MELANOMA AND MELANOCYTIC NAEVI

AUTOPHAGIC CELL DEATH PARTICIPATES IN POMC-INDUCED MELANOMA SUPPRESSION

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Introduction: Hypoxia in tumors is known to trigger the pro-survival pathways such as autophagy. Systemic proopiomelanocortin (POMC) gene therapy suppresses melanoma through apoptosis induction and neovascularization blockage.

Objective: In this study, we investigated the crosstalk between autophagic and apoptotic signaling in POMC-mediated melanoma suppression.

Materials and Methods: We use human MNT-1 melanoma cell, mouse (B16-F10) and human (A375 and A2058) melanoma cell for serial studies.

Results: By histological and immunoblot analysis, it was shown that POMC-treated melanoma tissues exhibited the prominent LC3 immunostaining, which was correlated with reduced CD31-positive tumor vascularization. Such
autophagy induction could be recapitulated in melanoma cells receiving POMC gene delivery and hypoxia-mimicking agent cobalt chloride (CoCl2). We then utilized the POMC-derived peptide α-MSH with CoCl2 to elicit the autophagy as well as apoptosis in cultured melanoma cells. To delineate the role of autophagy during cell death, application of autophagy-inducer rapamycin enhanced, whereas autophagy inhibitor 3-MA attenuated, the α-MSH-induced apoptosis in melanoma cells. Genetic silencing of ATG5, an autophagy regulator, by RNA interference perturbed the α-
MSH-induced apoptosis in melanoma cells. Finally, it was delineated that α-MSH stimulated the HIF-1α signaling as well as the expression of BNIP3/BNIP3L, thereby promoting the autophagy and apoptosis in melanoma cells.

Conclusion: Therefore, the present study unveiled a unique function of autophagy in promoting cell death during POMC-mediated melanoma suppression via α-MSH/HIF-1α/BNIP3/BNIP3L signaling pathway.