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Positional memory of fibroblasts may affect efficiency of iPSC reprogramming

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Induced Pluripotent Stem cells (iPSC) are pluripotent stem cells reprogrammed from adult somatic cells. Although iPSC hold great potential for applications in regenerative medicine, technical problems, mostly related to the low efficiency of reprogramming, are yet to be solved. Since the most used cells for iPSC reprogramming are skin fibroblasts (FB), and since FB preserve positional memory, we hypothesize that the anatomic origin of FB might influence iPSC reprogramming.

We isolated FB from skin of five different sites (neck, arm, thigh, breast, abdomen) of 13 patients undergoing plastic surgery or from heart wall or ascending aorta wall of the explanted heart of 3 patients receiving heart transplantation. FB from different anatomic sites and control FB from neonatal foreskin, were cultured for one week to evaluate morphology, proliferation rate and proneness to apoptosis. Additionally, expression of vimentin, cadherin, smooth muscle actin and Factor VIII was investigated to exclude the presence of other cell types. Transcriptome analysis including genes involved in stemness maintenance, embryogenesis, cell growth, activation and development, was performed by real-time PCR. Despite the similar morphology of FB from different sites, and immunopositivity for vimentin, along with the absence of other cell type markers, FB isolated from abdomen and heart had 1.5-fold higher doubling time, while FB from heart, abdomen and breast were less susceptible to apoptosis. Intriguingly, Real-Time PCR revealed that in abdomen, breast, neck, arm and heart FB genes involved in cell growth, development, proliferation, and migration, as TM4SF1, GPC4, CSPG2, DDIT4, ID1 were up-regulated, while genes regulating embryogenesis and tissue morphogenesis, like VCAN, FN1, HOXA5, CD49a were up-regulated in FB isolated from abdomen, arm and heart. However, all FBs had transcripts of markers of Mesenchymal Stem Cells (MSC), as CD105 and CD90. Our results provide evidence that human adult FB from different sites have different genetic program. Therefore, FB may respond to reprogram technology in different manner, thus affecting reprogramming efficiency. While offering novel perspective of the reprogramming technology, our study also demonstrates that abdomen and breast FB share cardiac genetic signature of cardiac FB while expressing markers of MSC and they might represent the ideal cell for cardiac reprogramming.

Keywords

iPSC; skin fibroblasts; direct reprogramming.