Cell-extracellular matrix and cell-cell adhesion are linked by syndecan-4

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Abstract

Cell-extracellular matrix (ECM) and cell-cell junctions that employ microfilaments are sites of tension. They are important for tissue repair, morphogenetic movements and can be emblematic of matrix contraction in fibrotic disease and the stroma of solid tumors. One cell surface receptor, syndecan-4, has been shown to regulate focal adhesions, junctions that form at the ends of microfilament bundles in response to matrix components such as fibronectin. Recently it has been shown that signaling emanating from this proteoglycan receptor includes regulation of Rho family GTPases and cytosolic calcium. While it is known that cell-ECM and cell-cell junctions may be linked, possible roles for syndecans in this process are not understood. Here we show that wild type primary fibroblasts and those lacking syndecan-4 utilize different cadherins in their adherens junctions and that tension is a major factor in this differential response. This corresponds to the reduced ability of fibroblasts lacking syndecan-4 to exert tension on the ECM and we now show that this may extend to reduced tension in cell-cell adhesion.

Introduction

Cells in a multicellular organism are subject to mechanical forces from the extracellular matrix [ECM] and neighboring cells. The cells respond to this tension by altering the gene expression, cytoskeletal organization and function [1,2,3]. Cells and ECM exert mechanical stress on each other mainly through focal adhesions, integrin-containing organelles at the termini of microfilament bundles, through which cells adhere to ECM [4,5]. Roles for syndecan-4 in cell-matrix adhesion are well documented previously [6,7,8,9]. This ubiquitously expressed proteoglycan co-localizes into focal adhesions along with integrins, enhancing cell attachment to extracellular matrix. It has been shown that absence of syndecan-4 leads not only to smaller focal adhesions but also to a less organized actin cytoskeleton and defective α-smooth muscle actin incorporation into stress fibers [10]. In part this may involve altered regulation of RhoGTPases [11,12,13]. Extracellular forces promote the strengthening of stress fibers and enhance the recruitment of adhesion molecules such as paxillin and vinculin into focal adhesions [14]. The importance of contractile forces generated through focal adhesions *in vivo* is demonstrated by mesenchymal cell interactions with fibronectin-rich provisional matrix in wound repair, where closure is effected by microfilament contraction [15,16].

Stress fibers are attached not only to focal adhesions, but may also be present at cell-cell junctions [17]. Maintenance of cell-cell adhesion is essential for the preservation of tissue structure. One prominent type of cell-cell adhesion is the adherens junction, the major transmembrane receptors of which are cadherins that form homotypic interactions with cadherins in the neighboring cell. Cadherins require extracellular calcium for conformational integrity in the

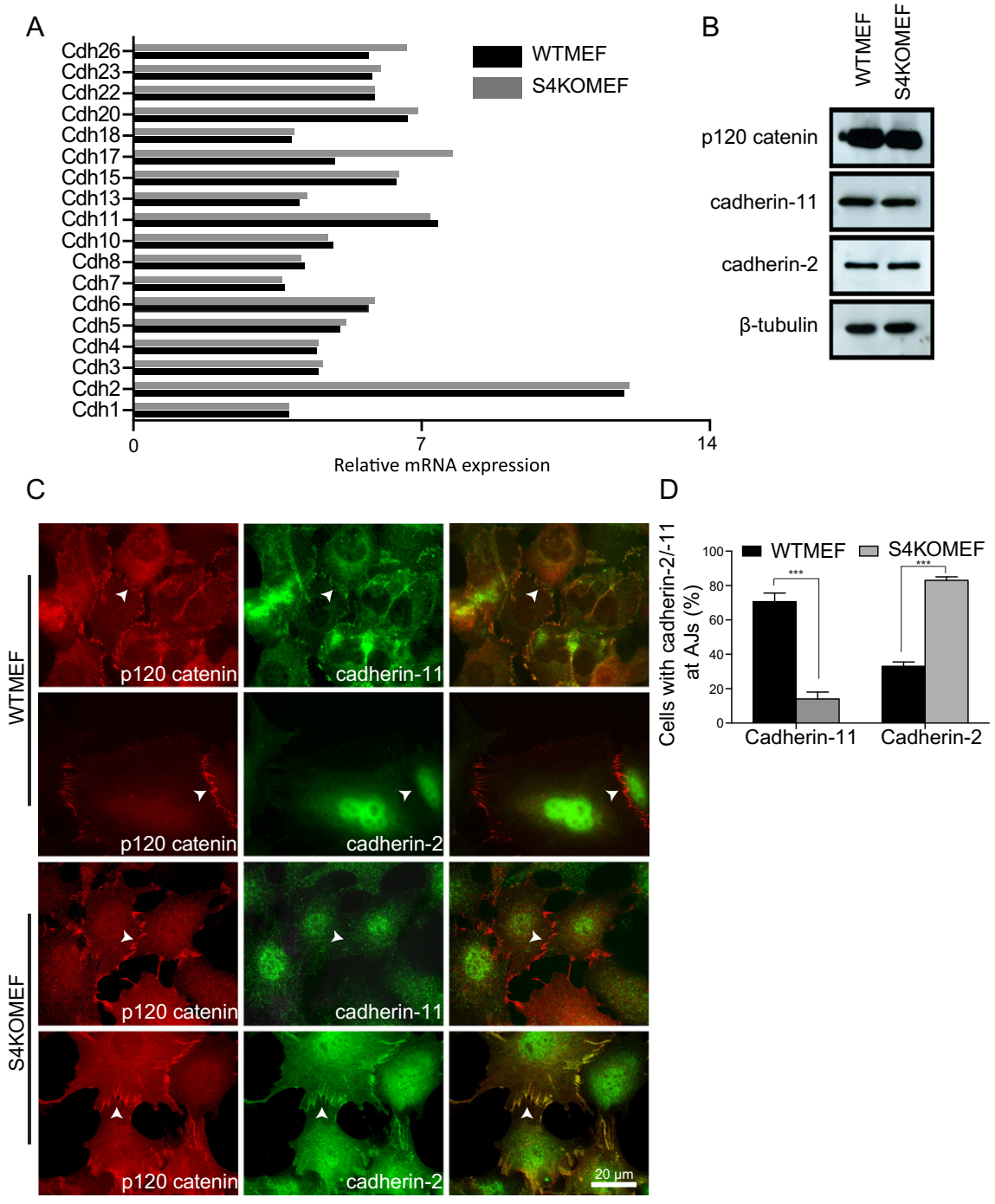

Fig. 1. Cadherin expression in wild type and syndecan-4 null fibroblasts. A. Microarray data shows that many of the principal cadherins are expressed at the mRNA level by wild type (WT) and syndecan-4 null (S4KO) fibroblasts. There is no significant difference in levels of expression between the two cell types. B. Levels of the two most abundantly expressed cadherins are similar in WT and S4KO fibroblasts at the protein level. Loading levels are shown by β-tubulin and p120 catenin. C. Cadherin-11 is characteristic of adherens junctions in WT mouse embryo fibroblasts (WTMEF), while cadherin-2 dominates in the S4KO cells (S4KOMEF). Junctions are marked in double immunofluorescence micrographs by p120 catenin. Single fluorescence and merged images are shown and cadherin frequency at adherens junctions (AJs) is quantitated in D. ***$p < 0.001$.