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Getting old and misbehaving: Can stromal aging drive melanoma initiation?

We have implemented a hybrid cellular automata model of skin that focuses on key variables implicated in the regulation of normal homeostatic skin function and its disruption in melanoma initiation and progression. The model consists of both 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 experimental observations, we know that when fibroblasts age they can become senescent and start producing factors that may disrupt the very homeostasis that they should maintain. We incorporate these phenotypic changes as fibroblasts age and use our model to examine how these changes affect skin function.

Specifically, we examined the effects of disrupting interactions between melanocytes, keratinocytes, fibroblasts and their microenvironment and the role of aged fibroblasts in driving melanoma initiation. Model simulations provide a series of virtual skin pathologies that readily recapitulate a spectrum of true aberrant clinical pathologies. Direct comparison between these pathologies allowed us to find the critical perturbations that drive melanoma initiation and progression. We also utilize an *in vitro* 3D organotypic skin model to further investigate some of the model predictions.