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P104 SYNOVIAL FIBROBLAST RELATIONSHIP STATUS: IT'S COMPLICATED

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Introduction The synovium is primarily built by fibroblast-like-synoviocytes (FLS). In the healthy synovium FLS form a complex tissue network via long-distance intercellular connexions (nanotubes). Using a 3D synovial micromass culture system, our previous research demonstrated that FLS exchange cytoplasmic cargo, i.e. organelles like mitochondria, via transfer through direct cell-to-cell connexions. The adaptive synovial tissue response to inflammation (i.e. to TNFa) likely depends upon the concerted communication between FLS.
Objectives To determine how the cellular organisation of the synovial tissue affects intercellular cargo exchange and how it changes under inflammatory conditions.
Methods Human FLS were isolated from joint tissues after synovectomies; passaged FLS were used to generate 3D micromass cultures using Matrigel (BD). For ultrastructural 3D reconstruction ultrathin sections of fixed micromasses were cut with an ATUMtom for FE-SEM scanning, followed by alignment and reconstruction of individual cells with Fiji TrackEM. To compare unstimulated and TNF-stimulated micromass cultures, cells were dyed with Cell- and Mitotracker dyes (TF). Using confocal microscopy, micromass cultures were analysed for cellular organisation within the 3D sphere, cell volume of individual cells, cell-to-cell interconnectivity and cargo transfer between cells. Analyses of the 3D confocal imaging data were done in Bitplane Imaris.
Results SEM 3D reconstruction of synovial micromass tissue revealed that FLS are compartmentalised, and thus, much larger and extended than expected. Thin membrane tubes not only connect different cells but also compartments of the same cell. Additionally, one nanotube may provide a link to several other cells and these connexions are in general separated by membranes. Treatment of micromasses with TNFa resulted in cellular condensation, reduced cell volume as well as diminished cellular connectivitiy when compared to unstimulated micromasses. In particular, the abundance of interconnecting nanotubes was significantly attenuated. The mitochondrial transfer rate increased as FLS clustered upon TNFa stimulation.
Conclusions TNFa directs FLS cellular re-organisation that is associated with increased intercellular transfer of mitochondria. These studies may provide insight into the concerted cooperation of FLS that is likely critical for the adaptive synovial response to inflammation.
Disclosure of interest None declared

P105 ENDOPLASMIC RETICULUM STRESS MEDIATES DERMAL FIBROSIS

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Introduction Systemic sclerosis is an autoimmune idiopathic connective tissue disease. The cells mainly responsible are the myofibroblasts that secrete copious amount of extracellular matrix molecules such as collagen. Endoplasmi reticulum stress is induced by a variety of stressors including misfolded proteins, this leads to a classic stress response and activation of X Box Binding Protien-1 (XBP-1) and ATF-6. This is induced in a variety of situations from multiple stressors and is a conserved pathway. Its role in systemic sclerosis is unknown.
Objectives To examine the role of endoplasmic reticulum stress in systemic sclerosis.
Methods Healthy dermal fibroblasts were treated with the ER stress inducing agent thaspigargin or nothing and then lysed and various proteins such as XBP-1 and ATF measured along with collagen by western blotting and reprobed for a loading control. In some experiments small interfering RNA against XBP-1, a mediator of ER stress, was transfected and treated with thaspigargin or non targeting controls. Also the belomycin mouse model of fibrosis was used and ATF6 mRNA was measured using qRT-PCR.
Results The classic ER stress inducer thaspigargin induced collagen expression in dermal fibroblasts as well as the markers of ER stress XBP-1 and ATF-6. The ER stress induced collagen expression in dermal fibroblasts was reduced with the reduction of XBP-1 in these cells using small interfering RNA compared to non targeting siRNA. The bleomycin model of skin fibrosis revealed increased ATF-6 mRNA levels compared to vehicle control tissue.
Conclusions Endoplasmic reticulum stress appears to regulated collagen expression in the skin and is involved in the bleomycin mouse model of disease. Targeting such a pathway may be useful in the disease.
Disclosure of interest None declared

P106 ABSTRACT WITHDRAWN

P107 TARGETING ACTIVATED SYNOVIAL FIBROBLASTS USING PHOTODYNAMIC THERAPY IN EXPERIMENTAL ARTHRITIS

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Introduction Activated synovial fibroblasts (SF) are characterised by the expression of Fibroblast Activation Protein (FAP). Here, we investigated the potential of photodynamic therapy (PDT) targeting FAP to selectively induce cell death in these