RESULTS: Flow cytometric assessment of surface marker expression of mASCs demonstrated the following mean (SEM) percentage positive cells for the indicated surface antigens: CD44, 80.6 (5.3); CD90, 79.7 (4.6); and CD105, 26.7 (6.3). mASCs expressed the following mean (SEM) percentage negative cells for the indicated surface antigens: CD14, 96.4 (0.5); CD31, 97.6 (0.1); and CD45, 98.2 (0.1). There were no statistically significant differences in marker expression between mASC groups that underwent successful trilineage induction (n=8) and those that failed one differentiation pathway (n=6). mASCs from BRCA negative vs. BRCA mutation patients produced lesser quantities of triglycerides after two weeks of induction; average fold-change of lipid production in non-inherited cancer mASCs was 3.45±1.96 vs. 0.79±0.89 (p=0.03). The mASC secretome of non-BRCA carriers vs. BRCA mutations differed in production of interleukin (IL) 1b (0.09 vs. 4.45-fold, p=0.02), IL10 (1.00 vs. 4.24-fold, p=0.04), and tumor necrosis factor (TNF) alpha (0.24 vs. 0.88-fold, p=0.02).

CONCLUSIONS: This is the first study to demonstrate an intrinsic, abnormal adipogenic differentiation block in mASCs from high-risk breast cancer patients (BRCA1/BRCA2), a process that has been implicated in breast tumor progression and invasiveness. Aggressive epithelial breast cancers are dependent on the local stromal environment that creates a favorable field for tumor growth and invasion, including a chronic pro-inflammatory cytokine profile, making the understanding of the stromal factors critically important for future risk stratification and/or prevention targets and strategies.

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The Suture Provides a Niche for Mesenchymal Stem Cells of Craniofacial Bones

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PURPOSE: Craniofacial bones are connected by sutures. It was generally proposed that sutures mainly function to connect the bones and to absorb shock. In the current study, we are proposing that suture mesenchyme contains stem cell to support the craniofacial bone turnover and injury repair.

METHODS: Gli1-LacZ reporter mice were used to study the expression pattern of Gli1 in the craniofacial bones. Lineage tracing analysis were performed to trace the fate of the Gli1+ cells. Gli1-CreERT2;R26DTAlox strain was used for cell ablation analysis. Various other transgenic mouse strains were used to analyze the function and regulations of the Gli1+ cells in the suture mesenchyme.

RESULTS: Gli1 expression is restricted to the suture mesenchyme specifically after postnatal 21 days. Gli1+ cells in the suture mesenchyme do not express any osteogenic differentiation markers including Runx2, Sp7, ALPase or osteopontin. Lineage tracing analysis based on Gli1-CreERT2;R26ZsGreen mice indicates that Gli1+ cells give rise to the entire suture mesenchyme, the periosteum, the dura and then to all the craniofacial bones under physiological condition or upon injury. Transplantation experiments indicate that suture transplants rapidly expand the size and are capable of repairing large size defects in the host mice. In vitro cell culture indicate that mesenchymal cells isolated from the suture express typical MSC markers and possess osteogenic, chondrogenic and adipogenic potentials. Cell ablation analysis based on Gli1-CreERT2;R26DTA mice indicates Gli1+ cell are indispensable for craniofacial postnatal growth and suture patency.

CONCLUSION: Gli1+ cells in the suture mesenchyme are stem cells supporting the postnatal growth, turnover and injury repair of craniofacial bones. Our study reveals a novel function for craniofacial suture mesenchyme, providing a new perspective for understanding the onset of craniosynostosis and other suture deformities, as well as a potential new therapy for craniofacial disorders.

Missense Variant in MAPK Inactivator PTPN5 is Associated with Decreased Severity of Post-Burn Hypertrophic Scarring

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PURPOSE: Hypertrophic scarring (HTS) is a common and often devastating sequela of burn injury, resulting in disfigurement, chronic pain, intractable pruritis, and functional impairment that can severely decrease quality of life. Although it is thought to result from an exaggerated inflammatory response to injury, its precise pathogenesis is unknown, limiting the development of effective therapies. Risk of HTS is known to depend on race, suggesting a genetic mechanism. However, the genetic determinants of HTS have not been identified. Mitogen-activated protein-kinases (MAPKs) are key mediators of inflammation, and inhibition of p38 MAPK decreases fibroproliferative scarring in a porcine model. The purpose of this study was to test whether single-nucleotide polymorphisms (SNPs) in MAPK-pathway genes would be associated with HTS severity following burn injury.