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Fibroblasts from Aged Donors Shape the Morphology of Reconstructed Human Skin Towards an Aged Skin Phenotyp

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Increasing numbers of multimorbid, elderly patients challenge translational pharmacology, which predominantly relies on young and healthy test subjects and animal models [1]. Several groups tried to model aged human skin in vitro, facing specific restrictions [2]. We studied the effects of normal human dermal fibroblasts (NHDF) from donors with varying age and sex on the morphology of reconstructed human skin (RHS). NHDF were either isolated from foreskin (medically-indicated circumcision of <9 year-old boys; juvenile RHS) or from breast skin (plastic surgery; 60 to 70 year-old women; aged RHS). Keratinocytes from the juvenile donors (<9 years) were used for the epidermal compartment of all RHS to investigate the influence of NHDF age and origin on epidermal development.

Microarray analysis revealed decreased collagen-1 and -3 expression only in RHS, but not in monolayer cultures. Sirtuin-1 and mitochondrial transcription factor-1 as well as apoptosis-related gene expression of E1A binding protein p300 declined with donor age. Dermal thickness, collagen content, and fibroblast count decreased markedly in aged RHS, whereas matrixmetalloproteinase-1 gene and protein expression increased. This is well in accordance to in vivo studies [3-6]. A thinner viable epidermis at the expense of a thickened stratum corneum and a decreased surface pH were observed in aged RHS, again being well in line to aged skin physiology [7]. Decreased free fatty acid content in the stratum corneum of aged RHS and increased amounts of cholesterol, cholesterol sulfate, and ceramide, in particular increased sphingosine-

and dihydrosphingosine based ceramides, indicate an overall increase in barrier lipids. This might explain the slight decrease of caffeine permeation as well as the faster penetration of tacrolimus into aged RHS, given the very poorly penetrating high molecular and very lipophilic drug is entrapped in the stratum corneum. Taken together, fibroblasts do not only shape the dermal compartment, but also affect the epidermal differentiation and thus barrier function. Understanding age-related changes in the barrier function will allow improving the dermatological treatment for the increasing number of aged patients – and might reduce animal testing as well.

References

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