Synopsis of Original Research Paper

Comprehensive screen of lipid species that prevent keratinocyte cell senescence

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Skin is exposed to a variety of DNA damage-inducible stimulations such as chemicals and ultraviolet rays. The accumulation of DNA damages causes cell senescence of keratinocytes, which causes solar keratosis and melanoma. Those diseases not only threaten the life of patients itself but also decrease the quality of life of the patients. Thus, it is important to uncover molecular mechanisms and signatures of keratinocyte senescence. We have previously found that knockdown of SPOP, a substrate recognition receptor for cullin-3 (CUL3) ubiquitin ligase, in non-cancerous human keratinocyte-derived HaCaT cells exhibited cell senescence phenotypes (e.g. upregulation of p21 mRNA) as well as dysregulation of intracellular cholesterol distributions. These results suggest the relationships between cell senescence and lipid metabolisms controlled by the CUL3/SPOP ubiquitin ligase. In this study, we aim to characterize SPOP-knockdown HaCaT cells from the standpoint of cell cycle and to measure lipid molecular species in SPOP-knockdown HaCaT cells using untargeted lipidomics by the combination of LC-MS/MS9030 and MS-DIAL 4. We showed that SPOP knockdown drastically inhibited the translation of CDC6 and CDT1, which is essential for DNA replication licensing, leading to the upregulation of p21 mRNA and G1/S arrest (Sanada, Maekawa et al., BBRC. 2023). Our untargeted lipidomics revealed that neutral lipids were decreased in SPOP-knockdown HaCaT cells. Our results suggest a decrease of neutral lipids as a lipid signature of G1/S arrest HaCaT cells that mimic keratinocyte senescence.