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CD157/BST1 regulates cell adhesion and spreading through the interaction with the heparin-binding domains of fibronectin

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CD157/BST1 is a glycosylphosphatidylinisotol-anchored glycoprotein belonging to the ADP-rybosil cyclase gene family expressed in myeloid, endothelial, mesothelial cells and in epithelial ovarian cancer cells. In leukocytes, CD157 controls migration, adhesion to extracellular matrix (ECM) proteins and diapedesis. To accomplish these functions, CD157 establishes structural and functional partnership with specific members of the integrin family. In ovarian cancer, CD157 enhances cell motility and invasion of surrounding tissues, ultimately increasing tumor aggressiveness by promoting mesenchymal differentiation. To exert these receptor activities, CD157 interacts with an unknown ligand. The crucial role of CD157 in cell adhesion and migration, and its functional partnership with integrins led us to hypothesize that the non-substrate ligand of CD157 might be found in the ECM. Using solid phase and Surface Plasmon Resonance binding assays, we demonstrated that CD157 binds to fibronectin, fibrinogen, laminin and collagen I but not to vitronectin or to the polysaccharide components of ECM (such as heparin and hyaluronan). We identified the CD157 binding site within the N-terminal and C-terminal heparin-binding domains of fibronectin (HBD1 and HBD2). The CD157-HBD binding is mediated by the protein core while the glycosidic chains contribute to stabilize the interaction. Molecular docking analysis performed to predict the geometry of the interaction between CD157 and HBD1 or HBD2 of fibronectin suggested that a high number of residues (outside the catalytic domain in CD157) are involved. The CD157-ECM interaction demonstrated using purified proteins was confirmed in non-tumorigenic mesothelial Met-5A cells. Indeed, i) membrane CD157 expressed by Met-5A cells binds fibronectin and its HBDs, and ii) anti-CD157 antibodies significantly reduce cell adhesion to selected ECM proteins. Moreover, knockdown of CD157 expression in Met-5A cells reduced cell spreading and remarkably decreased the fibronectin-mediated phosphorylation of FAK, SRC and Akt tyrosine kinases. These morphological and functional changes resulted in impaired cell adhesion. It is reasonable to envision that the broad interaction of CD157 with several ECM proteins may be responsible for many of the biological effects exerted by CD157 in different physiological (*e.g*., leukocyte trafficking) and pathological contexts (*e.g*, inflammatory diseases and cancer), where the composition of the ECM dictates the final outcome.