Integrin α3β1 - collagen VI axis increases chemotherapy resistance of ovarian cancer cells


Introduction

Ovarian cancer (OC) is the most lethal gynecological malignancy, which spreads aggressively via peritoneal fluid into abdominal organs. Even after initially efficient cytoreductive surgery and chemotherapy response, majority of OC patients suffers from relapse due to inability to eliminate all the widely spread microlesions with ability to sustain disease progression by the tissue (re)colonization and development of drug resistance.

Although acquiescent extracellular matrix (ECM) interactions contribute to these processes by promoting invasive cancer growth and cell survival, the key ECM adhesion pathways activated during OC evolution, including tumor tissue responses to chemotherapy, have remained unclear.

Desmoplastic reactions and adhesion to the evolving extracellular matrix (ECM) regulates cancer cell growth, apoptosis and invasion by as yet incompletely understood mechanisms.

Our results reveal α3β1-integrin and collagen 6 as efficient promoters of metastatic high grade serous ovarian cancer (HGSOC) lesions by enhancing invasiveness and resistance to platinum-based chemotherapy.

Goal

To identify significant drivers of HGSOC microenvironment communication underlying metastasis and chemoresistance.

Results

Figure 1. High integrin α3, α4, α5, α11 and β1, β8 expression is significantly associated with poor overall survival of HGSOC patients. (A) TCGA data analysis workflow. (B) Example Kaplan-Meier survival curves. (C) Relative mRNA of integrins α3, α4, α5, α11 and β1, β8 in patient-derived cancer cells.

Figure 2. Loss of integrin heterodimer subunits α3 and β1 reduces invasive OC cell growth in 3D collagen.

Figure 3. Expression of COL6, an α3β1-integrin ligand, increases upon HGSOC disease progression.

Figure 4. Overexpression of COL6 is associated with poor survival and altered cancer stemness & EMT marker expression.

Figure 5. Cytotoxicity assay of ascites-derived HGSOC organoids show the increased cell survival in 3D COL6 surrounding.

Considering the strong collagen 6-rich desmoplastic responses associated to OC aggressive properties, we propose the α3β1-integrin-collagen 6 pathway as means for re-sensitizing the refractory HGSOC to therapy.