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Dynamic Changes in microRNAs may Regulate Robustness of Wnt/Notch Signaling

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The mechanisms by which highly reproducible patterns are formed during embryonic development and organismal evolution despite stochasticity at the single cell level is one of the remaining mysteries in Biology. It has been proposed that a hidden layer of regulation formed through the interaction of microRNAs with protein coding gene networks maybe responsible. Recently developed next generation sequencing technologies afford an unprecedented opportunity to uncover novel aspects of miRNA function and evolution. We find extensive heterogeneity in sequences that correspond to mmu-let-7 (targets Wnt1) and mmu-miR-191 (targets Notch1). Approximately 20% of let-7 and miR-191 have undergone modifications to increase stability and binding to the Wnt1 and Notch1 targets and are likely to be destroyed. In contrast, 80% bind the targets with imperfect complementarity and lower stability and are likely to be sequestered and prevented from forming protein. We propose that these two species together form a highly fluid system that is able to absorb stochastic perturbations in gene expression. A gene that goes on to be translated into functional protein therefore must escape both buffers by significantly high expression.