MECHANISMS OF THROMBOSIS AND BLEEDING IN CANCER

FIBRIN CLOT SHIELDS PROMOTE CLONAL SELECTION IN CANCER CELLS: PROCOAGULANT ACTIVITY AND SURVIVAL OF CLOT-EMBEDDED CELLS. A NOVEL TUMOR MICROENVIRONMENT MODEL

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Introduction. Cancer cells (CaCe) expressing tissue factor (TF) initiate thrombin generation and fibrin formation, contributing to cancer-associated hypercoagulability. The resulting fibrin clot shield (FCS) acts as a barrier limiting exposure to therapeutic agents and as a scaffold facilitating CaCe migration and invasion.

Aim. To characterize CaCe embedded within FCS and assess their proliferative, procoagulant, and migratory properties.

Materials and Methods. Highly procoagulant pancreatic (BXPC3) and invasive breast (MDA-MB-231) CaCe were cultured in RPMI-1640 supplemented with 10% human platelet-poor plasma (PPP) to induce FCS formation. Mechanical clot disruption enabled isolation of CaCe within the FCS (clot-CaCe), while cells remaining adherent after clot removal were considered parental CaCe. Both populations were cultured separately. Cells maintained in RPMI-1640 without plasma or coagulation activation served as controls. Cell viability and proliferation were assessed using the crystal violet assay. Procoagulant activity was evaluated by calibrated automated thrombography (CAT®, Diagnostica Stago). FCS architecture and CaCe invasion within the fibrin network were analyzed by scanning electron microscopy (SEM), as described (Tran et al., Thromb Res, 2024).

Results. Clot-CaCe were successfully isolated and expanded. BXPC3 clot-CaCe showed higher proliferation than parental cells. Both BXPC3 and MDA-MB-231 clot-CaCe retained thrombin-generating capacity comparable to parental CaCe. In the presence of PPP, clot-CaCe and parental CaCe induced fibrin network formation and generated similar thrombin levels. SEM showed comparable migration of clot-CaCe, parental CaCe, and controls. However, fibrin structures generated by clot-CaCe displayed a looser architecture, characterized by thicker fibers, larger pores, and fewer intersections compared with networks formed by parental or control CaCe.

Conclusions. These findings provide the first evidence that fibrin-embedded CaCe remain viable and retain proliferative and procoagulant potential while generating new fibrin networks. Their distinct fibrin architecture suggests that clot-embedded CaCe represents a selected subpopulation. Overall, fibrin clots may promote selective survival and clonal expansion of CaCe while shielding them from immune surveillance and cytotoxic therapies. This model offers a useful tool to investigate cancer-associated hypercoagulability, recurrence, and therapeutic resistance.