The Osteogenic Potential of Human Mesenchymal Stem Cells

- Novel markers and key factors for differentiation

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The thesis is based on the following studies,
referred to in the text by their Roman numerals.

I. **Virtual ligand-based screening reveals purmorphamine analogs with the capacity to induce the osteogenic differentiation of human mesenchymal stem cells.**
Granéli C, Karlsson C, Lindahl A, Thomsen P.
Cells Tissues Organs 2013;197(2):89–102.

II. **The effects of PPAR-γ inhibition on gene expression and the progression of induced osteogenic differentiation of human mesenchymal stem cells.**
Granéli C, Karlsson C, Brisby H, Lindahl A, Thomsen P.
Connective Tissue Research 2014; Accepted for publication.

III. **Novel markers for osteogenic and adipogenic differentiation of human bone marrow stromal cells identified using a quantitative proteomics approach.**
Granéli C, Thorfve A, Rüetschi U, Brisby H, Thomsen P, Lindahl A, Karlsson C.
Stem Cell Research 2014;12(1):153–165.

IV. **The stimulation of an osteogenic response by classical monocyte activation.**
Omar O, Granéli C, Ekström K, Karlsson C, Johansson A, Lausmaa J, Larsson-Wexell C, Thomsen P.
Biomaterials 2011;32(32):8190-8204.

V. **The effects of bacterial cell-wall components and bacterial membrane vesicles on the osteogenic differentiation and secretory profiles of human mesenchymal stem cells**.
Granéli C, Wang X, Vazirisani F, Trobos M, Brisby H, Lindahl A, Omar O, Ekström K, Thomsen P.
In manuscript.

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ABSTRACT

Mesenchymal stem cells (MSCs) are multipotent stem cells with ability to differentiate into cells of the connective tissue lineage, such as adipocytes, osteoblasts and chondrocytes, both *in vitr*o and *in vivo*. The main objective of the present thesis was to study different aspects of the osteogenic potential of MSCs. By examining markers of differentiation, exploring approaches for enhanced osteogenesis through the use of small molecule substances, and studying the interactions between MSCs and inflammatory cells/signals, we aimed to gain new insights into factors and mechanisms involved in regulation of the osteogenic differentiation process.

Through both a virtual ligand-based screening method combined with several *in vitro* screening steps, and a chemical inhibition of the PPAR-γ transcription factor, it was demonstrated that osteogenic differentiation of MSCs can be modulated by the use of a small molecule substance. Furthermore, a link between PPAR-γ, leptin and osteogenic differentiation was revealed.

The surface markers CD10 and CD92, and intracellular protein CRYaB were demonstrated as suitable markers for monitoring and evaluating the differentiation of MSCs. CD10 and CD92 were shown to be markers of both osteogenic and adipogenic differentiation, whereas CRYaB was revealed as a marker specific for the osteogenic lineage.

Activated human monocytes communicate pro-osteogenic signals to MSCs, independent of direct cell-cell contact. Furthermore, membrane vesicles isolated from gram-positive bacterial strains *Staphylococcus aureus* and *Staphylococcus epidermidis* also promote osteogenic differentiation of MSCs as well as modulate their secretion of signals related to inflammation and immune-modulation.

In conclusion, the present thesis presents new findings regarding the phenotype of MSCs characteristic for osteogenic differentiation. Furthermore, through the results presented here insight is gained into several key factors, both of synthetic and biological origin, important in this process. This knowledge is valuable for future strategies with the aim of enhancing osteogenic regeneration.

Keywords: Mesenchymal stem cells, mesenchymal stromal cells, osteogenic differentiation, adipogenic differentiation, bone regeneration, inflammation, monocytes, infection, bacterial membrane vesicles, compromised bone healing, cell surface proteins, CD-markers, osseointegration, regenerative medicine.

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