Multiple myeloma (MM) is a plasma cell neoplasm that results from clonal expansion of an Ig-secreting terminally differentiated B cell. Advanced MM is characterized by tissue damage that involves bone, kidney, and other organs and is typically associated with recurrent genetic abnormalities. IL-6 signaling via the IL-6 signal transducer GP130 has been implicated as an important driver of MM pathogenesis. Here, we demonstrated that ectopic expression of constitutively active GP130 (L-GP130) in a murine retroviral transduction-transplantation model induces rapid MM development of high penetrance. L-GP130-expressing mice recapitulated all of the characteristics of human disease, including monoclonal gammopathy, BM infiltration with lytic bone lesions, and protein deposition in the kidney. Moreover, the disease was easily transplantable and allowed different therapeutic options to be evaluated in vitro and in vivo. Using this model, we determined that GP130 signaling collaborated with MYC to induce MM and was responsible and sufficient for directing the plasma cell phenotype. Accordingly, we identified Myc...
aberrations in the L-GP130 MM model. Evaluation of human MM samples revealed recurrent
activation of STAT3, a downstream target of GP130 signaling. Together, our results indicate that
deregulated GP130 activity contributes to MM pathogenesis and that pathways downstream of GP130
activity have potential as therapeutic targets in MM.