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# SYSTEMS BIOLOGY AND SYSTEMS PHYSIOLOGY: REGULATION OF BIOLOGICAL NETWORKS

## THE MEETING IS DEDICATED TO 75TH ANIVERSARY OF FAZLY ATAULLAKHANOV

HYBRID CONFERENCE 2021 ABSTRACTS

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comparison with the densities of the 2.0-nm 3D map, used to fit the 3JBH IHM-based model and the higher resolution (1.3 nm) thick-filament frozen-hydrated 3D maps. The R-factor for the IHM-based model and the ex vivo data was 4.9%, while those for the model and the 2.0- and 1.3-nm 3D-map densities were 4.0% and 8.4%, respectively, indicative of generally good fits.

**Conclusions:** The correctness of the cryo-EM based IHM model of myosin filaments for relaxed intact and chemically permeabilized muscles has been confirmed.

## Role of tropomyosin dynamics in regulation of cardiac muscle in health and disease

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**Background:** Muscle contraction is powered by the interaction of contractile proteins, myosin and actin that form the thick and thin filaments in the skeletal and cardiac muscles. The contraction-relaxation cycle is controlled by $Ca^{2+}$ ions via regulatory proteins, troponin (Tn) and tropomyosin (Tpm), associated with the thin actin filaments. Tpm is a long coiled-coil protein that polymerises into a long strand on the surface of the thin filament. In the absence of $Ca^{2+}$, Tn binds actin and keeps the Tpm strand in a blocking position where it prevents myosin binding to actin. Upon $Ca^{2+}$ binding to Tn, the Tpm strand releases from the blocking position, myosin binds actin and generates active force. The $Ca^{2+}$-regulation depends on many factors including Tpm properties. Theoretical analysis suggests that bending stiffness of Tpm is important for the regulation. Some mutations in Tpm are believed to be associated with myopathies or cardiomyopathies.

**Aims:** To study the structural and functional role of some conserved Tpm residues and the molecular mechanisms of pathogenicity of some Tpm mutations.

**Methods:** A combined approach based on an experimental study of structural and functional properties of recombinant Tpm with various amino acid substitutions or posttranslational modification and the molecular dynamics (MD) simulation was employed.

**Results:** The non-canonical Tpm residues D137 and E218 that destabilize the Tpm coiled-coil are important for its proper regulation of the actin-myosin interaction. The formation of a disulphide bridge between residues Cys190 of two Tpm chains destabilizes the Tpm molecule and might be involved in the development of heart failure upon hypoxia while the phosphorylation (pseudo-phosphorylation) of Tpm residues S283 and S61 mutations can reduce or even eliminate undesirable changes in functional properties of Tpm caused by some cardiomyopathy-associated mutations.

**Conclusions:** MD simulation is a useful tool for understanding the mechanisms of the regulation of cardiac muscle and its impairment in some genetic cardiomyopathies.

## AED Peptide stimulates human stem cell differentiation into dermal fibroblasts

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**Background:** Peptide regulation of the dermal fibroblasts functions is a new gerontotechnology. Peptide AED reduces the synthesis of proteins p53, p16, caspase-3, MMP9 during ageing of human skin fibroblasts.

**Aims:** The aim of this work is to evaluate the effect of the AED peptide on gene expression and protein synthesis of early (PDGFRα, Engrailed1) and late (Twist2 and Spry4) differentiation of human stem cells into dermal fibroblasts.

**Methods:** Human embryonic bone marrow mesenchymal stem cells (line FetMSC) were grown up to the 3rd passage, and the AED peptide (100 ng/ml) or saline solution (control) was added. Quantitative PCR was performed using a qPCRmix-HS SYBR + ROX kit and a DT322 detection amplifier. The concentration of the internal standard (GAPDH mRNA) was taken as a 1. Visual assessment of the synthesis of PDGFRα, Engrailed1, Twist2, Spry4 proteins was performed via immunocytochemistry and immunofluorescence microscopy. The results were statistically processed using the Statistica 10.0 software (Statsoft Inc., Tulsa, USA). Comparison of the mean values of the studied parameter in groups was carried out according to the Student's t-test at a statistical significance level of $p < 0.01$.

**Results:** The AED peptide significantly increased the expression of the PDGFRα, ENGRAILED1, TWIST2, SPRY4 genes in the FetMSC culture by 2.9, 3.8, 1.4, 1.9 times, respectively, compared to the control. The AED peptide stimulated the synthesis of PDGFRα, Engrailed1, Twist2, Spry4 proteins in the FetMSC culture. After the addition of the AED peptide, 60% of the cells acquired a stellate shape characteristic of fibroblasts, but this was not revealed in the control.

**Conclusions:** The AED peptide stimulates the expression of genes and synthesis of proteins involved in the differentiation of human skin fibroblasts.

## KE and KED peptides regulate PARP and SIRT gene expression during replicative and stationary human mesenchymal stem cells ageing

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**Background:** Short peptides are involved in the epigenetic regulation of gene expression during cellular ageing. KE peptide has an immunoprotective effect, regulates telomere length of blood lymphocytes and increases animal lifespan. KED peptide possesses vaso- and neuroprotective properties.

**Aims:** The aim of this work is to study the effect of KE and KED peptides on the expression of PARP-1, PARP-2, PARG, SIRT1 gerontogens in stationary and replicative ageing models of human mesenchymal stem cells of the FetMSC line.

**Methods:** FetMSC ageing was studied using the Schweigert method with modifications. To simulate replicative senescence, cells were grown up to 7th and 14th passages with the addition of peptides at a concentration of 20 ng/ml. An appropriate volume of saline was added to the control cultures. Quantitative PCR using SYBR Green I dye was performed by means of the QuantiFast SYBR Green PCR Kit (Qiagen, FRG) and a CFX96 Real-Time PCR Detection System (BioRad Laboratories, USA). The results were statistically processed in CFX Manager Software. The GAPDH mRNA was taken as the internal standard; its concentration was taken as a unit. Statistical data analysis was performed according to the two-tailed Student's t test at $p < 0.05$.

**Results:** KE peptide changed the expression of PARP-1, PARP-2, PARG, SIRT1 genes during replicative and stationary ageing of FetMSC by 1.9-5.5 times. KED peptide changed the expression of PARP-1, PARP-2, PARG, SIRT1 genes during replicative and stationary ageing of FetMSC by 1.9-26.7 times.

**Conclusions:** KE and KED peptides manifest geroprotective effect in the FetMSC models of replicative and stationary ageing through modulation of the expression of the PARP-1, PARP-2, PARG, SITR1 genes, involved in the regulation of cell repair, differentiation, and apoptosis.