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Induction of Activin A with Lenalidomide in Multiple Myeloma: Preclinical Rationale for Combination with the Activin A Inhibitor ACE-011.

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In this thesis, the combined administration of lenalidomide with an activin A-inhibitor, RAP-011, was tested in a co-culture system of stromal and Multiple Myeloma (MM) cells for its anabolic and cytotoxic activity within the MM microenvironment. MM is a hematological disorder of plasma cells proliferating in the bone marrow. It is characterized by an increase in bone resorption and a decrease in bone formation, which induce the development of osteolytic bone lesions. This unbalanced bone remodeling additionally supports tumor cell growth and proliferation in a vicious circle. Current approved anti-MM strategies include cytotoxic agents (such as melphalan and dexamethasone) and drugs altering the microenvironment by targeting BMSCs, immune and endothelial cells (e.g. proteasome inhibitors and thalidomide-derivatives). Lenalidomide, in particular, belongs to the immunomodulatory agents (IMIDs) and has anti-MM as well as anti-catabolic properties. Activin A mediates bone destruction in MM by interfering with the anabolic axis. Promising inhibitors of activin A are chimeric antibodies, deriving from the fusion of the extracellular component of the activin A receptor and the constant domain of the IgG: RAP-011, the murine compound, and ACE-011, the humanized counterpart. In this thesis I demonstrate for the first time that the addition of the activin A inhibitor RAP-011 potentiates the bone protective effect of lenalidomide. Specifically, lenalidomide treatment of patient-derived BMSCs alone and in co-culture with MM cells induces an increase in activin A secretion, which is, at least in part, mediated by the activation of the JNK/c-Jun pathway. Lenalidomide-induced activin A inhibits OB differentiation. Conversely, treatment with the activin A inhibitor RAP-011 restored osteogenesis. Importantly, inhibition of activin A had no impact on the anti-MM activity of lenalidomide. Therefore, this study sets the stage for the clinical combination of lenalidomide with anabolic agents targeting the activin A pathway. In addition, this strategy may have a positive effect on lenalidomide-induced anemia, since activin A inhibition increases the hematocrit and hemoglobin levels in healthy volunteers and in post-menopausal women. Clinical trials to evaluate safety and efficacy of co-treatment with lenalidomide and ACE-011 are currently undergoing.