PIGMENTATION

# IDENTIFYING A NOVEL MECHANISM OF HUMAN SKIN PIGMENTATION

*Roider Elisabeth [1] - Allouche Jennifer [1] - Fan Shaohua [2] - Pardo Cortes Luba [3] - Kato Shinichiro [1] - Kawakami Akinori [1] - Suita Yusuke [1] - Mujahid Nisma [1] - Lo Jennifer A. [1] - Kemeny Lajos V. [1] - Hermann Andrea [1] - Zhang Jianming [1] - Igras Vivien [1] - Evans Conor [1] - Weng Qingyu [1] - Wang Hequn [4] - Ito Shosuke [5] - Wakamatsu Kazumasa [5] - Kemeny Lajos [6] - Cozzio Antonio [7] - Marks Michael [8] - Goldberg Alfred [9] - Iliopoulos Othon [10] - Lee Juhee [1] - Nijsten Tamar [3] - Tishkoff Tishkoff [2] - Fisher David E. [1] - Alicia Mcconnell [11] - Leonard Zon [11]*

*Cutaneous Biology Research Center, Massachusetts General Hospital, Department Of Dermatology, Boston, United States [1] - University Of Pennsylvania, Departments Of Genetics And Biology, Philadelphia, United States [2] - Erasmus Mc, University Medical Center, Department Of Dermatology, Rotterdam, Netherlands [3] - Massachusetts General Hospital, Harvard Medical School, Wellman Center For Photomedicine, Boston, United States [4] - Fujita Health University, Department Of Chemistry, Toyoake Aichi, Japan [5] - University Of Szeged, Department Of Dermatology And Allergology, Szeged, Hungary [6] - Kantonsspital St. Gallen, Department Of Dermatology, Venerology, And Allergology, St. Gallen, Switzerland [7] - Children's Hospital Of Philadelphia Research Institute, Abramson Research Center, Philadelphia, United States [8] - Harvard Medical School, Department Of Cell Biology, Boston, United States [9] - Harvard Medical School, Massachusetts General Hospital Cancer Center, Boston, United States [10] - Stem Cell Program And Division Of Hematology/oncology, Boston Children's Hospital And Dana-farber Cancer Institute, Boston, Massachusetts, And At The Howard Hughes Medical Institute, Boston, Usa [11]*

Introduction: Skin pigmentation is essential to balance skin cancer risk and vitamin D production. UV light as well as expression of different genes balance skin color via regulating pheo- and eumelanin levels. Changes in skin color are commonly desired for medical and cosmetic reasons. The exact underlying mechanisms are however unclear, resulting in few available treatment options.

Objective: This study aims for a better understanding of human skin pigmentation, in particularly redox-based pigmentation changes, enabling the development of improved treatment options.

Material and Methods: Cell culture, human skin explants, qPCR, western blot, immunohistochemistry, immunofluorescence, absorbance-based assays, HLPC, as well as mice and zebrafish models were used. Linear regression association analysis testing skin

color and single-nucleotide polymorphism (SNP) mapping was performed in over 6600 individuals.

Results: Our work describes the existence of a novel conserved mechanism of skin pigmentation. Intramelanosomal redox changes impact ubiquitin-proteasome system-mediated tyrosinase protein degradation, changing the eu- and pheomelanin levels in in vitro, ex vivo and in vivo. Targeting of the nicotinamide nucleotide transhydrogenase (NNT) enzyme by topical small-molecules induce striking skin color changes. Association analysis between NNT SNPs and skin color was performed showing a significant association between skin color and one intronic SNP. ChIA-PET analysis suggested this SNP to regulate NNT gene expression. In addition, mice showing a dysfunctional NNT protein and zebrafish low in NNT gene expression displayed increased pigmentation. Skin of patients with postinflammatory hyperpigmentation, melasma and lentigines displayed decreased NNT levels emphasizing the clinical relevance of this mechanism.

Conclusion: This data suggests the existence of a redox-dependent pigmentation mechanism, affecting human tyrosinase protein stability, which can be modified by changing NNT enzyme activity. Application of NNT-modifying topical drugs might be used for medical and cosmetic purposes, as well as potential skin cancer prevention strategies.