Organ-specific Stochastic Phenotype Switching is Required for Endothelial Health

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Among unicellular organisms, stochastic phenotype switching is a documented strategy for survival. These populations "hedge their bets": while the majority of their cells are adapted to their present environment, a minority remains poised to thrive under drastically different conditions. Bet hedging has also been described in metazoan cells, primarily in vitro. However, its role in tissue homeostasis has yet to be established. Here, we show that von Willebrand factor (vWF) is expressed in a spatially heterogeneous manner in a small fraction of capillary endothelial cells in the heart, skeletal muscle, lung and brain. Moreover, these mosaic patterns are dynamic, in that vWF expression stochastically toggles ON/OFF over time. By contrast, expression of vWF in the aorta and liver is static in time. In cultured primary endothelial cells, biological noise resulted in mosaic vWF heterogeneity through a promoter-level DNA methylation switch. Finally, vWF/-/- mice demonstrated extensive endothelial cell damage in capillaries of the heart and impaired cardiac function, but not kidney or aorta. Taken together, these findings suggest that dynamic mosaicism of vWF expression is functionally relevant and that bet hedging represents a previously unrecognized strategy for adaptive, organ-specific homeostasis.