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DIVERSE EFFECTS OF MUTATED PAI-1 ON THE CANCER CELLS BIOLOGICAL ACTIVITY

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Plasminogen activator inhibitor type 1 (PAI-1) *via* complexing with urokinase and its receptor inhibits plasmin driven proteolysis and therefore regulates tumor-related angiogenesis, invasion and metastasis formation. It was however suggested that PAIs biological effect depends on its active concentration in the cellular milieu, with lower concentrations inducing cancer cells bioactivity and supraphysiological exerting opposite effect. In order to assess the impact of PAI-1 anti-proteinase activity on the process of lung cancer cells proliferation we analyzed the effect of PAI-1 cysteine mutant (VLHL PAI-1) characterized by the prolonged half-life time ($T_{1/2}$= 6931.47 h) and therefore enzymatically much more stable than wild type PAI-1 ($T_{1/2}$=1.57 h). Two functionally different lung cancer cell systems A 549 and H1299 characterized respectively by normal and high urokinase production were evaluated. In H1299 cultures significant inhibitory effect was exerted by high (100 mcg/ml) and extremely high (200.30 mcg/ml) PAI-1 concentrations ($p<0.001$). Its time-dependence was also observed as the inhibition was considerably more pronounced after 72 hr of culture than 48 or 24 hr (respectively ($p<0.001$, $p<0.05$). In A 549 proliferation was suppressed only by the high PAI-1 concentration following 72 hr of culture ($p<0.01$). Accordingly, the dosage- and time-dependent down-regulation of VEGF production was demonstrated, though inhibition rate was significantly higher for the H1299 cells. No changes in the bFGF, MMP-9, nor TIMP-1 by cultured lung cancer cells were seen. PAI-1 is a negative regulator of lung cancer cells due to its anti-proteinase activity. Its biological effect is time and dose-dependent.