A bioengineered 3D ovarian cancer model for the assessment of peptidase-mediated enhancement of spheroid growth and intraperitoneal spread.

Cancer-associated proteases promote peritoneal dissemination and chemoresistance in malignant progression. In this study, kallikrein-related peptidases 4, 5, 6, and 7 (KLK4-7)-cotransfected OV-MZ-6 ovarian cancer cells were embedded in a bioengineered three-dimensional (3D) microenvironment that contains RGD motifs for integrin engagement to analyze their spheroid growth and survival after chemotreatment. KLK4-7-cotransfected cells formed larger spheroids and proliferated more than controls in 3D, particularly within RGD-functionalized matrices, which was reduced upon integrin inhibition. In contrast, KLK4-7-expressing cell monolayers proliferated less than controls, emphasizing the relevance of the 3D microenvironment and integrin engagement. In a spheroid-based animal model, KLK4-7-overexpression induced tumor growth after 4 weeks and intraperitoneal spread after 8 weeks. Upon paclitaxel administration, KLK4-7-expressing tumors declined in size by 91% (controls: 87%) and showed 90% less metastatic outgrowth (controls: 33%, P< 0.001). KLK4-7-expressing spheroids showed 53% survival upon paclitaxel treatment (controls: 51%), accompanied by enhanced chemoresistance-related factors, and their survival was further...
reduced by combination treatment of paclitaxel with KLK4/5/7 (22%, P = 0.007) or MAPK (6%, P = 0.006) inhibition. The concomitant presence of KLK4-7 in ovarian cancer cells together with integrin activation drives spheroid formation and proliferation. Combinatorial approaches of paclitaxel and KLK/MAPK inhibition may be more efficient for late-stage disease than chemotherapeutics alone as these inhibitory regimens reduced cancer spheroid growth to a greater extent than paclitaxel alone.