**Supplementary information S4. Mechanocoupling by desmosomes and intermediary filaments.**

Apart from tight and adherens junctions epithelial cells feature a third type of intercellular junctions called desmosomes, which are tightly associated with keratin (type of intermediary filaments)\(^1\,^2\). Desmosomes are composed of desmosomal cadherins, desmogleins and desmocollins, that form densely packed adhesion plaques anchored to keratins via plakoglobin and plakophilins\(^3\). Desmosomes contribute to the mechanical integrity of epithelia. For example, keratin-free cells display an increased deformability\(^4\). Further stabilization or destabilization of the interaction between desmosomes and intermediary filaments in human keratinocyte-like cells using mutant desmoplakins was associated with, respectively, strengthening or lowering cell stiffness as well as with increasing or decreasing forces at cell–cell and cell–matrix adhesions in cell pairs and sheets of cells\(^5\). In addition, these keratin-coupled adhesion complexes sense and respond to mechanical cues as do actomyosin-coupled adhesions\(^3\). Intermediate filaments act as stretch sensors, participating in mechanosensing and mechanotransduction\(^6\). However, since intermediary filaments proteins are diverse and their expression is tissue specific and developmentally regulated (only for epithelial cells, there is a combination of 54 keratin isoforms the expression of which is tissue- and environment- regulated) as well as strongly altered with cancer cell invasive capacities\(^7\) their roles in mechanical cell coupling are complex. Keratins 8 and 18 (K8 and K18) are simple epithelial cell-specific proteins and their knockdown in cancer cells increases intercellular cohesion, collective migration and invasiveness\(^8\). By contrast, K14 is upregulated in multicellular fingers pulled by leader cells in mouse mammary tumour organoids embedded in 3D collagen I matrix, replacing keratin 8. Knockdown of K14 is sufficient to block this collective invasion\(^9\). A similar upregulation of K6 or K16 and K17 at the wound edge of the epidermis to replace K1 has been reported\(^7\). The upregulation of vimentin, another intermediary filament protein marker of epithelial to mesenchymal transition, replacing keratins at the wound edge of MCF-17 cells has been reported, contributing to collective cell migration\(^10\). Moreover, there is evidence for direct interaction and mutual crosstalk between vimentin and focal adhesions, and in migrating cells, plectin — a constituent of focal adhesions — serves as a docking site for vimentin\(^7\,^11\). A crosstalk with mechanotransduction pathways at adherens junctions was also reported with a potential impact on the regulation of cell polarity in *Xenopus laevis* mesendoderm cells\(^12\). In these cells, increased tension applied at cadherin-based cell–cell contacts induced the relocalisation
of plakoglobin to the stressed cell–cell junctions. Plakoglobin then was found to drive the reinforcement and reorganization of intermediary filaments by recruiting keratin bundles to the stressed site, which induced a force-dependent, protrusive activity away from the direction of the applied force.

References