PZ-19b activates CISD2 to attenuate senescence in human senior keratinocytes and rejuvenates naturally aged skin in mice

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Background: CDGSH iron-sulfur domain-containing protein 2 (CISD2), a pro-longevity gene, mediates healthspan in mammals. CISD2 is down-regulated during aging. Interestingly, a persistently high level of CISD2 promotes longevity and ameliorates an age-related skin phenotype in transgenic mice. Here we translate the genetic evidence into a pharmaceutical application using a potent CISD2 activator PZ-19b to enhance CISD2 expression in HEK001 human keratinocytes from an older person and to treat naturally aged mice in order to study its anti-aging efficacy.
Methods: We study the biological effects of PZ-19b on aging skin using a cell platform, namely an HEK001 human keratinocyte cell line established from an older person, and two mouse models, namely ultraviolet B (UVB)-induced photoaging and old mice at 21-month old. We investigated the beneficial efficacy of PZ-19b on skin aging, as well as delineating the underlying mechanism and potential biological pathways involved by transcriptomic analysis. CISD2 knockdown HEK001 keratinocytes and Cisd2 knockout mice were used to study the Cisd2-dependent effects of PZ-19b on skin aging.
Results: Four findings are pinpointed. **Firstly**, in human skin, CISD2 is mainly expressed in proliferating keratinocytes from epidermal basal layer and CISD2 is down-regulated in sun-exposed epidermis. **Secondly**, in HEK001 human keratinocytes, PZ-19b enhances mitochondrial function, and protects against reactive oxygen species (ROS)-induced oxidative stress via enhancing CISD2 expression; this enhancement is CISD2-dependent. Additionally, PZ-19b alleviates UVB-induced damage while suppressing matrix metalloproteinases-1 (MMP-1), a major indicator of UVB-induced damage in keratinocytes. **Thirdly**, transcriptomic analysis revealed that PZ-19b modulates a panel of differential expression genes (DEGs) associated with mitochondrial function, redox homeostasis, keratinocyte function, and inflammation to attenuate senescence. Intriguingly, PZ-19b appears to activate two longevity-associated regulators, namely FOXO3a and FOXM1, to suppress the senescence-associated secretory phenotype. **Finally**, in mouse skin, PZ-19b enhances CISD2 expression to ameliorate UVB-induced photoaging and this occurs via a mechanism involving CISD2. Most strikingly, late-life treatment with PZ-19b, started at 21-month old and lasting for 5 months, is able to retard skin aging and rejuvenate naturally aged skin in mice.
Conclusions: These results demonstrate that pharmacological elevation of CISD2 protein levels at a late life stage via PZ-19b treatment is feasible and effectively mitigates both intrinsic and extrinsic skin aging. Our findings reveal that PZ-19b could act as a functional food or as a skincare product for fighting skin aging.

Keywords: CISD2, skin aging, skin rejuvenation, cellular senescence, CISD2 activator, mitochondrial function.