Quantitative analysis of Nodal/Lefty-mediated pattern formation

Informe

Información del proyecto

QUANTPATTERN

Identificador del acuerdo de subvención: 637840

Sitio web del proyecto

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10.3030/637840

Proyecto cerrado

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Periodic Reporting for period 4 - QUANTPATTERN (Quantitative analysis of Nodal/Lefty-mediated pattern formation)

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Resumen del contexto y de los objetivos generales del proyecto

How a homogeneous population of cells self-organizes to form a patterned embryo is a long-standing mystery in the field of developmental biology. In 1952, Alan Turing postulated the reaction-diffusion model to explain how embryos might self-organize to develop tissues and organs. The reaction-diffusion model comprises a system of two diffusible substances that must satisfy two requirements in order to form a pattern: (i) one substance activates its own production and is inhibited by the other, and (ii) the diffusivity of the inhibitor has to be higher than the diffusivity of the activator. Genetic and embryological experiments suggest that several patterning events in developing embryos are controlled by reaction-diffusion systems, but a mechanistic, quantitative understanding of how these systems dynamically control robust pattern formation in developing tissues has been lacking.

It has been proposed that the two developmental signals Nodal and Lefty form a reaction-diffusion system during tissue patterning. Within the QUANTPATTERN project, we focused on three key questions about how the Nodal/Lefty system leads to patterning. First, how do activator/inhibitor pairs such as Nodal and Lefty achieve their different diffusivities despite their high sequence similarity and similar molecular weights? Second, how does the range of reaction-diffusion systems such as Nodal and Lefty adjust to natural fluctuations in embryo size? Finally, how do reaction-systems such as Nodal and Lefty self-organize to induce spatially restricted tissues in the absence of pre-patterns?

The QUANTPATTERN project used a combination of quantitative experimental and theoretical approaches to address these questions and had three major aims:

Aim 1: Identify the factors regulating the dispersal of Nodal and Lefty during zebrafish development
Aim 2: Determine how the Nodal/Lefty system mediates scale-invariant patterning of zebrafish embryos
Aim 3: Quantitative analysis of self-organized patterning in mouse embryonic stem cells

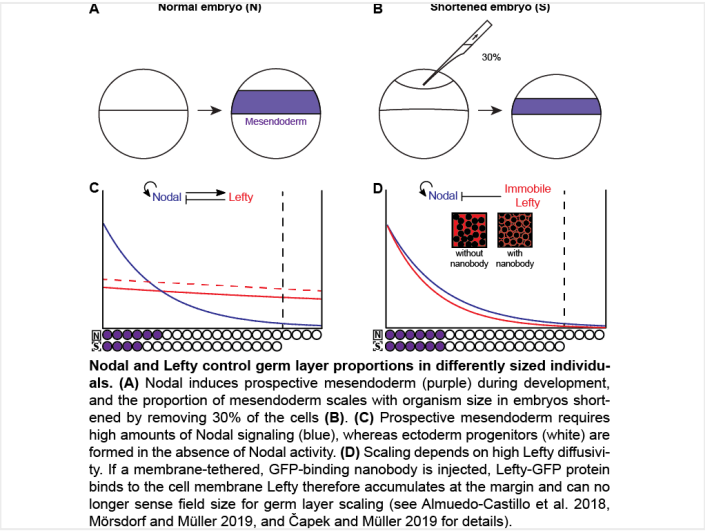
Trabajo realizado desde el comienzo del proyecto hasta el final del período abarcado por el informe y los principales resultados hasta la fecha

We have made new discoveries for all three research aims of the QUANTPATTERN project. To identify factors regulating Nodal and Lefty dispersal during zebrafish development, we generated mutations in candidate diffusion regulators and optimized unbiased screening approaches, subcellular localization methods, and biophysical measurement techniques. Our findings point to a major role of specific receptors in regulating Nodal diffusion and tissue distribution. To understand how the Nodal/Lefty system mediates scale-invariant patterning of zebrafish embryos, we have performed large-scale computational screens and identified realistic signaling networks. Using quantitative experimentation and systems biology approaches, we have systematically tested the predictions of the resulting models. Our work demonstrated that a size-dependent increase in Lefty levels is crucial to adjust Nodal-dependent germ layer proportions in smaller embryos. Finally, to understand self-organized patterning in mouse embryonic stem cells, we have quantitatively characterized the kinetics of developmental markers during embryoid body formation using live imaging by light-sheet

fluorescence microscopy. Based on a mathematical screen for gene regulatory networks that can drive self-organization in mouse embryonic stem cells, we have developed realistic models to explain how Nodal signaling controls symmetry breaking and self-organized patterning.

Avances que van más allá del estado de la técnica e impacto potencial esperado (incluida la repercusión socioeconómica y las implicaciones sociales más amplias del proyecto hasta la fecha)

In summary, the QUANTPATTERN project has identified and characterized mechanisms underlying spatial regulation of germ layer patterning and improved our molecular understanding of signal movement and tissue distribution. Our experimental and theoretical work on self-organized patterning has the potential to inform new strategies for human tissue engineering from embryonic stem cells.



Nodal and Lefty control germ layer proportions in differently sized individuals. (A) Nodal induces prospective mesendoderm (purple) during development, and the proportion of mesendoderm scales with organism size in embryos shortened by removing 30% of the cells **(B)**. **(C)** Prospective mesendoderm requires high amounts of Nodal signaling (blue), whereas ectoderm progenitors (white) are formed in the absence of Nodal activity. **(D)** Scaling depends on high Lefty diffusivity. If a membrane-tethered, GFP-binding nanobody is injected, Lefty-GFP protein binds to the cell membrane Lefty therefore accumulates at the margin and can no longer sense field size for germ layer scaling (see Almuedo-Castillo et al. 2018, Mörsdorf and Müller 2019, and Čapek and Müller 2019 for details).

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