

Stress and homeostasis in the bone and the intervertebral disc

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The skeleton is continuously subjected to several stresses. However, although intense stresses can be detrimental, it is well-documented that mild stresses represent an important regulatory factor during development and in postnatal life. Nevertheless, although data available today provide some insights into how cells sense these stimuli and convert them into biochemical responses, the precise molecular mechanisms that underlie these phenomena are still obscure. Here, we present some evidence on the role of exogenous stresses on the maintenance of homeostasis.

By using an *in vitro* model for the application of static mechanical stretching in osteoblast-like cells, we have found that this stress, very rapidly stimulates the activation of major signaling pathways (e.g. members of the MAPK family) and transcription factors (e.g. the c-Jun and c-Fos proteins). These events lead to the stimulation of DNA synthesis in these cells. Interesting, in contrast to other cell types, this stimulation is unrelated to autocrine growth factor action^{1, 2}. In addition, this mechanical load is able to directly up-regulate the expression and DNA binding of the master regulator of osteoblast differentiation Cbfa1, and this effect seems to be regulated by the stretch-triggered induction of distinct MAPK cascades³.

The intervertebral disc is also subjected to various types of stress, such mechanical, nutritional, hypoxic and osmotic. We have studied some of these stresses, hypothesizing that they can, in some extent, regulate the homeostasis of this tissue. More specifically, we have investigated the effect of hyperosmotic stress on intervertebral disc cells and have shown that it affects their proliferation via the regulation of signaling pathways, such as the MAPK pathways, and cell cycle regulators, e.g. the p53 oncosuppressor protein⁴. Finally, as it has been reported that growth factor secretion is a consequence of disc degeneration, we have studied the effect of isolated growth factors on disc cell proliferation and the activation of pivotal signaling pathways, as well as the role of the extracellular matrix components in these responses⁵.

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