Non-muscle alpha-actinin-4 interacts with plasminogen activator inhibitor type-1 (PAI-1).

Abstract:

PAI-1 modulates many biological processes involving fibrinolysis, cell migration or tissue remodelling. In addition to inhibiting serine proteases (mainly tPA and uPA), PAI-1 interacts with vitronectin (Vn), fibrin or alpha(1)-acid glycoprotein, interactions which are important for PAI-1-mediated effects in inflammation, tumor invasion and metastasis. To further identify proteins interacting with PAI-1, the yeast two-hybrid strategy was employed. Screening of a human placenta cDNA library identified--in addition to the C-terminal region of cytokeratin 18 (CK18(182-430))--a large C-terminal fragment of alpha-actinin-4 (Act-4) as a binding partner for PAI-1. Two different cDNA clones encoding Act-4(287-911) and Act-4(330-911) respectively, were isolated. An Act-4(330-911)/GST-fusion protein, but not GST alone, was immunoprecipitated together with active PAI-1. In solid phase binding assays, active wild-type PAI-1 as well as the PAI-1 variant Q123K (which does not interact with multimeric Vn) was found to bind to Act-4(330-911)/GST. Latent PAI-1, latent Q123K, and the inactive PAI-1 variant Q55P did not display any binding activity. Act-4 is mainly present intracellularly and is involved in cellular motility via interaction with the actin cytoskeleton, thus probably affecting the metastatic potential of tumor cells. However, an extracellular Act-4-derived fragment (mactinin) has
previously been identified, which (i) is generated by proteolytic action of uPA, (ii) displays significant chemotactic activity for monocytes, and (iii) promotes monocyte/macrophage maturation. We suggest that PAI-1, via interaction with both Act-4 and uPA, may function as a modulator of this mononuclear phagocyte response, not only in inflammation but also in tumor invasion and metastasis.