**KLOTHO AND HAIR**

Singh B, Schoeb TR, Bajpai P, Slominski A, Singh KK. Reversing wrinkled skin and hair loss in mice by restoring mitochondrial function. Cell Death Dis. 2018 Jul 20;9(7):735. doi: 10.1038/s41419-018-0765-9. PMID: 30026579; PMCID: PMC6053453.

**Mitochondrial DNA (mtDNA) depletion is involved in mtDNA depletion syndromes,** **mitochondrial diseases, aging and aging-associated chronic diseases, and other human pathologies. We demonstrate that ubiquitous depletion of mtDNA in mice leads to predominant and profound effects on the skin resulting in wrinkles and visual hair loss with an increased number of dysfunctional hair follicles and inflammatory responses. Development of skin wrinkle was associated with the significant epidermal hyperplasia, hyperkeratosis, increased expression of matrix metalloproteinases, and decreased expression of matrix metalloproteinase inhibitor TIMP1. We also discovered markedly increased skin inflammation that appears to be a contributing factor in skin pathology. Histopathologic analyses revealed dysfunctional hair follicles. mtDNA-depleter mice also show changes in expression of aging-associated markers including IGF1R, KLOTHO, VEGF, and MRPS5. mtDNA-repleter mice showed that, by turning off the mutant POLG1 transgene expression, mitochondrial function, as well as the skin and hair pathology, is reversed to wild-type level. To our knowledge that restoration of mitochondrial functions can reverse the skin and hair pathology is unprecedented.**

Jin XH, Pi LQ, Lee WS. Expression Pattern and Role of Klotho in Human Hair Follicles. Ann Dermatol. 2019 Oct;31(5):511-517. doi: 10.5021/ad.2019.31.5.511. Epub 2019 Aug 30. PMID: 33911642; PMCID: PMC7992569.

**We examined the klotho expression patterns in human hair follicles from young and aged donors. Furthermore, we examined the functional roles of klotho on human hair growth using klotho siRNA and klotho recombinant protein.**

**Interestingly, klotho was expressed in human hair follicles at both gene and protein levels. In hair follicles, prominent klotho expression was mainly observed in the outermost regions of the outer root sheath and hair bulb matrix cells. Quantification of klotho protein expression in young and aged donors showed that klotho expression decreased with aging. In human hair follicle organ culture, klotho silencing promoted premature catagen induction and inhibited human hair growth. Otherwise, klotho protein prolonged human hair growth.**

**These results indicate that klotho might be an important regulatory factor for human hair growth and hair cycle change.**

Wu HC, Fan X, Hu CH, Chao YC, Liu CS, Chang JC, Sen Y. Comparison of mitochondrial transplantation by using a stamp-type multineedle injector and platelet-rich plasma therapy for hair aging in naturally aging mice. Biomed Pharmacother. 2020 Oct;130:110520. doi: 10.1016/j.biopha.2020.110520. Epub 2020 Jul 21. PMID: 32707439.

**The mechanism of hair loss caused by aging is related to mitochondrial dysfunction. Pep-1-mediated mitochondrial transplantation is a potential therapeutic application for mitochondrial disorders, but its efficacy against hair aging remains unknown. This study compared platelet-rich plasma (PRP) therapy with mitochondrial transplantation for hair restoration and examined the related regulation in naturally aging mice. After dorsal hair removal, 100-week-old mice received weekly unilateral injections of 200 μg of allogeneic mitochondria-labeled 5-bromo-2'-deoxyuridine with (P-Mito) or without Pep-1 conjugation (Mito) or human PRP with a stamp-type electric injector for 1 month. The contralateral sides were used as corresponding sham controls. Compared with the control and corresponding sham groups, all treatments stimulated hair regrowth, and the effectiveness of P-Mito was equal to that of PRP. However, histology revealed that only P-Mito maintained hair length until day 28 and yielded more anagen follicles with abundant dermal collagen equivalent to that of the PRP group. Mitochondrial transplantation increased the thickness of subcutaneous fat compared with the control and PRP groups, and only P-Mito consistently increased mitochondria in the subcutaneous muscle and mitochondrial DNA copies in the skin layer. Therefore, P-Mito had a higher penetrating capacity than Mito did. Moreover, P-Mito treatment was as effective as PRP treatment in comprehensively reducing the expression of aging-associated gene markers, such as IGF1R and MRPS5, and increasing antiaging Klotho gene expression. This study validated the efficacy of mitochondrial therapy in the restoration of aging-related hair loss and demonstrated the distinct effects of PRP treatment.**

Hasegawa Y, Hayashi K, Takemoto Y, Cheng C, Takane K, Lin B, Komohara Y, Kim-Mitsuyama S. DPP-4 inhibition with linagliptin ameliorates the progression of premature aging in klotho-/- mice. Cardiovasc Diabetol. 2017 Dec 1;16(1):154. doi: 10.1186/s12933-017-0639-y. PMID: 29195509; PMCID: PMC5709858.

**The potential of anti-aging effect of DPP-4 inhibitors is unknown. This study was performed to determine whether linagliptin, a DPP-4 inhibitor, could protect against premature aging in klotho-/- mice.**

**Klotho-/- mice exhibit multiple phenotypes resembling human premature aging, including extremely shortened life span, cognitive impairment, hippocampal neurodegeneration, hair loss, muscle atrophy, hypoglycemia, etc. To investigate the effect of linagliptin on these aging-related phenotypes, male klotho-/- mice were divided into two groups: (1) control group fed the standard diet, and (2) linagliptin group fed the standard diet containing linagliptin. Treatment with linagliptin was performed for 4 weeks. The effect of linagliptin on the above mentioned aging-related phenotypes was examined.**

**Body weight of klotho-/- mice was greater in linagliptin group than in control group (11.1 ± 0.3 vs 9.9 ± 0.3 g; P < 0.01), which was associated with greater gastrocnemius muscle weight (P < 0.01) and greater kidney weight (P < 0.05) in linagliptin group. Thus, linagliptin significantly prevented body weight loss in klotho-/- mice. Survival rate of klotho-/- mice was greater in linagliptin group (93%) compared to control group (67%), although the difference did not reach statistical significance (P = 0.08). None of linagliptin-treated klotho-/- mice had alopecia during the treatment (P < 0.05 vs control klotho-/- mice). Latency of klotho-/- mice in passive avoidance test was larger in linagliptin group than in control group (P < 0.05), indicating the amelioration of cognitive impairment by linagliptin. Cerebral blood flow of klotho-/- mice was larger in linagliptin group than in control group (P < 0.01), being associated with greater cerebral phospho-eNOS levels (P < 0.05) in linagliptin group. Neuronal cell number in hippocampal CA1 region was greater in linagliptin group than in control group (P < 0.05). Linagliptin group had greater cerebral phospho-Akt (P < 0.05) and phospho-CREB (P < 0.05) than control group. Thus, linagliptin ameliorated brain aging in klotho-/- mice. The degree of hypoglycemia in klotho-/- mice was less in linagliptin group than in control group, as estimated by the findings of OGTT.**

Haussler MR, Haussler CA, Whitfield GK, Hsieh JC, Thompson PD, Barthel TK, Bartik L, Egan JB, Wu Y, Kubicek JL, Lowmiller CL, Moffet EW, Forster RE, Jurutka PW. The nuclear vitamin D receptor controls the expression of genes encoding factors which feed the "Fountain of Youth" to mediate healthful aging. J Steroid Biochem Mol Biol. 2010 Jul;121(1-2):88-97. doi: 10.1016/j.jsbmb.2010.03.019. Epub 2010 Mar 20. PMID: 20227497; PMCID: PMC2906618.

**The nuclear vitamin D receptor (VDR) binds 1,25-dihydroxyvitamin D3 (1,25D), its high affinity renal endocrine ligand, to signal intestinal calcium and phosphate absorption plus bone remodeling, generating a mineralized skeleton free of rickets/osteomalacia with a reduced risk of osteoporotic fractures. 1,25D/VDR signaling regulates the expression of TRPV6, BGP, SPP1, LRP5, RANKL and OPG, while achieving feedback control of mineral ions to prevent age-related ectopic calcification by governing CYP24A1, PTH, FGF23, PHEX, and klotho transcription. Vitamin D also elicits numerous intracrine actions when circulating 25-hydroxyvitamin D3, the metabolite reflecting vitamin D status, is converted to 1,25D locally by extrarenal CYP27B1, and binds VDR to promote immunoregulation, antimicrobial defense, xenobiotic detoxification, anti-inflammatory/anticancer actions and cardiovascular benefits. VDR also affects Wnt signaling through direct interaction with beta-catenin, ligand-dependently blunting beta-catenin mediated transcription in colon cancer cells to attenuate growth, while potentiating beta-catenin signaling via VDR ligand-independent mechanisms in osteoblasts and keratinocytes to function osteogenically and as a pro-hair cycling receptor, respectively. Finally, VDR also drives the mammalian hair cycle in conjunction with the hairless corepressor by repressing SOSTDC1, S100A8/S100A9, and PTHrP. Hair provides a shield against UV-induced skin damage and cancer in terrestrial mammals, illuminating another function of VDR that facilitates healthful aging.**