

A novel 3D vertex model predicts the biomechanical factors of cell delamination in stratified epithelial tissues

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Multilayered epithelial tissues, such as skin and gut, comprise major organs in humans. These tissues perform multiple functions, including serving as a barrier to mechanical insults, and pathogens. They are constantly self-renewing while balancing proliferation in the basal layer with a tightly controlled differentiation program in which cells move upward while undergoing stepwise transcriptional and cell shape changes to form the distinct suprabasal layers. Misregulation of these self-renewal processes causes disease, including cancer and many inflammatory diseases. Understanding how mechanosensitive mechanisms at the scale of molecules couple to the collective mechanical behavior of the self-renewing tissue and help regulate stratified tissue homeostasis is thus essential. The stratified epithelium displays apico-basal polarization, with differential expression of polarity proteins across layers. It is not clear how stratified epithelial tissues like the epidermis integrate local and global changes in mechanochemical signals to allow single or multiple cells of the basal layer to differentiate and move upward crossing the sharp basal-suprabasal boundary. Here we develop a biomechanical model to help unravel such complexities. We use the model to investigate several experimentally-driven hypotheses for what drives delamination: i) changes in the adhesion of basal cells to extra cellular matrix in the basement membrane, ii) local fluidization of surrounding tissue due to fluctuations or nearby cell divisions, or iii) cell autonomous changes to cell-cell adhesion and cortical tension. Future work will also investigate cell-autonomous changes to cell mechanics during symmetric or asymmetric cell division.

We investigate these hypotheses using computational simulations of a novel dynamic 3D Vertex model of stratified epithelia, recently developed in our group. Experimental data from the developing mammalian epithelium in the Niessen and Wickström labs have identified specific changes to the transcriptome of cells committed to delamination. Many of these changes are associated with cell-cell and cell-substrate adhesion pathways. We incorporate them in the computational models as changes to the model parameters describing heterotypic and homotypic cell-cell interfacial tensions and adhesion to a fiber network substrate. We make quantitative predictions for cell shapes, delamination probabilities, and delamination speeds that we compare directly to experiments, in both control and perturbed systems, in order to determine how different mechanisms are driving delamination.

Abstract Category

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