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J Cancer Sci Ther 2019, Volume 11
DOI: 10.4172/1948-5956-C1-160

32nd Euro Congress on

Cancer Science & Therapy

March 07-08, 2019 | Barcelona, Spain

The Role of Tumor Microenvironment in Chemoresistance: 3D Extracellular Matrices as Accomplices

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Background: The functional interplay between tumor cells and their adjacent stroma has been suggested to play crucial roles in the initiation and progression of tumors and the effectiveness of chemotherapy. The extracellular matrix (ECM), a complex network of extracellular proteins, provides both physical and chemicals cues necessary for cell proliferation, survival, and migration. Understanding how ECM composition and biomechanical properties affect cancer progression and response to chemotherapeutic drugs is vital to the development of targeted treatments. Methods: 3D cell-derived-ECMs and esophageal cancer cell lines were used as a model to investigate the effect of ECM proteins on esophageal cancer cell lines response to chemotherapeutics. Immunohistochemical and qRT-PCR evaluation of ECM proteins and integrin gene expression was done on clinical esophageal squamous cell carcinoma biopsies. Esophageal cancer cell lines (WHCO1, WHCO5, WHCO6, KYSE180, KYSE 450 and KYSE 520) were cultured on decellularised ECMs (fibroblasts-derived ECM; cancer cell-derived ECM; combinatorial-ECM) and treated with 0.1% Dimethyl sulfoxide (DMSO), 4.2 μM cisplatin, 3.5 μM 5-fluorouracil and 2.5 μM epirubicin for 24 h. Cell proliferation, cell cycle progression, colony formation, apoptosis, migration and activation of signaling pathways were used as our study endpoints. Results: The expression of collagens, fibronectin and laminins was significantly increased in esophageal squamous cell carcinomas (ESCC) tumor samples compared to the corresponding normal tissue. Decellularised ECMs abrogated the effect of drugs on cancer cell cycling, proliferation and reduced drug induced apoptosis by 20–60% that of those plated on plastic. The mitogen-activated protein kinase-extracellular signal-regulated kinase (MEK-ERK) and phosphoinositide 3-kinase-protein kinase B (PI3K/Akt) signaling pathways were upregulated in the presence of the ECMs. Furthermore, our data show that concomitant addition of chemotherapeutic drugs and the use of collagen- and fibronectin-deficient ECMs through siRNA inhibition synergistically increased cancer cell sensitivity to drugs by 30–50%, and reduced colony formation and cancer cell migration. Conclusion: Our study shows that ECM proteins play a key role in the response of cancer cells to chemotherapy and suggest that targeting ECM proteins can be an effective therapeutic strategy against chemoresistant tumors.

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