Pharmacogenomics and chemical library screens reveal a novel SCFSKP2 inhibitor that overcomes Bortezomib resistance in multiple myeloma

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Abstract:

While clinical benefit of the proteasome inhibitor (PI) bortezomib (BTZ) for multiple myeloma (MM) patients remains unchallenged, dose-limiting toxicities and drug resistance limit the long-term utility. The E3 ubiquitin ligase Skp1–Cullin-1–Skp2 (SCFSkp2) promotes proteasomal degradation of the cell cycle inhibitor p27 to enhance tumor growth. Increased SKP2 expression and reduced p27 levels are frequent in human cancers and are associated with therapeutic resistance. SCFSkp2 activity is increased by the Cullin-1-binding protein Commd1 and the Skp2-binding protein Cks1B. Here we observed higher CUL1, COMMD1 and SKP2 mRNA levels in CD138+ cells isolated from BTZ-resistant MM patients. Higher CUL1, COMMD1, SKP2 and CKS1B mRNA levels in patient CD138+ cells correlated with decreased progression-free and overall survival. Genetic knockdown of CUL1, COMMD1 or SKP2 disrupted the SCFSkp2 complex, stabilized p27 and increased the number of annexin-V-positive cells after BTZ treatment. Chemical library screens identified a novel compound, designated DT204, that reduced Skp2 binding to Cullin-1 and Commd1, and synergistically enhanced BTZ-induced apoptosis. DT204 co-treatment with BTZ overcame drug resistance and reduced the in vivo growth of myeloma tumors in murine models with survival benefit. Taken together, the results provide proof of concept for rationally designed drug combinations that incorporate SCFSkp2 inhibitors to treat BTZ resistant disease.

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