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Integrins as therapeutic targets for angiogenesis and metastasis

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In vivo tumors interact with a variety of host cells such as endothelial cells and platelets, and these interactions are mediated by integrins GPIIb/IIIa and αvβ3. We used chimeric (c) 7E3 Fab (abciximab, ReoPro™) and murine (m) 7E3 $F(ab')_2$ to elucidate the role of host and tumor-derived integrins in angiogenesis, tumor growth and metastasis. c7E3 Fab is used in patients undergoing precutaneous coronary interventions. These antibodies are potent inhibitors of GPIIb/IIIa and αvβ3. c7E3 Fab inhibited αvβ3-mediated cell adhesion, migration, invasion and bFGF stimulated proliferation of endothelial cells. In an *in vitro* angiogenesis assay, c7E3 Fab inhibited bFGF- and platelet-stimulated capillary formation of endothelial cells (IC_{50}=10-15 μg/ml), demonstrating that endothelial αvβ3 is important for sprouting, and platelet-stimulated sprouting is mediated by GPIIb/IIIa. In a lung metastasis assay, a single treatment of human melanoma cells with c7E3 Fab (2.5 μg/ml) inhibited lung colonization of the tumor cells in SCID mice. *In vivo*, m7E3 $F(ab')_2$ partially inhibited growth of human melanoma tumors in nude mice compared to control treated animals. Since c7E3 Fab and m7E3 $F(ab')_2$ do not crossreact with murine integrins, this inhibition of metastasis and tumor growth was attributable to direct blockade of human tumor αvβ3 integrins. m7E3 $F(ab')_2$ completely blocked tumor formation and growth of human melanoma tumors in nude rats. In this xenograft model, m7E3 $F(ab')_2$ binds to both human tumor and host platelet GPIIb/IIIa and endothelial αvβ3 integrins, thus participating as an anti-angiogenic, anti-platelet and anti-tumor agent. Collectively, these results indicate that combined blockade of GPIIb/IIIa and αvβ3 affords anti-angiogenic and anti-metastatic benefit.