Mitochondrial skin aging.
Is it possible to stop it?

Aging is a natural and inevitable process. Skin, as an organ which is directly exposed to external factor activity usually ages faster and the effects of this process are easier visible than in case of other organs. Skin aging is caused by two simultaneous processes – intrinsic and extrinsic aging. There are **5 main theories of intrinsic skin aging**, which may occur simultaneously and are closely related to each other. These theories concerning chronological aging, related to age, which begins around 25th year of life. The second type of intrinsic aging is **menopausal aging** connected with decrease of estrogen. Another, the fasted noticed type of skin aging is **mimic aging**, which is caused by expressing emotions – laugh, sadness, anger, surprise. Repeated muscles tension transport the tensioning on fibroblasts and skin supporting fibers. **Extrinsic aging** is caused by external factors, mainly UV radiation and cigarette smoke (so called *smoker's skin*). As it comes to extrinsic aging of skin we can observe a few mechanisms, which are defined by 5 basic theories:

Genetic theory

Genes which are responsible for the character and pace of aging are placed in skin cells. Currently there are over 100 genes that can influence skin aging. They belong to three groups: genes of antioxidant protection, genes responsible for DNA repairing and genes responsible for apoptosis (programmed death of damaged cell). In aging skin the processes of fibroblasts multiplication are constrained as the expression of genes responsible for proliferation is also staunched.

Protein glycation

The process of protein glycation stands for incorporating sugar elements, mainly glucoses, to free groups of amine protein. As a result of this complex process we obtain products called AGEs (*Advanced Glycation End-Products*), e.g. carboxymethyllysine (CML). Glycations has especially negative influence on the proteins of the dermal extracellular, mainly collagen. Fructose and glucose have bif affinity to lysine which is present in pro-collagen structure and AGEs which are created in this way cause the changes in spatial conformation of proteins – membrane enzymes and slow down proteolysis (splitting of harmful proteins in organism). As a result, collagen loses its biomechanical attributes and skin loses its firmness and elasticity. Also elastin, fibronectin and laminin go through glycation process.

Telomeres shortening

Telomeres are the ending parts of chromosome, so called 'caps' which protect DNA against damage. Unfortunately, every cell division makes telomeres shortened, which is programmed in and derives from genetic code. The last pair of chromosome basis loses its ability to replication at every division which results in shortening the ending part of chromosome. Shorter telomeres unable transcription and cells lose the ability to division. It means their ageing and apoptosis.

Free radicals

Reactive forms of oxygen (ROS) are mage during the process of cell breathing and are present in human body all the time, regardless the state of health. But their synthesis is stronger during the oxidant stress and physiological imbalance. The factors which cause ROS synthesis acceleration are chemical

poisonings with e.g. pesticides, nitrogen oxide or ingredients of cigarette smoke or UV radiation. Despite of antioxidant protection in cells, free radicals damage cell ingredients constantly – especially proteins and DNA.

Mitochondrial aging

Disorders in mitochondria is a vast topic, which is described in this article. Mitochondria disorders start number of reactions leading to aging and the mechanism relate to genetic theory, free radicals and UVA radiation. Mitochondria protection is one of the key elements for good skin condition. If mitochondria are faulty, the whole cell are influenced by apoptosis. The latest scientific experiments show that mitochondria dysfunction play the main role in creating cancer cells and longevity depend majorly on mitochondrial respiratory chain.

Mitochondria functions

Mitochondria are called *power stations* or *life torches* because they produce 80% of energy available for cells in the form of ATP (adenosine triphosphate). The energy is released in the process of cell breathing in the internal mitochondrial membrane and is necessary for regeneration, protection and efficiency of the cell. Every live cell has got dozens of mitochondria and their number in more specialized cells rises to few hundreds. In these organelles free radicals are produced during cell breathing and their overproduction leads to the death of the whole cell as a result of disorders in respiratory chain. According to this we might say that mitochondria play key role in apoptosis.

The mechanisms of mitochondrial skin aging

Unfortunately, the number and mitochondria activity declines with age and gathering damages determine decrease of energetic efficiency of skin. More and more free radicals are collected in the skin and its protection and repairing system is much slower. As a result cell get older, wrinkles appear or get deeper, skin is deprived of energy to regenerate and repair the existing damages. There are three main mechanisms of mitochondrial aging: damages in mitochondrial DNA (mtDNA), balance disorders between free radical production created in oxidant phosphorylation and their disposal by antioxidants and potassium channels deactivation in the internal membrane of skin cells. The discovery of potassium channels in skin mitochondria changed the view on the process of so calles mito-aging (mitochondrial skin aging).

Mutations in mtDNA

Mitochondria have their own DNA (mtDNA) including 37 genes, which code in some proteins of respiratory chain. Currently it is thought that mtDNA is more vulnerable to damages than nuclear DNA, as does not contain histones – protection proteins. Additionally mitochondrial DNA possesses low-efficient repairing system which results in much faster evolution. Changes that are being created may cause physiological functions disorder in mitochondria and lead to illnesses, which symptoms are related to tissues with high-energetic demand – in muscles and nerves. Because of less effective rebuilding mechanism than in case of nuclear DNA, mtDNA is more often vulnerable to mutation. Frequent mutations disorder the right functioning of mitochondria and lead to lower energy production. Damaged inhalation chain produces more free radicals, which cause damages in the whole cell and lead to apoptosis. It is estimated that the ability to repair mitochondrial DNA decreases by 0,6% every year. Mutations and deletions in mtDNA are regarded as the main cause of aging and illnesses related to it. Numerous examinations showed increased number of mutations and deletions in mitochondria of different tissues at elder people.

The influence of UVA on mtDNA damages

The exposure on UV radiation cause increased production of free radicals, indirectly damaging mitochondrial DNA. Skin is an organ which is especially vulnerable to radiation and oxidant damages. The examinations showed that skin which is exposed to photoaging the number of mutations and deletions in mtDNA is ten times higher than in skin which is protected against sun radiation. Multiple exposition of keratynocytes, fibroblasts or human skin on physiological doses of UVA radiation leads to mutations in mtDNA. The most frequents mutation in mtDNA, created as a result of UVA radiation is so called common deletion, which concerns 1-25% of mtDNA particles in skin mitochondria. This mutation was observed almost only in those parts of the skin which were exposed on sun and the number of mutated mtDNA particles was higher in the fragments of skin more exposed on UV radiation. Moreover, free radicals activate enzymes which are responsible for collagen and elastin decomposition.

Imbalance between free radicals production and their disposal by antioxidants

The next mechanism of mitochondrial skin aging are disorders between the number of free radicals in the process of antioxidant phosphorylation and their disposal by intracellular antioxidants, which include enzymes of superoxide dismutase (SOD), catalase, glutathione peroxidase and Q10 coenzyme and vitamin E. The excessive release is followed by oxidant cells stress. The gradients of protons concentration at both sides of mitochondrial membrane is disordered then. The gradient is equaled by proton pumps which use vast majority of the energy created in respiratory chain. The result of this is slowing down the process of oxidant phosphorylation deficiency of ATP.

Deactivation of potassium channels in internal mitochondrial membrane of skin cells

Inactive potassium channels in the internal mitochondrial membrane is another mechanism influencing disorders in work of the whole cell and as a consequence – its death. Potassium channels are integral proteins, which task is to transport ions through the cell membrane, which means the regulation of the regeneration of the whole internal mitochondrial membrane. The first potassium channel was identified at the beginning of 90s in internal mitochondrial membrane of liver cells. It was the channel mitoKATP, discovered by patch-clamp technique. Potassium channels were also identified in cardiomyocytes (heart muscle cell) and in neurons. It occurred that their activation prevents heart attacks and neurodegeneration diseases like Parkinson or Alzheimer. In 2008 scientists discovered in human mitochondria keratynocytes from the cell line of HaCat potassium channel TASK-3. It was proved that the activations of this channel protects keranocytes against harmful impact of UVB radiation. In 2013 for the first time a multidisciplinary team of scientists from Nencki Institute and Dr Irena Eris Centre for Science and Research

discovered and described potassium channel of mitoKATP and mitoBKCa in internal mitochondrial membrane od skin cells, both in epidermis and dermis. This discovery began searching for substances activating potassium channels in keratynocyte and fibroblasts mitochondria. The consequence of improving the potassium keratynocyte is increasing the ATP synthesis, reduction of the level of reactive oxygen forms produced in mitochondria and also cytoprotection (protecting cells against damage followed by different factors, e.g. hypoxia. It has indirect influence on collagen and elastin production by fibroblasts and visible deceleration of aging.

How to decelerate mitochondrial skin aging?

The best known and most frequently used in cosmetology mechanism of mitochondria protection is **antioxidant activity**. The most efficient antioxidants used in cosmetics are: vitamins C and E, superoxide dismutase (SOD), resveratrol, coenzyme Q10, plants and algae extracts such as wakame. Another method is to use substances **stimulating ATP synthesis by activating oxygen consumption by mitochondria** and activation of respiratory chain protein. Thanks to this skin cells gain more energy, regain activity and collagen synthesis. One of the substances in this mechanism is Omega-CH-Activator® F (INCI: *Glycine, Hydrolyzed Soy Protein, Bis(Tripeptide-1) Copper Acetate)*. It is a complex of three active ingredients – aminoacid, soya proteins and tripeptide of copper. Glycine present in this complex has the same concentration as in collagen particle. Tripeptide of copper is a biomimetic substance, simulating tripeptide of copper present in human organism – it stimulates collagen and elastin synthesis and repairs damaged cells and tissues. The complex activates one of the most important antioxidants – superoxide dismutase SOD. Another substance with proved **protective impact on mitochondrial DNA** is ergotioneine. It is an exogenous amino acid, which is not included in protein composition, an efficient antioxidant instantly used by skin cells. It participates in fatty acids transportation into mitochondria, stimulates their beta-oxidation and improves cell metabolism. It also influences the number and morphology of mitochondria in fibroblasts and keratynocytes, which might stimulate the ATP synthesis. It was shown the preventive/ protective effect of L-ergothioneine on mtDNA damages in skin cells exposed to UVA. The fourth, recently discovered mechanism of **activating potassium channels in mitochondria** is such a new solution, that there have not been discovered many active substances yet, which might cause opening of potassium channels in mitochondrial skin cells. The scientists team which discovered the channels presence was continuing the research on the substances activating potassium channels. The effect of this research is the confirmation of flavonoid which is present in citrus fruits, impact on mitoBKCa activation.

To protect the mitochondria and deaccelerate mitochondrial skin aging, apart from using cosmetics containing the substances which were describes above, it is also worth avoiding exposure on damaging environmental factors, such as UV radiation, air pollution or cigarettes smoke. Another meaningful factor is a proper diet, excluding fried meals, reducing carbohydrates, alcohol and long enough sleep.

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