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### **MMP activity is an essential link between mechanical stimulus and mesenchymal stem cell behaviour**

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#### **Introduction:**

Mechanical boundary conditions as well as the function of mesenchymal stem cells (MSCs) play a pivotal role during bone regeneration. However, the molecular mechanisms underlying the dependency of the regeneration process on mechanical loading remain unclear. This study has therefore investigated how matrix metalloproteases (MMP) activity is influenced by mechanical stimulation and whether MMP activity affects MSC behaviour.

#### **Methods:**

MSCs were isolated from bone marrow aspirates and subsequently characterised functionally and by flow cytometry. The influence of mechanical stimulation was analysed in a bioreactor system that aims to resemble the early phase of bone healing (compression of 10 kPa, 1Hz, 3 days) using a fibrin/cancellous bone construct. A furin inhibitor was added to investigate the

mechanism of MMP regulation. RNA and protein expression were determined by means of gene arrays and ELISAs. Gelatinolytic activity of MMPs was detected by zymography. Functional assays investigating migration, proliferation and differentiation were supplemented with specific inhibitors for MMP-2, MMP-3 and MMP-13. Three independent experiments using different MSC donors with at least duplicates in each were conducted.

#### **Results:**

Mechanical stimulation of MSCs led to an upregulation of their extracellular gelatinolytic activity, which was consistent with the increased protein levels seen for MMP-2, -3, -13 and TIMP-2. However, mRNA expression levels of MMPs/TIMPs showed no changes in response to mechanical stimulation. The furin protease was proved to be involved in the regulation of MMP-2. Specific inhibition of MMP-2, -3 and -13 showed MMP-13 to be associated with osteogenic differentiation.

**Discussion:**

The observed independency of mRNA and protein expression levels indicates the involvement of post transcriptional processes for MMP regulation, such as the alteration in MMP activity demonstrated for MMP-2. To summarise, the results of this study suggest that MSC function is controlled by MMP activity, which in turn is regulated by mechanical stimulation of these cells. Thus MMP/TIMP balance seems to play an essential role in transferring mechanical signals into MSC function. In the future, details of this cascade are to be unravelled before such understanding could be translated into stimulation of bone healing even in unloaded clinical conditions.

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