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Targeting cancer stem cells in multiple myeloma therapy

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Abstract

Multiple myeloma (MM) is a difficult malignancy to cure. A sub-population of MM cancer stem cells (MM-CSCs) exhibit increased tumorigenicity, self-renewal, and unfortunately greater resistance to myeloma drugs. Among frontline drugs is the proteasome inhibitor bortezomib (BTZ), which is effective in inducing MM remission, however resistance can arise. To inhibit disease relapse, we are evaluating more potent BTZ-based drug combination therapies that are designed to eliminate MM-CSCs along with myeloma cells by selectively inducing metabolic oxidative stress in MM-CSCs relative to normal stem cells. Our published work shows that combination protocols with anti-myeloma drugs and radiation along with inhibition of enzymatic removal of superoxide anion radical results in increased killing of myeloma cells (Brown et al, Biochemical Journal, 2012; 444(3) : 515-527). Interestingly, BTZ can induce redox perturbations in myeloma cells but BTZ effects on oxidative metabolism in MM-CSCs remain unidentified. Our results show that MM-CSCs exhibit lower steady-state levels of reactive oxygen species (ROS) with increased expression of antioxidant genes involved in hydroperoxide metabolism. Treatment with metformin, a clinically active metabolism-modifying drug increased ROS levels and induced cytotoxicity in MM-CSCs. Furthermore, combined treatment with metformin and auranofin, an inhibitor of thioredoxin-dependent hydroperoxide metabolism, enhanced mitochondrial ROS production in MM-CSCs. Ongoing studies are evaluating the fundamental differences in mitochondrial oxidative metabolism between MM-CSCs and normal stem cells, such that a combination therapeutic approach can be designed to inhibit myeloma relapse that can be easily translated into clinical trials and may offer improved overall cure rates.

Biography

Dr. Goel is currently an Assistant Professor in the Free Radical and Radiation Biology Program within the Department of Radiation Oncology at the University of Iowa, USA. One of the focuses of research in Goel lab is on understanding and circumventing resistance to frontline chemotherapeutic drugs in multiple myeloma. Dr. Goel has published over 30 papers in reputed journals, and authored review articles and book chapters. She is actively serving as grant reviewer and scientific reviewer for several agencies and journals.