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Mitochondrial dynamics shoot an arrow at skin aging

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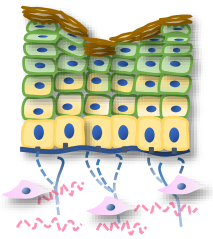
Katsuyama, Yushi; Yamawaki, Yumiko; Okano, Yuri; Masaki, Hitoshi
CIEL CO., LTD, Kanagawa, Japan

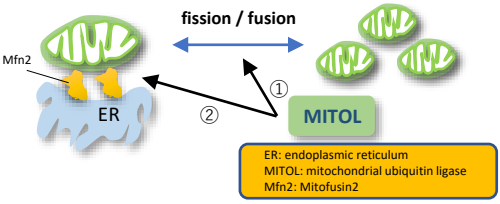
Introduction:

Characterization of the photo-aged dermis



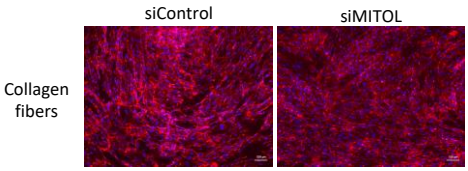
- ✓ Decrease of collagen fibers and disappearance of oxytalan fibers.
- ✓ Oxidized proteins such as carbonylated proteins (CPs) and glycated proteins (AGEs), are found in a higher level.
- ✓ Fibroblast having decreased quality of MT (mitochondria) are observed in higher frequency.

MITOL regulates MT dynamics and suppresses ER stress



① MITOL maintains Mitochondrial quality through regulating their balance between fission and fusion.
② MITOL suppresses ER stress by binding MT to the ER through interactions between Mfn2.

Background evidence



Similar to UVA, MITOL knock-downed fibroblasts induced insufficient formation of collagen fibers[1)]

Questions (Purpose of this study)

- ✓ What is a trigger which decreases MITOL?
- ✓ How does the MITOL depletion involve in the insufficient fiber formation?
  Is it caused by ER stress induced by MITOL depletion ?

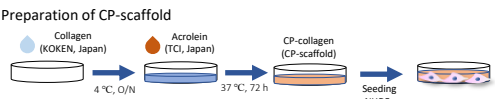
Materials & Methods:

To obtain answers for questions, normal human dermal fibroblasts (NHDFs) treated with follows were prepared.

- UVA : 2 J/cm²
- siMITOL : 100 nM for 24 h
- Tunicamycin, an inducer of ER stress : 100 ng/mL for 24 h
- Cultured onto carbonylated scaffold (CP-scaffold) for 48 h

→ ROS↑

Preparation of CP-scaffold



These cells were used for the experiments as shown in the Results section.

Results & Discussion:

MITOL protein in NHDFs was decreased immediately after UVA irradiation and by culture on CP-scaffolds

Fig. 1 MITOL protein expression in NHDFs irradiated with UVA or cultured onto CP-scaffold.

ER stress in NHDFs was induced by UVA irradiation and by MITOL knock-down

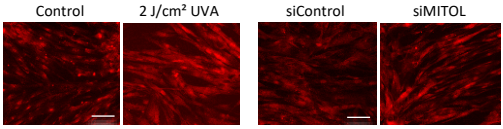


Fig. 2 ER stress in NHDFs irradiated with UVA irradiation and knock-downed MITOL To assess the ER stress, IRE1α, an ER stress marker, in NHDFs was detected with the immunostaining. These are representative images. .Scale bars; 100 μm IRE1α: Inositol-requiring enzyme type 1α.

ER stress enhanced MMP-1 secretion via IL-6 in NHDFs

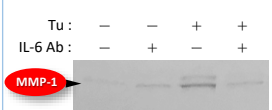


Fig. 3 MMP-1 protein in NHDFs treated with tunicamycin (Tu) which is an inducer of ER stress. After the treatment without or with Tu and IL-6 neutralizing antibody (Ab) for 24 h, secretion of MMP-1 from NHDFs were measured.

N-acetyl L-cysteine (NAC) rescued the MITOL and ER stress, and suppressed MMP-1 secretion in UVA-irradiated NHDFs

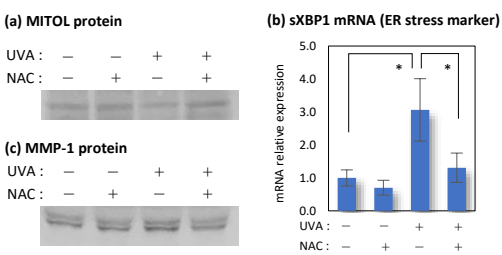
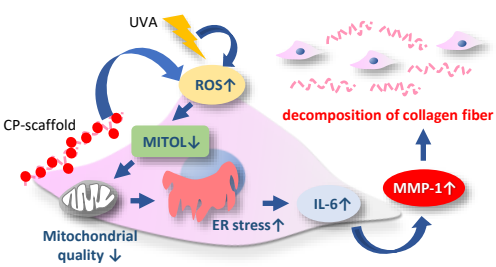


Fig. 4 MITOL protein (a), sXBP1 mRNA (b) and MMP-1 protein (c) levels in UVA-irradiated NHDFs treated with 1 mM NAC for 24 h. (n=3. *p<0.05)
sXBP1: spliced form of X-box binding protein 1

Conclusions:

Decrease of MITOL caused by oxidative stress triggers the decrease in collagen fibers by enhancing their decomposition due to the increased levels of MMP-1 via ER stress



References:

1) Katsuyama Y, Yamawaki Y, Sato Y, et al (2021) The dysfunction of dermal fibers in photoaging is caused by the impairment of mitochondrial function. The 26th IFSCC Mexico Conference: Proceedings.