BLOOD COAGULATION PROTEINS AS TARGETS FOR CANCER TREATMENT

Robson Monteiro

Institute of Medical Biochemistry, Federal University of Rio de Janeiro, RJ, Brazil.

Several lines of evidence indicate that blood clotting proteins play an important role in cancer biology including growth, metastasis and angiogenesis. Also, a family of G protein-coupled receptors known as protease-activated receptors (PARs) has been implicated in tumor aggressiveness. These receptors may be activated by blood coagulation proteases including thrombin, FVIIa and FXa, thus eliciting a variety of cellular responses. In this context, it has been proposed that anticoagulants could be useful for cancer treatment. Glioblastoma (GBM) is the highest-grade primary brain tumor which is frequently associated with prothrombotic events. Thus, we have studied GBM biology by using the human cell lines U87MG and A172. Both cell lines express Tissue Factor, a membrane-bound 46-kDa protein that triggers blood coagulation. In addition, we have also demonstrated the exposure of phosphatidylserine at the outer surface of viable U87MG and A172 cells. Therefore, tumor cells supported the assembly of intrinsic tenase (FIXa/FVIIIa/FX) and prothrombinase (FVa/FXa/prothrombin) complexes, accounting for the production of, respectively, FXa and thrombin. Remarkably, the exogenous anticoagulant Ixolaris inhibited the tumor-dependent generation of FXa and thrombin by all multimolecular coagulation complexes tested. U87MG cells strongly shortened the coagulation time of human plasma, this effect being efficiently reverted by Ixolaris. In addition, Ixolaris (250 μg/kg) inhibited the in vivo tumorigenic potencial of U87MG cells in nude mice. Taken together, our data suggest that targeting blood clotting proteins may be a promising anti-tumor therapy of human GBMs.

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