3951
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TIMP-2 Inhibits Tumor Growth in Murine Model of Lung Cancer through EGFR signaling

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The tissue inhibitor of metalloproteinase family of proteins (TIMPs 1-4) function as natural MMP inhibitors, and have been shown to play a role in maintenance and remodeling of the ECM as well as other cellular processes including proliferation, apoptosis and angiogenesis. TIMP-2 is widely expressed in the stromal compartment of normal tissues, and has been shown to possess many MMP-independent functions within the tumor microenvironment including inhibition of tumor growth and angiogenesis, reduced vascular permeability, and decreased tumor cell migration and invasion. In the current study, we used congenic mutant TIMP-2 mice (mT2) with a loss of function mutation in the *Timp-2* gene to study TIMP-2 associated effects in mice following intratracheal installation of Lewis Lung carcinoma cells labeled with luciferase (LL2-Luc). The bioluminescence (BLI) data on 28 days post installation revealed a higher tumor burden in mT2 mice compared to wild type (wt) littermates, suggesting that loss of function mutation in *Timp-2* gene increases tumor growth ($p<0.05$), as well as an increase in the lung/body weight ratio ($p<0.01$). In agreement with these findings, Kaplan-Meier analysis exhibited significantly higher mortality in mT2 mice compared to wt controls ($p<0.01$). Histologic analysis of H&E stained lung sections revealed a significant increase in the number of tumor nodules in mT2 mice compared to wt controls ($p<0.01$). In addition, we found that daily treatment (intraperitoneal injection) with exogenous recombinant TIMP2 (rTIMP2) protein (200ug/kg/day) significantly inhibited tumor growth ($p<0.05$) and lung/body weight ratio ($p<0.01$) in both mT2 and wt mice. Furthermore, both normal and tumor tissues from mice harboring the TIMP-2 loss of function mutation demonstrated increased levels of EGFR phosphorylation (Tyr-1068) by western blot analysis. In support of these findings, treatment of Lewis lung carcinoma cells by rTIMP-2 inhibited EGF-induced phosphorylation of EGFR (Tyr-1068) in a dose dependent manner. In conclusion, these data indicate that the loss of function *Timp-2* mutation accelerates lung tumorigenesis, and that exogenous rTIMP-2 treatment inhibits LL2 tumor growth via inhibition of EGFR signaling.

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