TARGETING THE PROCOAGULANT PROPERTIES OF GLIOMA CELLS: A POSSIBLE TREATMENT FOR GLIOBLASTOMA?

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The expression levels of the clotting initiator, Tissue Factor (TF), correlate with the histological grade of malignancy in glioma patients. In fact, an increased procoagulant tonus in glioblastoma seems to play a significant role in the disease progression, suggesting that anticoagulants could be used as adjuvants for its treatment. Our objectives in this study were: 1-To determine the molecular mechanisms responsible for the highly procoagulant pattern of the aggressive human glioma cell line, U87MG and 2-To investigate the inhibitory effects of Ixolaris, a FVIIa/TF complex inhibitor, on the U87MG procoagulant properties. Activation of FX to FXa in the presence of U87MG cells and FVIIa indicated constitutive expression of TF. Further flow-cytometric analyses employing annexin V and propidium iodide also demonstrated the exposure of phosphatidylserine (PS) at the outer surface of viable U87MG cells. Therefore, U87MG cells supported the assembly of intrinsic tenase (FIXa/FVIIIa/FX) and prothrombinase (FVa/FXa/prothrombin) complexes, accounting for FXa and thrombin production, respectively. Accordingly, blocking of PS binding sites by annexin V inhibited tumor-dependent zymogen activation. Remarkably, Ixolaris inhibited tumor-dependent generation of FXa and thrombin by all multimolecular coagulation complexes tested. Finally, U87MG cells strongly shortens the coagulation time of human plasma, being this effect efficiently reverted by Ixolaris. We conclude that Ixolaris seems an excellent candidate to target the *in vivo* pro-thrombotic properties of glioblastoma.