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Senescent fibroblasts: Passive players or deliberate drivers of melanoma initiation and progression

We have developed a hybrid cellular automata model of skin that focuses on key variables implicated in the regulation of normal homeostatic skin function. The model consists of discrete cellular species such as melanocytes, transformed melanocytes, keratinocytes, and fibroblasts, and continuous microenvironmental variables such as growth factors and extracellular matrix. The behavior of each of the discrete cell species is defined using life cycle flowcharts. Based on our current biological understanding, we developed a cell-cell interaction network which defines local interactions between cells and their microenvironment. These local interactions lead to the emergence of *in vivo* normal skin structure.

Using our model, we first examined how robust it was to perturbations. The model not only recovers from massive loss of its constituents but also finds an equilibrium after super-physiological deviations in microenvironmental factors present in normal skin. However, when the model was perturbed by factors not typically present in normal skin, such as proteases, its robustness was dependent upon the duration of exposure. With long-term exposure skin was transformed to a pathologic state. This implies that the regulation of microenvironmental factors contributes to skin transformation from a normal to an abnormal state. When fibroblasts age they can become senescent and start producing factors that may disrupt the skin homeostasis. We incorporated these phenotypic changes into our model to examine how these changes affect skin function. Simulations show that senescent fibroblasts can stimulate melanocyte growth and invasion. We also integrated transformed melanocytes into the model and show that they can exploit stromal activation (or senescence) and change skin structure significantly. Model simulations also provide a series of virtual skin pathologies that readily recapitulate a spectrum of true aberrant clinical pathologies.

To validate our model predictions, we carried out several *in vitro* experiments that showed senescent fibroblasts enhance the growth of both melanocytes and early-stage melanoma cells. Furthermore, we found that senescent fibroblasts enhance melanoma migration almost twice as much as normal fibroblasts. Based on our integrated computational/experimental perspective, we speculate that senescent fibroblasts may create a pro-oncogenic environment that synergies with mutations to drive melanoma initiation and progression.