Cellular and Molecular Mechanisms Underlie the Anti-Tumor Activities Exerted by Walterinnesia aegyptia Venom Combined with Silica Nanoparticles against Multiple Myeloma Cancer Cell Types.

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Abstract:

Multiple myeloma (MM) is a clonal disease of plasma cells that remains incurable despite the advent of several novel therapeutics. In this study, we aimed to delineate the impact of snake venom extracted from Walterinnesia aegyptia (WEV) alone or in combination with silica nanoparticles (WEV+NP) on primary MM cells isolated from patients diagnosed with MM as well as on two MM cell lines, U266 and RPMI 8226. The IC(50) values of WEV and WEV+NP that significantly decreased MM cell viability without affecting the viability of normal peripheral mononuclear cells (PBMCs) were determined to be 25 ng/ml and 10 ng/ml, respectively. Although both WEV (25 ng/ml) and WEV+NP (10 ng/ml) decreased the CD54 surface expression without affecting the expression of CXCR4 (CXCL12 receptor) on MM cells, they significantly reduced the ability of CXC chemokine ligand 12 (CXCL12) to induce actin cytoskeleton rearrangement and the subsequent reduction in chemotaxis. It has been established that the binding of CXCL12 to its receptor CXCR4 activates multiple intracellular signal transduction pathways that regulate MM cell chemotaxis, adhesion, and proliferation. We found that WEV and WEV+NP clearly decreased the CXCL12/CXCR4-mediated activation of AKT, ERK, NF□B and Rho-A using western blot analysis; abrogated the CXCL12-mediated proliferation of MM cells using the CFSE assay; and induced apoptosis in MM cell as determined by PI/annexin V double staining followed by flow cytometry analysis. Monitoring the expression of B-cell CCL/Lymphoma 2 (Bcl-2) family members and their role in apoptosis induction after treatment with WEV or WEV+NP revealed that the combination of WEV with NP robustly decreased the expression of the anti-apoptotic effectors Bcl-2, Bcl(XL) and Mcl-1; conversely increased the expression of the pro-apoptotic effectors Bak, Bax and Bim; and altered the mitochondrial membrane potential in MM cells. Taken together, our data reveal the biological effects of WEV and WEV+NP and the underlying mechanisms against myeloma cancer cells.

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