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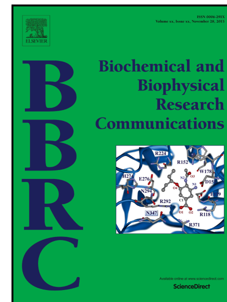

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ACCEPTED MANUSCRIPT

The role of Protein Disulfide Isomerase and thiol bonds modifications in activation of integrin subunit alpha11

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Running title: PDI and integrin alpha11

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Keywords: Protein Disulfide Isomerase, integrin alpha11, thiol groups, disulfide bonds, oxidation-reduction reactions, redox state

ABSTRACT

Integrins belong to a family of transmembrane receptors that mediate cell migration and adhesion to ECM. Extracellular domains of integrin heterodimers contain cysteine-rich regions, which are potential sites of thiol-disulfide exchanges. Rearrangements of extracellular disulfide bonds regulate activation of integrin receptors by promoting transition from an inactive state into a ligand-binding competent state. Modifications of integrin disulfide bonds dependent on oxidation-reduction can be mediated by Protein Disulfide Isomerse (PDI). This paper provides evidences that binding to integrin ligands initiate changes in free thiol pattern on cell surface and that thiol-disulfide exchange mediated by PDI leads to activation of integrin subunit α11. By employing co-immunoprecipitation and confocal microscopy analysis we showed that α11β1 and PDI create complexes bounded by disulfide bonds. Using surface plasmon resonance we provide biochemical evidence that PDI can interact directly with integrin subunit α11.

INTRODUCTION

Integrins belong to the large family of glycoprotein receptors. The basic feature of integrins is their ability to bind different extracellular matrix proteins [1]. Due to their role in cell-ECM contacts, integrins are involved in maintenance of tissue homeostasis [2], but cancer development and progression can also be linked to integrins activity [3].

Integrins are composed of α and β chains that form non-covalently bounded heterodimers. Integrin receptors in an inactive state adopt so called “bent” conformation that placed ligand binding site hidden near membrane surface [4]. During integrin activation, straightening of both subunits leads to developing “upright” conformation with high competency to ligands. Activation of integrin receptors can occur through two pathways: from the outside of the cell (outside-in signalling) and from the interior (inside-out signalling) [5].

Crucial role of thiol-disulfide exchange in activation of integrins has been proposed by several independent groups [6,7]. The most significant cysteine-rich regions in integrin molecules are the I-EGF (epidermal growth factor-like) domains of β subunits. Substitution of a serine into one or both sides of cysteines that form the initial bond may lead to four different outcomes: 1) it may have no effect on integrin activity, 2) it may lead to reduced expression of integrin molecules on the cell surface, 3) it may maintain integrin receptor in an inactive state or 4) it may initiate a constitutively active state of integrin [8,9].

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