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Wnt/Notum spatial feedback inhibition controls stem cell activity to regulate planarian brain size in a program of reversible regenerative growth

Awardee: Christian P. Petersen Award: New Innovator AwardEric Hill and Awardee Institution: Northwestern University

Co-author: Eric Hill Co-author Institution: Northwestern University

Signaling pathways that influence growth have been described in detail, but the developmental mechanisms that direct organ size and proportion are incompletely understood. Animals capable of adult regeneration perfectly restore their form after injury, providing an informative model for identification of processes that enable attainment of appropriate size. The planarian Schmidtea mediterranea can undergo whole-body regeneration due to a population of adult pluripotent stem cells as well as information that coordinates their activity, and is capable of reversible and proportional growth over an order of magnitude in size by regulating cell number. Using quantitative assays of regeneration extent, we find that planarians proceed from divergent initial tissue compositions created by injury toward a final form with appropriate organ proportions. We find that planarian notum and wntA, expressed at opposite axes of the planarian brain, exert opposing functions on brain proportion in contexts of both regenerative growth and degrowth. Notum proteins are conserved secreted hydrolases that antagonize Wnt signaling through an unknown mechanism. Double RNAi and expression analyses suggest that notum engages in feedback inhibition of wntA to control a set-point of brain size attained by divergent regeneration programs. This signaling does not modulate injury-induced cell death or global proliferation but instead directs the neural specification of neoblasts, a cell population that contains adult pluripotent stem cells. These results indicate spatial feedback inhibition can regulate organ size through stem cell control and establish planarians as a system for studying the developmental mechanisms that enable proper growth.