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Understanding therapy resistance in multiple myeloma

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Multiple myeloma (MM) is hematologic malignancy characterized by the accumulation of malignant plasma cells in the bone marrow. The disease initially responds to alkylating agents, corticosteroids, and thalidomide but eventually becomes refractory. MM is extremely susceptible to radiation treatment and targeted radiotherapy with bone-seeking radiopharmaceuticals now offer a new paradigm to target this systemic malignancy. Samarium-153-ethylene diamine tetramethylene phosphonate (153-Sm-EDTMP) demonstrates good therapeutic ratio for palliation of pain in cancer patients with osseous metastases. We have shown that the proteasome inhibitor bortezomib (BTZ) can sensitize myeloma cells to conventional radiotherapy by both intrinsic and extrinsic apoptotic pathways. BTZ acts as a radiation modifier in MM predominantly by attenuating endogenous and radiation-induced NF- κ B activity. In a mouse myeloma model, we demonstrated that the combination of BTZ with 153-Sm-EDTMP resulted in increased survival time without a corresponding increase in the myelosuppressive effects of 153-Sm-EDTMP. We have recently proposed a novel combination of dexamethasone (Dex) plus radiation for treatment of MM in which the combination of 153-Sm-EDTMP radiotherapy and Dex selectively enhanced killing of myeloma cells. Our ongoing studies provide evidence that increases in glutathione metabolism and manganese superoxide dismutase expression play a role in IL-6-induced resistance to Dex and radiation in myeloma cells. An increased understanding of the role of endogenous and therapy-induced oxidative stress, which results from an imbalance in the production of reactive oxygen species and cellular antioxidant defenses, may offer a biochemical rationale for designing novel ways to induce oxidative stress-mediated killing of myeloma cells by radiotherapy and/or chemotherapy.

Biography

Dr. Goel completed her PhD from Punjab University in India and postdoctoral studies from University of Nebraska Medical Center and Mayo Clinic. She is currently an Assistant professor in the Department of Radiation Oncology at the University of Iowa. She has published more than 25 papers in reputed journals. Dr. Goel's research interest is on B-cell malignancies (B-cell lymphoma and multiple myeloma). Their lab is studying mechanistic pathways that can result in selective radiosensitization of tumor cells..