Cancer cell implantation through deposited fibrin on the cicatrices and injured peritoneum

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Aim: The fact that any tissue traction or peritoneal injury increase the risk of cancer recurrence, is well known. Here, we show i*n vitro* and *in vivo* study of the molecular mechanism of cancer cell implantation and nodule formation on the injured peritoneum.

Material and methods: CT26 (mice colon cancer) and human mesothelial cell (HMC) (all from ATCC-USA), were used. BALB/C mice were injected intra-peritoneally with CT26 cancer cell. Wounds inducted on the peritoneal wall via sterilized Q-tip in addition to the surgery area. Anti-adherence (Ico-dextrin also was used for inhibition of cancer cell implantation. Fibrin deposits on the injured zones were investigated via anti-plasmin peptide F13. For *in vitro* study, Fibrin was obtained by adding thrombin to a pool of normal plasmas. The cell-fibrin interaction was observed in optic, electronic and confocal microscopies as well as by micro cinematography. Aprotinin as a plasmin inhibitor and anti-trypsin were used in the study for the regulation of cell-fibrin interaction. evaluation Plasminogen activators, t-PA and u-PA as well as their inhibitor PAI-1 in the cell and supernatants were quantified by qPCR and ELISA respectively. The presence and interaction of PAR1-thrombin was investigated in mesothelial cells by qPCR.

Results: i) cancer cell lines adhere and implant to in the wound area in the presence of the fibrin net (*in vivo and in vitro)*. ii) Fibrin net - cancer cells interaction generates a lysis area and D-dimer level in culture medium increased in time dependent manner. iii) Aprotinin, by inhibiting lysis of the fibrin network prevents cancer cell invasion and implantation. iv) Thrombin via PAR activate mesothelial cell, upregulates PAI-1 and tissue factor (TF) and down regulates the PA expression. v) Icodextrin inhibits significantly nodules formation in cicatrices zone as well as in the incision or on the peritoneal damaged areas after surgery.

Conclusion: The fibrin integrity in the injured areas of the peritoneum due to in situ generation of thrombin via PAR Mesothelial cells receptors stimulation which will lead to PAI-1 upregulation. Fibrin was detected in the tumoral nodule where cells penetrated through the its lines. Fibrin serve as a niche for cancer cell implantation, nodule formation and invasion via generation of plasmin activity in cancer cell microenvironment.