HEDGEHOG PATHWAY IN THE PATHOGENESIS OF MULTIPLE MYELOMA
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The Hedgehog (Hh)-pathway belongs to the “stem cell signaling network”. It is required for cell growth and differentiation during the embryos life, tissue homeostasis and repair in the adult life. Several evidences supported a role of Hh-signaling in regulating a “stem cell” niche also in Multiple Myeloma (MM). It is still controversial if it can play a role in terminally differentiated plasma cells (PCs). We already provided evidence that overexpression of ciliary proteins might lead to constitutive Hh-signaling activation in MM. Here we demonstrate that CD138+ cells derived from MM patients and MM cell lines express Shh-ligand, Ptch1 and Smo receptors as well as Gli transcription factors, suggesting Hh-activity in MM. We show a ligand-dependent Hh-activation using NVP-LDE225, a novel synthetic Smo-inhibitor (Novartis), that affects viability of MM cell lines inducing a specific down-regulation of Gli1 and Ptch1, hallmarks of Hh-activity. Moreover we detect an unexpected nuclear localization of Gli1 which is completely abrogated by Forskolin, a Gli1 modulating compound, suggesting additional mechanisms of Hh-activity in MM. Finally, we find that MM patients-derived bone-marrow stromal cells (BMSCs) are source of Shh-ligand, although they show resistance to Hh-inhibitor, probably due to defective Smo-expression as well as to Ptch1 up-regulation. In vivo study shows little anti-tumor activity of NVP-LDE225 as single agent, but a significant delay of tumor re-growth after Bortezomib treatment. All together, our data demonstrate canonical as well non canonical mechanisms of Hh-pathway activation and provide the rationale to the use of Hh-inhibitors to improve the outcome of MM patients.