

“Stem cells of the suture mesenchyme in craniofacial bone development, repair and regeneration”

Takamitsu Maruyama PhD

Development of the skeleton is mediated through two distinct ossification mechanisms. Craniofacial bones are formed mainly through intramembranous ossification, a mechanism different from endochondral ossification required for development of the body skeleton. The skeletal structures are quite distinct between the two, thus they are likely to have their unique stem cell populations. The sutures serve as the growth center critical for healthy development of the craniofacial skeleton. Defects in suture morphogenesis cause its premature closure, resulting in development of craniosynostosis, a devastating disease affecting 1 in $\sim 2,500$ individuals. The suture mesenchyme has been postulated to act as the niche of skeletal stem cells essential for calvarial morphogenesis. However, very limited knowledge is available for suture biology and suture stem cells (SuSCs) have yet to be isolated. Here we report the first evidence for identification and isolation of a stem cell population residing in the suture midline. Genetic labeling of SuSCs shows their ability to self-renew and continually give rise to mature cell types over a 1-year monitoring period. They maintain their localization in the niches constantly produce skeletogenic descendants during calvarial development and homeostatic maintenance. Upon injury, SuSCs expand drastically surrounding the skeletogenic mesenchyme, migrate to the damaged site and contribute directly to skeletal repair in a cell autonomous fashion. The regeneration, pluripotency and frequency of SuSCs are also determined using limiting dilution transplantation. In vivo clonal expansion analysis demonstrates a single SuSC capable of generating bones. Furthermore, SuSC transplantation into injured calvaria facilitates the healing processes through direct engraftments. Our findings demonstrate SuSCs are bona fide skeletal stem cells ideally suited for cell-based craniofacial bone therapy as they possess abilities to engraft, differentiate