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Osteogenic differentiation factors of multipotent mesenchymal stromal cells in the current understanding

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Abstract

Background: Molecular genetic mechanisms, signaling pathways, conditions, factors, and markers of the osteogenic differentiation of mesenchymal stem cells (MSCs) are being actively studied and are among the most studied areas in the field of cellular technology. This attention is largely due to the mounting contradictions in the seemingly classical knowledge and the constant updating of results in the analyzed areas. In this regard, we focus on the main classical concepts and some new factors and mechanisms that have a noticeable regulatory effect on the differentiation potential of postnatal MSCs.

Results: This review considers the importance of the sources of MSCs for the realization of their differentiation potential; molecular genetic factors and signaling pathways of MSC differentiation; the role of inflammatory cytokines and chemokines in osteogenesis; biomechanical signals; and the effect of conformational changes in the cellular cytoskeleton on MSC differentiation.

Conclusion: It is concluded that it is necessary to move from studies focused of the effects of local genes to those taking multiple measurements of the gene-regulatory profile and the biomolecules critical for the implementation of numerous, incompletely studied osteogenic factors of endogenous and exogenous origin. Among the cornerstones of

future (epi)genetic studies, whether osteomodulatory effects are realized through specific signaling pathways and/or whether cross-signaling with known genes drives the osteogenic differentiation of MSCs remain to be determined.

Keywords: cell source; cytokines and chemokines; differentiation markers; genes; mechanotransduction.; transcription factors.

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Cell Adhesion-Mediated Piezoelectric Self-Stimulation on Polydopamine-Modified Poly(vinylidene fluoride) Membranes

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Abstract

Cell adhesion-mediated piezoelectric stimulation provides a noninvasive method for in situ electrical regulation of cell behavior, offering new opportunities for the design of smart materials for tissue engineering and bioelectronic medicines. In particular, the surface potential is mainly dominated by the inherent piezoelectricity of the biomaterial and the dynamic adhesion state of cells. The development of an efficient and optimized material interface would have important implications in cell regulation. Herein, we modified the surface of poled poly(vinylidene fluoride) (PVDF) membranes through polymerization of dopamine and investigated their influence on cell adhesion and electromechanical self-stimulation. Our results demonstrated that mesenchymal stem cells seeded on the poled PVDF membrane exhibited stronger cell spreading and adhesion. Meanwhile, the surface modification through polydopamine significantly improved the hydrophilicity of the samples and contributed to the formation of cell actin bundles and maturation of focal adhesions, which further positively modulated cell piezoelectric self-stimulation and

induced intracellular calcium transients. Combining with theoretical simulations, we found that the self-stimulation was enhanced mainly due to the increase of the adhesion site and adhesion force magnitude. These findings provide new insights for probing the cell regulation mechanism on piezoelectric substrates, offering more opportunities for the rational design of piezoelectric biomaterial interfaces for biomedical engineering.

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Transformed Canine and Murine Mesenchymal Stem Cells as a Model for Sarcoma with Complex Genomics

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Abstract

Sarcomas are rare mesenchymal tumors with a broad histological spectrum, but they can be divided into two groups based on molecular pathology: sarcomas with simple or complex genomics. Tumors with complex genomics can have aneuploidy and copy number gains and losses, which hampers the detection of early, initiating events in tumorigenesis. Often, no benign precursors are known, which is why good models are essential. The mesenchymal stem cell (MSC) is the presumed cell of origin of sarcoma. In this study, MSCs of murine and canine origin are used as a model to identify driver events for sarcomas with complex genomic alterations as they transform spontaneously after long-term culture. All transformed murine but not canine MSCs formed sarcomas after subcutaneous injection in mice. Using whole genome sequencing, spontaneously

transformed murine and canine MSCs displayed a complex karyotype with aneuploidy, point mutations, structural variants, inter-chromosomal translocations, and copy number gains and losses. Cross-species analysis revealed that point mutations in *Tp53/Trp53* are common in transformed murine and canine MSCs. Murine MSCs with a cre-recombinase induced deletion of exon 2-10 of *Trp53* transformed earlier compared to wild-type murine MSCs, confirming the contribution of loss of p53 to spontaneous transformation. Our comparative approach using transformed murine and canine MSCs points to a crucial role for p53 loss in the formation of sarcomas with complex genomics.