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Spatiotemporal reprogramming of differentiated cells underlies regeneration and neoplasia in the intestinal epithelium

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Although the mammalian intestinal epithelium manifests robust regenerative capacity after various cytotoxic injuries, the underlying mechanism has remained unclear. Here we identify the cyclin-dependent kinase inhibitor p57 as a specific marker for a quiescent cell population located around the +4 position of intestinal crypts. Lineage tracing reveals that the p57^{+} cells serve as enteroendocrine/tuft cell precursors under normal conditions but dedifferentiate and act as facultative stem cells to support regeneration after injury. Single-cell transcriptomics analysis shows that the p57^{+} cells undergo a dynamic reprogramming process after injury that is characterized by fetal-like conversion and metaplasia-like transformation. Population-level analysis also detects such spatiotemporal reprogramming widely in other differentiated cell types. In intestinal adenoma, p57^{+} cells manifest homeostatic stem cell activity, in the context of constitutively activated spatiotemporal reprogramming. Our results highlight a pronounced plasticity of the intestinal epithelium that supports maintenance of tissue integrity in normal and neoplastic contexts.

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