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Compression-induced damage in engineered skeletal muscle

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Introduction

Tissue compression may induce collapse of blood vessels resulting in tissue ischemia (insufficient blood flow). In addition, cellular deformation due to tissue compression may initiate tissue degeneration. These are two of the hypotheses that have been proposed to explain the development of (deep) pressure ulcers. Skeletal muscle tissue, in particular, is susceptible to compression induced breakdown.

A model system was developed to investigate the relative contributions of deformation and ischemic factors to compromising tissue viability or metabolism.

Material and methods

Engineered skeletal muscle tissue was molded from murine muscle cells (C2C12) in a collagen I gel (fig. 1). Differentiation of the cells was induced by serum reduction to form more mature muscle tissue.

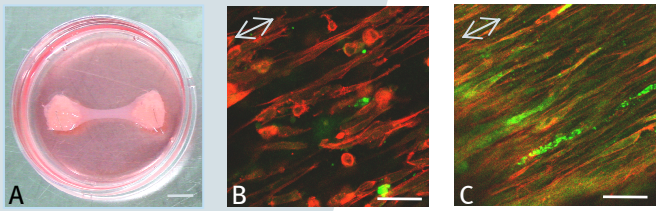

Figure 1 (A) *Engineered skeletal muscle (bar 5 mm),* (B) *Immuno-staining showing the microstructure following differentiation in horse serum (gold standard) or* (C) *improved differentiation in a serum-free substitute[1] (bars 50 µm). Arrows indicate long axis of the tissues.*

Deformation and ischemic factors were imposed on the engineered muscle. Therefore, indentation devices were custom made, enabling microscopic or metabolic monitoring of the tissue (fig. 2). They were additionally equipped with control over the ischemic factors hypoxia (insufficient oxygen supply), glucose deprivation, and acidification.

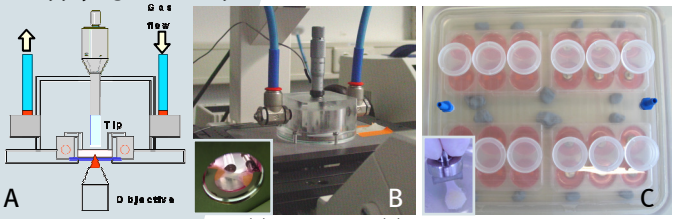

Figure 2 *The schematic* (A) *and photo* (B) *of a set-up is shown. Inset presents bottom view for microscopic monitoring.* (C) *A set-up for medium sampling is shown, with in the inset a load for compression.*

Viability and metabolism were assessed microscopically and by photometric analyses. For viability measurements, apoptotic and necrotic cell death development were monitored in real time applying fluorescent markers.[2] In addition LDH release from damaged tissue was determined. For determining tissue metabolism, glucose and lactate assays were applied in combination with an end point MTT conversion assay (a metabolic indicator).

Results

Deformation caused increases in tissue damage with time and with the amount of deformation within the first 24 h.[3]

Hypoxia induced elevated glucose utilization and significantly enhanced lactate production within 24 hours. This may be ascribed to a transition to anaerobic metabolism (fig. 3A). However, increased amounts of cell death were measured after 48 hours (fig. 3B).

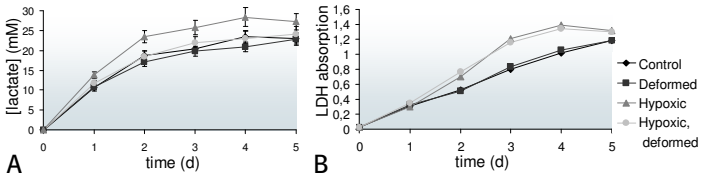

Figure 3 *Temporal profiles for lactate* (A) *and LDH* (B) *release during deformed and hypoxic experimental conditions.*

Glucose deprivation resulted in downregulation of metabolic activity. The amount of cell death increased, once all glucose had been consumed.

Acidification by the presence of lactate appeared to downregulate tissue metabolism (fig. 4). However, if the concentration of lactate exceeded a certain threshold, cell metabolism was arrested and cell death initiated.

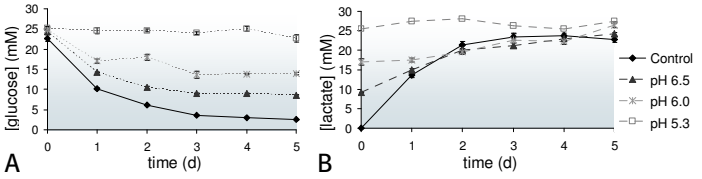

Figure 4 *Temporal profiles for glucose* (A) *and lactate* (B) *concentrations for control and acidic conditions (pH values of 5.3, 6.0, and 6.5).*

Conclusions

- Deformation rather than ischemia caused early cell death in compressed engineered muscle tissue
- Ischemic factors induced adaptational metabolic behavior before resulting in cell death
- These findings will contribute to improve European guidelines for pressure ulcer prevention by implementation of the role of tissue deformation in development of tissue damage on a short time scale

References:

[1] *Gawlitta et al., Cells Tissues Organs, submitted, 2006*
[2] *Gawlitta et al., Cytotechnology, 46, 139-150, 2004*
[3] *Gawlitta et al., Ann Biomed Eng, accepted, 2006*

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