FACULTEIT GENEESKUNDE EN GEZONDHEIDSWETENSCHAPPEN

NFAT5 in myositis and Duchenne muscular dystrophy: localization, expression and interactions with glucocorticoids in *in vitro* cell models

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Curriculum vitae

Sandrine Herbelet graduated in 2004 as doctor in veterinary medicine (DVM) at Ghent University with great distinction. She spent 8 years in veterinary clinics, research and teaching in Ghent and at Ghent University and Bern University (CH), were she focused on veterinary dermatology and bacteriology. Since 2010, she holds the position of grant and research officer of the european society of veterinary dermatology (ESVD).

In 2012, she took the step to human medicine in the Lab of Prof. Dr. De Bleecker, Department of Head and Skin, Ghent University as scientific personnel and from 2014 on as PhD-student. Since 2014, she combined her PhD with a 30% teaching assistant position at the Department of Basic and Applied Medical Sciences, Ghent University, where she teaches around 1.900 students in first aid and resuscitation practical skills at the Faculty of Medicine and Medical Sciences and Faculty of Pharmaceutical Sciences. She is author of 8 A1 articles (h=5) and 3 book chapters, co-author of 5 A1 articles and 3 books and received the Prix. Denyse Bourgeois 2015 from the Association Belge contre les Maladies Neuro-Musculaires (ABMM) of €2.500.

Summary

In both myositis and Duchenne muscular dystrophy (DMD), skeletal muscles are affected by chronic inflammation, degeneration and compromised regeneration by skeletal muscle progenitor cells called 'satellite cells'. In DMD, debilitating scar tissue is produced by fibroblasts. Both satellite cells and fibroblasts are controlled in their growth by, among other factors, nuclear factor of activated T-cells 5 (NFAT5). This protein is best known for its homeostatic properties and the maintenance of cell volume through the production of organic osmolyte carriers in case of water shortage or excess of ions in the cell. In addition, NFAT5 plays a role in immunity and cell metabolism.

Research hypotheses

In DMD, skeletal muscle cells are overloaded with sodium due to increased sodium influx as part of the disease pathology. Since NFAT5 is sensitive to an excess of ions, the influence of excess NaCl exposure on NFAT5 in cells issuing from skeletal muscle tissue was investigated. Initially, it was investigated whether healthy satellite cells and healthy skeletal muscle fibroblasts, as well as DMD skeletal muscle fibroblasts, could still respond in a physiological manner to excess NaCl by NFAT5 migration to the cell nucleus. The same was investigated when exposed to the pro-inflammatory molecules IFN-γ, IL-1β and TNF-α, present in chronic inflammation. The influence on cell growth was monitored over time. NFAT5 was also searched for in biopsies of patients with various forms of myositis.

Results

1) In healthy satellite cells, NFAT5 reacts in a normal physiological manner when exposed to high salt concentration as expected, by migrating to the nucleus. However, this does not happen after adding only pro-inflammatory molecules IFN-γ and IL-1β; then NFAT5 does not migrate to the nucleus and forms aggregates in the cell. This is also reflected in skeletal muscle biopsies from patients with some forms of myositis.

2) In healthy fibroblasts harvested from skeletal muscle, NFAT5 reacts in the same way as in healthy satellite cells. Adding only pro-inflammatory molecules IFN-γ, IL-1β and TNF-α leads to growth retardation. However, in fibroblasts harvested from skeletal muscles affected by DMD, we see an inverse pattern. Adding a high salt concentration induces cell death and growth retardation, while the addition of pro-inflammatory molecules IFN-γ, IL-1β and TNF-α has no influence on cell growth. Fibroblasts continue to grow over time. It is noticeable that in DMD fibroblasts, NFAT5 is mainly located in the nucleus.

3) In fibroblasts harvested from healthy skeletal muscle supplemented with soluble glucocorticoids, cells continue to grow and NFAT5 does not bind to the glucocorticoid receptor in the cell. However, when the same is performed in DMD fibroblasts, we see growth retardation over time and binding of NFAT5 to the glucocorticoid receptor.

Conclusions

These results could show that in healthy satellite cells and skeletal muscle fibroblasts, NFAT5 recognizes which stimulus is present and decides whether the cell can survive or not. Exposure to high salt concentration would lead to survival, whilst severe inflammation could cause cell death. In DMD fibroblasts, the cell could turn this over by keeping NFAT5 mainly in its nucleus and thus inducing permanent DMD fibroblast growth. When soluble glucocorticoids are administered, NFAT5 would bind to its receptor and thus cause the fibroblast to slow down in growth, possibly reducing scar tissue formation, deleterious in DMD patients.

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https://www.telethon.be

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