A synthetic circuit architecture for mutant stem cell suppression

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Summary

Stem-cell differentiation is a crucial multicellular trait. However, it is inherently susceptible to mutant stem cells that fail to differentiate. These mutants outcompete normal stem cells by excessive self-renewal, driving certain cancers. It remains unclear what mechanisms can suppress such mutations. Here we demonstrate a solution by engineering a synthetic differentiation circuit in Escherichia coli that selects against these mutants. The circuit provides tunable production of stem, progenitor, and differentiated cells, and resists mutations by coupling differentiation to production of an essential enzyme — disadvantaging non-differentiating mutants. The circuit selected for positive differentiation rate and maintained this rate in long-term evolution. Surprisingly, the rate remained constant across vast changes in growth conditions. We found that transit-amplifying cells underlie this environmental robustness, suggesting similar roles for such cells in mammals. Our results provide insight into stability of natural differentiation and demonstrate a powerful method for engineering consistent cell-type ratios in multicellular consortia.