MEDICAL THERAPIES AND PHARMACOLOGY

ENHANCEMENT OF LYSOSOMAL FUNCTION CONTRIBUTES TO IMIQUIMOD-ACQUIRED RESISTANCE IN SKIN CANCER CELLS

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Introduction: Development of acquired resistance to chemotherapy is the major problem in current clinical cancer treatment. Imiquimod (IMQ), a synthetic nucleotide-like Toll-like receptor (TLR) 7 ligand and a FDA proved drugs, contains both anti-tumor and anti-viral activity for various skin malignancies and viral warts in clinical treatment. Accumulated clinical cases had shown that some patients with melanoma and non-melanoma did not respond to IMQ treatment and the malignancies are relapse in the original lesions.

Objective: There are no available reports indicating the mechanisms of IMQ acquired resistance.

Materials and Methods: In this study, we generated two IMQ-acquired resistant cell lines, BCC-R25 and B16F10-R25, from IMQ-sensitive human BCC/KMC-1 and mouse B16F10 melanoma cells.

Results: We demonstrated inefficiency of IMQ-induced apoptosis in both IMQ-acquired resistant cells. Additionally, we not only found the up-regulation of lysosomal pathway in BCC-R25 by genome-wide transcriptional profiling analysis, but also demonstrated the enrichment of lysosomal number and alteration of lysosomal function in two IMQ-acquired resistant cell lines. We also found that pharmacological inhibition of autophagic flux or the use of lysosomotropic drugs sensitized IMQ-antitumor activity in vitro and in vivo. Finally, we not only demonstrated the expression of Transcription factor EB (TFEB) was associated with IMQ-acquired resistant, but also enhanced IMQ-induced cell death by depletion of TFEB in both IMQ-acquired resistant cells.

Conclusions: Based on our finding, we might generate novel targeting strategies to improve the clinical application of IMQ for treatment of IMQ-acquired resistant skin cancer.