

# THE MODULATION OF THE AGING PROCESS

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## Summary

The effects of lyophilized fetal sheep testis and mesenchymal homogenates on aging changes were tested in a series of experiments in rats and mice. Testis material was used in a long term cohort study (10 - 30 months) with male Sprague Dawley rats, using a model of biological age (BA) comprising 23 age related parameters. Fetal testis was applied subcutaneously at 9, 15 and 24 months. Six to ten months after the last injection the tests were performed. The majority of variables showed a shift towards a lower BA, which was also shown by multivariate models using multiple regression and discriminant analysis. Follow-up studies revealed a long-term increase in plasma testosterone levels and an improved survival which came into effect only after 24 months of age. Fetal mesenchymal tissue preparations had even more pronounced effects on survival and a number of aging changes, e.g. in the connective tissue of tail tendons and skin and DNA repair in several organs. In a survival study with a cohort of 400 male OF-1 outbred mice, the animals turned out to bear lymphatic leucosis, the incidence of which increased progressively with age. At the age of 50 % survival one half of the remaining cohort was treated with a single block of injections with fetal mesenchymal material. This led to a separation of the survival curves: the last controls (Ringer solution) died at the age of 700 days, whereas the last animals of the treated group attained an age of 1100 days. It is assumed that non-species-specific factors in the material may have acted at the genome regulatory level and helped to control the expression of leucosis for a considerable length of time.

Besides these investigations into the global system modulation was studied in several subsystems, as there are skin, other connective tissues and cell respiration. In skin, the aging process was influenced by application of several fetal and juvenile proteins; connective tissues were studied after systemic influences; and tissue respiration was measured using the direct method of Warburg following the  $O_2$  - uptake over a period of 2h.

Therefore we conclude that fetal mesenchymal cells not only have a long term effect after using them for in vivo treatment, but also act immediately, possibly activating enzymes or changing membrane properties or by other mechanisms. **This short term effect may be one of the factors enhancing longevity.**

Finally we try to explain the modulation effects by the action mechanisms. We have got several hypotheses concerning action mechanisms:

- a) the possibility of signal transduction (from the matrix to the cells in skin, from the extracellular fluid to all the cells of the body),
- b) conformational changes and mechanical signal transduction,

- c) biochemical signals: from the receptors in the cell membrane by growth factors or similar molecules and along cytosolic phosphorylation cascades,
- d) changes in gene expression, mitosis and cytokinesis,
- e) incorporation extent and kinetics of modulation molecules.

**From all the obtained results we conclude that modulation of the aging process is really possible. Future ways of intervention are discussed.**