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Commentary on the Differential Healing Capacity of Calvarial Bone

David D. Lo, MD*, **Adrian McArdle, MB, BCh***, **Kshemendra Senarath-Yapa, MA, MB***, and **Michael T. Longaker, MD, MBA*†**

*Hagey Laboratory for Pediatric Regenerative Medicine, Division of Plastic and Reconstructive Surgery, Department of Surgery, Stanford University School of Medicine, Stanford, California

†Institute for Stem Cell Biology and Regenerative Medicine, Stanford University School of Medicine, Stanford, California

In the original study by Docherty Skogh et al,¹ the use of a hyaluronan-based hydrogel along with bone morphogenetic protein (BMP)-2 to achieve bone healing in critical-sized cranial defects in humans was examined. Although the authors found that the addition of BMP-2 to hydrogel did not significantly enhance bone healing when compared with hydrogel alone and Tissel (Baxter Bioscience, Heidelberg, Germany) with autologous bone, the data did provide meaningful evidence to support the functional differences of the dual embryonic origins of human cranial vault by demonstrating improved healing capacity in the frontal bone as compared with the parietal-temporal bones in humans for the first time.

Skeletal defects, specifically calvarial bone defects, remain a challenge in craniofacial surgery and regenerative medicine, and contemporary reconstructive approaches, such as autologous bone grafts, allografts, or synthetic biomaterials, often do not offer the most optimal solution. We, surgeons and scientists alike, have been trying to elucidate the relationships between the embryonic cell populations and the calvarial bone to which they directly contribute in hopes to define a source of robust progenitor cells with enhanced osteogenic potential to optimize calvarial bone healing. The current school of thought is that the frontal and parietal bones of the cranial vault are of neural crest and mesodermal origin, respectively. What is our current knowledge of the embryonic origin of the cranial vault in a human? How does this knowledge allow us to investigate osteogenesis and osseous healing more critically?

The morphogenesis of the craniofacial elements is a unique integration of cells of distinct embryonic origin. It is the result of complex spatiotemporal interactions between these various cellular components of the neurocranium and the viscerocranium, most of which is derived from the cranial neural crest (CNC), a population of multipotent embryonic progenitor cells that arises from the dorsal margins of the neural folds.^{2,3} The rostral craniofacial elements differ from the more posterior axial skeletons derived from cephalic paraxial mesoderm.⁴ The human cranial vault is a dynamic structure formed primarily from intramembranous ossification of 5 membranous flat bones (paired frontal and parietal bones and unpaired interparietal bone) connected by fibrous sutures. However, with respect to the embryonic origin, the direct contributions of migratory CNC and cephalic paraxial

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Address correspondence and reprint requests to Michael T. Longaker, MD, MBA, Hagey Laboratory for Pediatric Regenerative Medicine, Stanford University School of Medicine, 257 Campus Dr, Stanford University, Stanford, CA 94305-5148; longaker@stanford.edu.

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mesoderm of regions of the human cranial vault remain controversial. Numerous model systems have been used in attempts to provide “fate maps” that depict end derivatives of the embryonic tissues in the cranial vault. These model systems include bony fish and reptiles, amphibians, quail chick and domestic chicken, and mouse.⁵⁻¹¹ However, early avian studies offered conflicting accounts of the embryonic derivation of the cranial vault, ranging from complete derivation of the frontal and parietal bones from CNC, to mesodermal derivation of the parietal bones and composite derivation (CNC and mesoderm) of the frontal bones, to a largely mesodermal derivation of both bones. The discrepancies in these studies may lie in differences of the experimental methods, contamination of grafts with other cell types, or, perhaps, the innate variation between different strains of the animal models.¹⁰

Similarities in craniofacial development and molecular pathways between a mouse and a human have made it the model organism to study human cranial vault origin. With the advent of transgenic *Wnt1-Cre/R26R* mice, researchers have been able to, more conclusively, define the pattern of CNC cell migration in mouse embryos and to demonstrate that the frontal bone is of neural crest origin, whereas the parietal bone is of paraxial mesodermal origin.^{12,13} Furthermore, functional implications of the distribution of neural crest and mesodermal tissue in the developing cranium have been delineated: migration and differentiation of the skeletogenic CNC depend on interactions with surrounding tissues, including the sagittal and coronal sutures juxtaposed between neural crest-derived and mesodermal mesenchyme. These 2 sutures provide major sites of growth and signaling centers that control proliferation and differentiation of osteogenic progenitor cells during craniofacial morphogenesis. Changes in the expression of several morphogenetic growth factor and hormone signaling pathways, including Wnt/ β -catenin, BMP, and transforming growth factor β , and the responses by the CNC control CNC migration and differentiation and are central to the evolution of craniofacial development.¹⁴⁻¹⁶

On the basis of the understanding of the developmental tissue origins of mammalian frontal and parietal bones, studies have begun to examine regional differences in calvarial healing in hopes to exploit differential osteogenic potential and regenerative capacity that is innately linked to the distinct embryonic tissues (CNC and cephalic paraxial mesoderm) that compose the calvaria. Studies from our laboratory by Quarto et al¹⁴ have demonstrated enhanced osteogenic potential and healing capacity of CNC-derived frontal bones via more robust endogenous canonical Wnt/ β -catenin signaling and higher expression of FGF-ligand compared with mesoderm-derived parietal bones.^{17,18}

Extrapolation of the embryonic origin and the differential healing capacity of each contributing embryonic tissue in mouse skulls to the human cranial vault, however, are, perhaps, inappropriate. To date, there is no definitive evidence that substantiates the true embryonic origin of the regions of the calvarial bones in humans. The conclusion of dual origin of the cranial vault is only known by inference of mammalian studies of mice. We would like to commend Docherty Skogh et al on their original article that shed some light to the regional differences in the osteogenic potential of the frontal and parietal bones in human participants, which is congruent with the current literature in the mouse model. Not only did this study demonstrate that the frontal bone in humans have increased bone healing potential compared with the parietal bone but it also lends credence to the hypothesis of the dual origin of the human cranial vault similar to that seen in the mouse (Fig. 1). Cranial skeletal repair is a distinctive process with great complexity, and elucidation of the underlying biology is of great clinical relevance, as evidenced by the data presented by Docherty Skogh et al, which exquisitely merged clinical and basic science research. Further studies to identify cells with greater osteogenic potential, to elucidate the molecular signals that drive their differentiation, and to develop delivery methods for these cells are studies

with worthy objectives that will allow us to target therapy more appropriately for our patients on the basis of innate, regional differences of osteogenic cells derived from different embryonic structures.

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FIGURE 1.

Comparison between the embryonic origins of mammalian frontal and parietal bones in mouse and human.