The study on marine natural product a new isoindolone FGFCI for fibrinolysis

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Fungi fibrinolytic compound 1 (FGFC1) is a rare pyran-isoindolone derivative with fibrinolytic activity. The aim of this study was to further determine the effect of FGFC1 on fibrin clots lysis in vitro. We constructed a fibrinolytic system containing single-chain urokinase-type plasminogen activator (scu-PA) and plasminogen to measure the fibrinolytic activity of FGFC1 using the chromogenic substrate method. After FITC-fibrin was incubated with increasing concentrations of FGFC1, the changes in the fluorescence intensity and D-dimer in the lysate were measured using a fluorescence microplate reader. The fibrin clot structure induced by FGFC1 was observed and analysed using a scanning electron microscope and laser confocal microscope. We found that the chromogenic reaction rate of the mixture system increased from (15.9 ± 1.51) × 10^{-3} min^{-1} in the control group to (29.7 ± 1.25) × 10^{-3} min^{-1} for 12.8 μM FGFC1 (p < 0.01). FGFC1 also significantly increased the fluorescence intensity and D-dimer concentration in FITC fibrin lysate. Image analysis showed that FGFC1 significantly reduced the fiber density and increased the fiber diameter and the distance between protofibrils. The inhibition of fibrinolytic activity of FGFC1 by 6-aminohexanoic acid (EACA) and tranexamic acid (TXA) together with the docking results revealed that the lysine-binding sites (LBSs) play a crucial role in the process of FGFC1 binding to plasminogen. The action mechanism of FGFC1 binding to plasminogen was inferred, and FGFC1 was able to induce plasminogen to exhibit an open conformation by binding through the LBSs. The molecular docking results showed that docking of ligands (EACA, FGFC1) with receptors (KR_1–KR_5) mainly occurred through hydrophilic and hydrophobic interactions. In addition, the binding affinity values of EACA to KR_1–KR_5 were −5.2, −4.3, −3.7, −4.5, and −4.3 kcal/moL, respectively, and those of FGFC1 to KR_1–KR_5 were −7.4, −9.0, −6.3, −8.3, and −6.7 kcal/moL, respectively. The findings

demonstrate that both EACA and FGFC1 bound to KR_1–KR_5 with moderately high affinity. These results show that FGFC1 can effectively promote fibrin lysis in vitro and may represent a novel candidate agent for thrombolytic therapy.

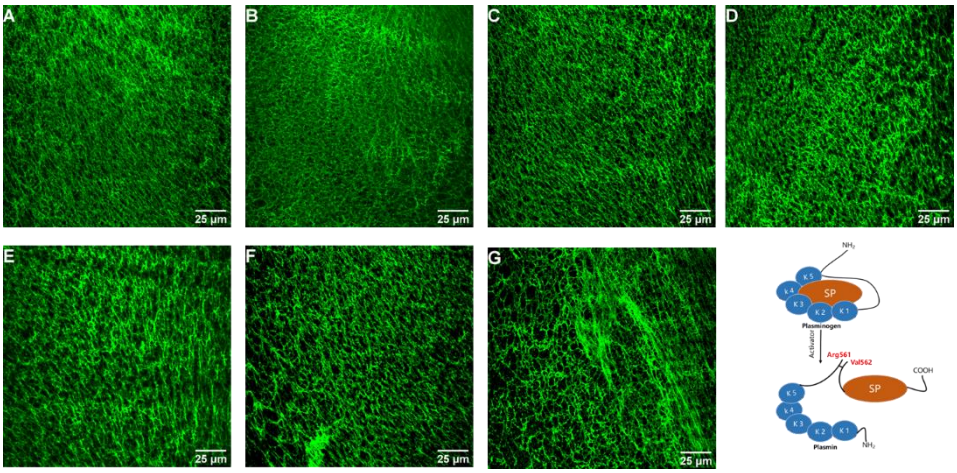

Fig. Confocal laser microscopy images of fibrin networks based on fibrinolysis by FGFC1

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