MELANOMA AND MELANOCYTIC NAEVI

GANODERMA IMMUNOMODULATORY PROTEIN AND CHIDAMIDE INHIBIT METASTATIC MELANOMA VIA REGULATION OF INTEGRIN-RELATED SIGNALING PATHWAY

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Introduction: Metastasis is a multistep, complex process. Recent advances in melanoma have been made in target therapies and immune checkpoint inhibitors, but durable remission is rare. Ganoderma immunomodulatory proteins (GMI) induce a cytotoxic effect in cancer cells via autophagy. However, the role of GMI in melanoma is not clear.

Objectives: The aims of this study are to investigate the inhibiting effects of GMI combined with chidamide on survival and metastases of melanoma cells with strategies for combining GMI, chidamide, and pembrolizumab.

Materials and Methods: We analyzed the effects of GMI on the morphology, viability, and migration of melanoma cells (A375.S2 and B16F10). Cell morphology and viability were measured by cell counting Kit-8. The activities of apoptosis- and migration-related proteins were detected on Western blot assay. Flow cytometry was used to analyze cell cycle distribution and sub-G1 fraction in treated melanoma cells. The synergistic effect of combination treatment of GMI and chidamide was analyzed on Western blot. To evaluate the activity of combination GMI, chidamide and pembrolizumab treatment, an in vivo anti-tumor metastasis study was performed.

Results: GMI significantly inhibited cell growth and migration of A375.S2 cells on Boyden chamber assay. GMI combined with chidamide synergistically induced apoptosis of melanoma cells. GMI inhibited the expressions of Integrin α5, αV, β1, and β3. The levels of p-FAK, FAK, phospho-Rb, phosphor-Chk1 and Survivin decreased and the levels of cleaved caspase-7 and LC3 II/I increased with combination treatment of GMI and chidamide. Integrin-αV overexpression activated p-FAK pathways in A375.S2 cells. In vivo, GMI combined with pembrolizumab and chidamide suppressed distal tumor metastasis.

Conclusions: GMI inhibits the migration and growth of melanoma cells via integrin-related signaling pathway. In vivo, GMI synergistically reduces distant metastases. GMI is a

potential immunotherapeutic adjuvant for metastatic melanoma.