Mechanical constraints to cell cycle progression in a pseudostratified epithelium

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Mechanical feedback has been proposed to constraint growth in developing epithelia. So far, much of the attention has been focused on the role of adherens junctions as mechanical sensors. Here we consider the possible role of mechanical influences that operate throughout the epithelial volume. This is particularly relevant in pseudostratified epithelia, where nuclei must migrate to the apical surface in order to proceed through mitosis. We explore how the mechanical constraints imposed by nuclear crowding and space confinement affect interkinetic nuclear migration and hence cell cycle progression. We develop an individual-based model that treats nuclei as deformable objects constrained by their cell membrane and the presence of other nuclei. In this model, the duration of G1 and S phase are imposed whereas the duration of the G2 phase is a read-out of the model. Our simulations recapitulate the increased crowding and number of nuclear layers observed in fixed tissues, and show how increase crowding impedes apical-ward movement, forcing nuclei more time in G2 before they can reach the apical surface for mitosis. The simulations also predicts that an active downward movement in G1 is required to reproduce the apical/basal distribution of nuclei in this phase, a prediction that we validate experimentally. Finally, we explore the necessity of a basal signal required for S phase entry, to account for the observed reduction of the G1 phase duration. Thus, while the crowding increases only the nuclei that are able to migrate to the basal region and back to the apical surface would be able to complete the cell cycle. Our two-gate model of cell cycle progression could account for the progressive slowing down of growth and the finite thickness of pseudostratified epithelia.