Mechanoelectrical transduction at the cell-substrate interface

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The ability of cells to sense and respond to their physical environment is fundamental to a broad spectrum of biological processes. Cells express an array of force sensors that can transduce mechanical inputs into biochemical signals, including mechanically activated (MA) ion channels. These ion channels form pores in the plasma membrane and their open probability increases with increasing mechanical input. Several tools have been developed to evoke mechanically-activated currents in order to study MA channel function and regulation. MA channels have traditionally been activated by membrane stretch (using high- speed pressure clamp) or cellular indentation (using a glass probe). More recently we have established a technique to apply deflection stimuli at the interface between cells and their substrate (using elastomeric pillar arrays as force transducers). Studying the activation of MA channels using this array of different techniques has highlighted how important context is in understanding MA channel activation: the PIEZO1 channel is activated by stretch, indentation and deflection and TRPV4 by deflection alone. As such, TRPV4 is only activated by mechanical stimuli when it is integrated into the cell-substrate interface. In addition, the mechanical properties of the substrate to which cells are bound can regulate the sensitivity of PIEZO1 and TRPV4, in a fashion dependent on cytoskeletal elements within the cell. We propose that the integration of transduction *via* multiple MA channels could engender cells with a tuneable and diverse repertoire of mechanical sensing.