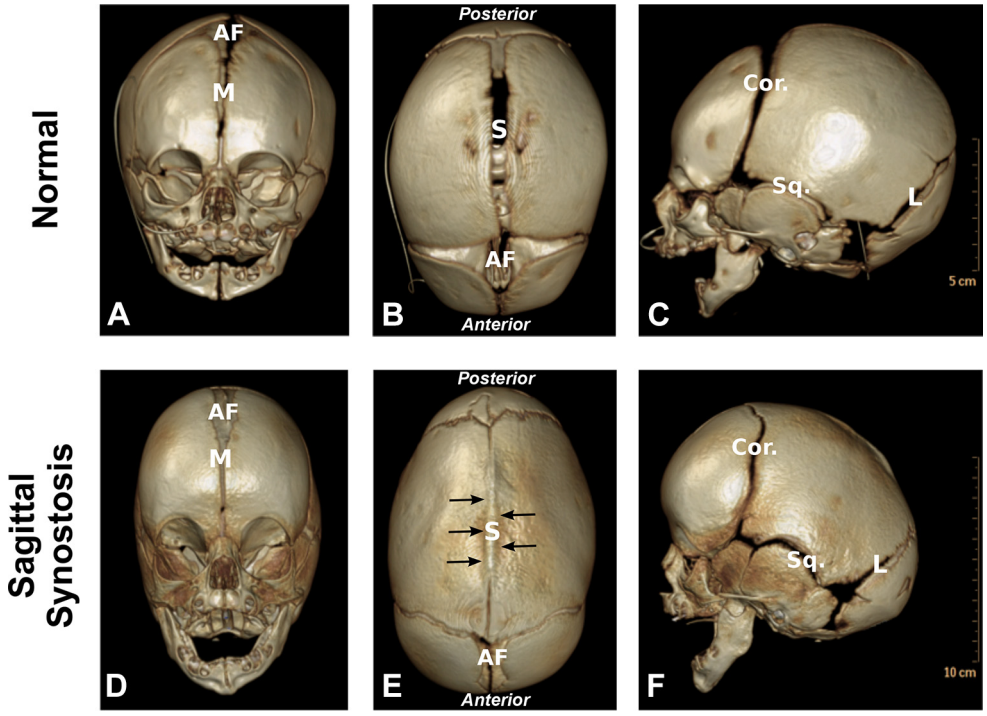

Figure 1 Three-dimensional computed tomography reconstructions of a 4-week-old patient with normal suture development (A—C) and an 8-week-old patient with sagittal synostosis (E—F). Anterior (A & D), vertex (B & E), and lateral (C & F) views. (A—C) Typical skull contour with patent sutures. (C—F) Elongated skull shape associated with fusion of the sagittal suture (arrows). AF, anterior fontanelle; M, metopic suture; S, sagittal suture; Cor., coronal suture; Sq., squamosal suture; L, lambdoid suture.