Synopsis of Original Research Paper

Elucidating the Role of Plasma Membrane Phospholipids in Cellular Senescence of Keratinocytes

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Aging research has increasingly focused on molecular mechanisms, with the 2023 "Hallmarks of Aging" listing twelve key factors but omitting lipid-related contributors. The role of lipids in aging remains unclear, particularly in skin aging, which has both medical and social implications. Our study investigates the role of phosphatidylinositol 4,5-bisphosphate [$PI(4,5)P_2$] in epidermal aging. We previously observed that DNA damage stress, a primary factor in extrinsic aging, reduces $PI(4,5)P_2$ levels in keratinocytes. Overexpression of $PI(4,5)P_2$-degrading enzymes induces cellular senescence phenotypes, while increasing $PI(4,5)P_2$ synthesis enhances resistance to stress-induced senescence. However, *in vivo* evidence remained limited. Here, we generated transgenic (TG) mice expressing a $PI(4,5)P_2$-degrading enzyme under the K15 promoter (K15::Lyn-INPP5Ecat-GFP TG). At 9 months, these mice exhibited a reduction in hair follicles and decreased type XVII collagen expression, suggesting potential premature hair follicle aging. Additionally, in *vitro* analysis using HaCaT cells revealed that $PI(4,5)P_2$ depletion disrupted plasma membrane localization of the scaffold protein Par3, which interacts with the exocyst complex to regulate exocytosis. By expressing a plasma membrane-targeted Par3 exocyst-binding domain (Lyn-hPar3(710-1089)-V5), we partially rescued $PI(4,5)P_2$ depletion-induced cellular senescence phenotypes, including increased cell area, SA-β-gal activity, and p21 expression. Our findings suggest that $PI(4,5)P_2$ plays a critical role in cellular senescence of keratinocytes by modulating exocytosis through PAR3. While in *vivo* phenotypes were mild at 9 months, long-term studies are needed to determine the full extent of $PI(4,5)P_2$'s role in epidermal and hair follicle aging in mice. These results highlight $PI(4,5)P_2$ as a potential target for interventions against skin aging and provide novel insights into lipid-mediated aging mechanisms.