Signal fold-change controls pattern formation

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Short Abstract — Biological signals are encoded and interpreted dynamically while embryos develop characteristic patterns, whose sizes scale with tissue sizes even when cell numbers or sizes are changed. Despite long-lasting efforts, signal encoding of positional information for vertebral segmentation remained elusive. To address this fundamental question, we developed a novel zebrafish explant system that recapitulated scaling of segment sizes in growing embryos. We then performed surgical and pharmacological experiments, quantified segment scaling and computationally modeled the signaling network. The results strikingly showed a previously unnoticed mechanism that a spatial signal differentiator circuit encodes the positional information for segmental determination and pattern scaling.

Keywords — pattern formation, scaling, segmentation, cell signaling, morphogen gradient, fold-change, systems biology, mathematical modeling.

I. BACKGROUND

Vertebrate embryos pattern their major body axis as segmented somites—premiers of vertebrae. Segmentation is versatile with different segment numbers and periodicity among species but is also very precise leading to the same segment number and size distribution within a given species [1]. Pattern formation is regulative; embryos form a fixed number of patterns and the sizes of patterns scale with body or tissue sizes even when total cell number, cell sizes or growth rate are changed experimentally [2,3]. To explain this extraordinary scaling behavior, Wolpert’s positional information model proposes that commitment of a cell to a given state depends on its interpretation of a graded molecule across tissue at a constant threshold [4]. The clock and wavefront (CW) model was built on the positional information model to explain periodic and precise segmentation of somites by the interaction of the segmentation clock and a posteriorly-moving morphogen gradient (wavefront) [5]. Pioneering discoveries of molecular oscillators and signaling gradients supported this model [6]. Although extended variants of constant-threshold gradient interpretation models have been proposed, a recent work has challenged current CW models and instead proposed a Turing-type reaction diffusion model to explain segment patterning [7]. Thus, there is still a lack of consensus on this fundamental question in development, and the precise mechanism underlying segment patterning and scaling remains to be determined.

II. RESULTS

Segment sizes are determined by the posterior regression of wavefront during a segmentation clock cycle. Wavefront regression depends both on the speed of tail elongation, which varies throughout somitogenesis [1], and the dynamics of the yet-to-be discovered molecular circuit encoding the wavefront. Coupling of tail growth and wavefront regression speeds poses a great challenge for obtaining quantitative data to discriminate competing models for pattern formation and scaling. To that end, we developed a 3-D zebrafish tail explant system where we prevented tail growth and recapitulated scaling of somite segment sizes as observed in growing embryonic tails. We carried out predictive surgical and pharmacological experiments, quantified changes in segment scaling and computationally modeled the system. The results disfavored both variants of the constant threshold CW models as well as the new Turing-type model. We found that a spatial fold-change of signaling encodes the positional information of the wavefront for segmental determination and pattern scaling [8].

III. CONCLUSION

Our results showed that cells compare the fold-change in signal with neighbors to accurately interpret positional information along the tissue and commit to segmentation and differentiation at appropriate sites. The mechanism controlling somite segment scaling discovered here is strikingly different from previously studied scaling examples as patterning is not achieved at steady-state and scaling is not achieved via scaling of the morphogen gradient [3].

REFERENCES


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