Heparanase: a novel target for therapy of multiple myeloma

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Heparanase is an endoglucuronidase that trims heparan sulfate chains of proteoglycans leading to release of growth factors, cytokines and other effectors that regulate tumor behavior. In myeloma patients, heparanase expression is associated with poor prognosis, and tumor cells that survive extensive drug therapy express much higher levels of heparanase than they did prior to treatment. Laboratory studies demonstrate that heparanase stimulates expression of VEGF, HGF, MMP-9 and RANKL, it promotes ERK signaling and shedding of syndecan-1 (CD138) from the myeloma cell surface and it represses expression of CXCL10. Through these actions, heparanase dynamically impacts multiple regulatory pathways within the tumor microenvironment that together drive myeloma survival, growth, dissemination and osteolysis. Moreover, heparanase plays a role in modulating the sensitivity of myeloma cells to therapy. Increased expression and secretion of heparanase was detected in myeloma cell lines following treatment with bortezomib or melphalan and high expression of heparanase by these cells rendered them less susceptible to the cytotoxic effects of bortezomib or melphalan. These data may be clinically relevant as they are consistent with our finding that heparanase gene expression increases in myeloma patients following chemotherapy. Importantly, there is only a single, enzymatically active form of heparanase in humans, it is expressed in low levels in most normal tissues and heparanase knock-out animals exhibit no obvious deficits. Together, these findings imply that heparanase is a desirable and druggable therapeutic target whose inhibition will disrupt the myeloma microenvironment, diminish tumor growth while causing minimal side effects in patients, and possibly at the same time increase tumor sensitivity to other anti-myeloma agents.

Roneparstat (SST0001) is a potent inhibitor of heparanase enzyme activity (IC_{50}~3 nM). It consists of a chemically modified heparin that is non-anticoagulant and is not degraded by the enzyme. We have extensively studied Roneparstat in several models where human myeloma tumor cells were injected either subcutaneously, into fragments of human fetal bone implanted in mice (SCID-hu) or intravenously into the mouse tail vein. Roneparstat at concentrations of 60-120 mg/kg/day s.c. significantly inhibited growth of myeloma tumors in subcutaneous and SCID-hu models. Consistent with the compound's ability to inhibit heparanase activity, analysis of subcutaneous tumors from animals treated with Roneparstat revealed that the level of VEGF, HGF and MMP-9 were dramatically reduced and angiogenesis was repressed. When cells expressing a high level of heparanase were injected intravenously, they homed to, and grew almost exclusively, in bone. In this model, Roneparstat as a single agent did not significantly inhibit tumor growth; however it was highly effective when used in combination with bortezomib (0.5 mg/kg twice weekly) or melphalan (1 mg/kg weekly).

Conclusions: Extensive mechanistic studies and the in vivo efficacy of Roneparstat demonstrate that heparanase is a viable target for myeloma therapy. The ability of Roneparstat to dramatically reduce tumor growth in bone when used in combination with either bortezomib or melphalan indicates that blocking heparanase diminishes drug resistance in myeloma. A multicenter phase I clinical study of Roneparstat is currently ongoing in multiple myeloma patients.