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New therapeutic targets for uterine leiomyosarcoma: Gant61 as a blocker to non-canonical activation of Sonic Hedgehog pathway

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Introduction: Leiomyoma (LM) and leiomyosarcoma (LMS) are uterine mesenchymal tumors, presenting variable clinical behavior. They are associated with infertility, pelvic pain and abnormal uterine bleeding. LM is a benign tumor commonly affecting women at reproductive age whereas LMS represents 40% of all uterine sarcomas. Additionally, some researchers believe that degenerated LM may to turn into LMS. Studies show that aberrant activation of the Sonic Hedgehog (SHH) signaling plays an important role in development of different types of cancer. In a previous study, we found SMO and GLI1 overexpression in LMS patients, compared to LM and myometrium (MM). Objective: To evaluate in vitro inhibitors of the Sonic Hedgehog signaling pathway in LM and LMS. Methods: MM, LM and LMS cell lines were used to analyze gene expression of PTCH1, SMO, SUFU and GLI1-3. SMO and GLI1 protein expression were evaluated by Western blotting. Cells were treated with 0.1, 1, 10 and 100 µM of Gant58 and Gant61 (GLI1 inhibitor) for 96 hours, and drug replacement was performed each 24 hours. Cells viability was evaluated using GloMax (Promega) equipment. Results: SMO, GLI1 and SUFU genes were upregulated in LMS compared to MM and LM cells. PTCH1, GLI2 and GLI3 were downregulated in LMS cells. SHH gene was not detected in MM, LM and LMS. SMO protein presented increased expression in MM, LM and LMS cells. GLI1 protein was not expressed in MM cells, whereas its expression was increased in LM and LMS cells. MM and LM cells treated with Gant58 had their growth inhibited in approximately 50% at a concentration of 100µM, after 96h of treatment. LMS cells did not present growth difference at the evaluated concentrations, compared to the controls. MM cells treated with Gant61, at a concentration of 100µM, had almost 100% of cell death in the first 24 hours. LM and LMS cells had change in their growth profile only at concentration of 100µM; however, at the end of the test (96h) these cells showed 100% of death. Conclusion: Non-canonical activation of SHH signaling in LMS may occur due to over expression of SMO and GLI1 proteins. SHH signaling may be a therapeutic target for the treatment of LMS. Treatment with GLI1 inhibitor (Gant61) showed efficient decrease of growth in LMS cells. However, more studies are necessary to show the efficacy of Gant61 as an antitumor agent in LMS.

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