Reconstruction of dynamic mammary mini gland in vitro for normal physiology and oncogenesis

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Abstract

Organoid culture has been extensively exploited for normal tissue reconstruction and disease modeling. However, it is still challenging to establish organoids that mimic in vivo-like architecture, size and function under homeostatic conditions. Here we describe the development of a long-term adult stem cell-derived mammary mini gland culture system that supports robust three-dimensional outgrowths recapitulating the morphology, scale, cellular context and transcriptional heterogeneity of the normal mammary gland. The self-organization ability of stem cells and the stability of the outgrowths were determined by a coordinated combination of extracellular matrix, environmental signals and dynamic physiological cycles. We show that these mini glands were hormone responsive and could recapitulate the entire postnatal mammary development including puberty, estrus cycle, lactation and involution. We also observed that these mini glands maintained the presence of mammary stem cells and could also recapitulate the fate transition from embryonic bipotency to postnatal unipotency in lineage tracing assays. In addition, upon induction of oncogene expression in the mini glands, we observed tumor initiation in vitro and in vivo in a mouse model. Together, this study provides an experimental system that can support a dynamic miniature mammary gland for the study of physiologically relevant, complex biological processes.