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Signals, grids, and geometry: In pursuit of understanding cell fate switches

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After a degree in Biology at the University of Nottingham in the early 90s, I studied for a PhD focusing on frog endoderm formation with Prof. Hugh Woodland at the University of Warwick (Hudson et al., 1997). When I was looking for a lab to do postdoctoral studies, I was undecided whether to continue with *Xenopus* or switch to a different system. My fate was sealed at a postdoc interview with Patrick Lemaire at the IBDM in Marseille when I caught his enthusiasm for ascidian embryos, although at that time his lab was still working only with *Xenopus*. I accepted the challenge to help him establish ascidians as a model in the lab, but with hindsight I was a little naive, not realizing how much of a challenge it was going to be! During this period, we were fortunate to also have help from experienced ascidian embryologists Hitoyoshi Yasuo and Sébastien Darras. What attracted me most about ascidian embryos, as a developmental biologist, was the invariant cell division pattern and lineage, which is extremely useful, as it allows one to identify and name the same cell in every embryo and thus to know the embryonic origin and eventual fate of cells as they progress through each developmental transition. In that pre-genomic era, I started off looking for homologues of vertebrate regulatory genes using degenerate PCR. A breakthrough came when I isolated a couple of genes expressed in neural tissue (*Otx* and *Gsx*) and the next step of my adventure with ascidians began. In Patrick's lab, I focused mainly on neural induction in ectoderm cells ("brain" induction) and the role of the FGF-ERK signaling pathway, work which contributed to a more molecular understanding of this process (Hudson & Lemaire, 2001). In 2003, I became a staff scientist of the Centre National de Recherche Scientifique (CNRS), joining the "Cell

Fate" team led by Hitoyoshi Yasuo ("Yas") in the Laboratoire de Biologie du Développement de Villefranche-sur-mer (LBDV).

My studies were greatly inspired by beautiful descriptions from the laboratory of Dr. Ian Meinertzhagen, showing the regular grid-like organization of the developing neural plate and the ordered pattern of neural plate cell divisions (Nicol & Meinertzhagen, 1988). These neural plate maps helped us show that each neural plate cell is characterized by a unique gene expression profile (Esposito et al., 2016; Hudson et al., 2007; Hudson & Lemaire, 2001; Hudson & Yasuo, 2005). We could then show how the neural plate is patterned across the medial-lateral axis by Nodal and Delta/Notch signals and along the anterior-posterior axis by differential ERK activity (Esposito et al., 2016; Haupaix et al., 2014; Hudson et al., 2007; Hudson & Yasuo, 2005; Figure 1a). Remarkably, within each neural lineage, each precursor receives a unique combination of signaling pathways, promoting its unique transcriptional state (Figure 1a).

More recently, we have teamed up with computational chemists, forming the "ERKtivation" team (Figure 2), in a project addressing a fundamental problem of how cells can interpret noisy or graded signals to make decisive cell fate decisions. The project focuses on the very first step of neural induction in ectoderm cells at the 32-cell stage. We have adopted quantitative and computational approaches to try to understand how, during this process, among the eight cells of the anterior ectoderm, one pair of neural precursors is specified in the same position in every embryo (pink cells in Figure 1b; Bettoni et al., 2023; Guillaume et al., 2021). We found that, in each ectoderm cell, ERK activation levels correlate with the area of the cell in contact

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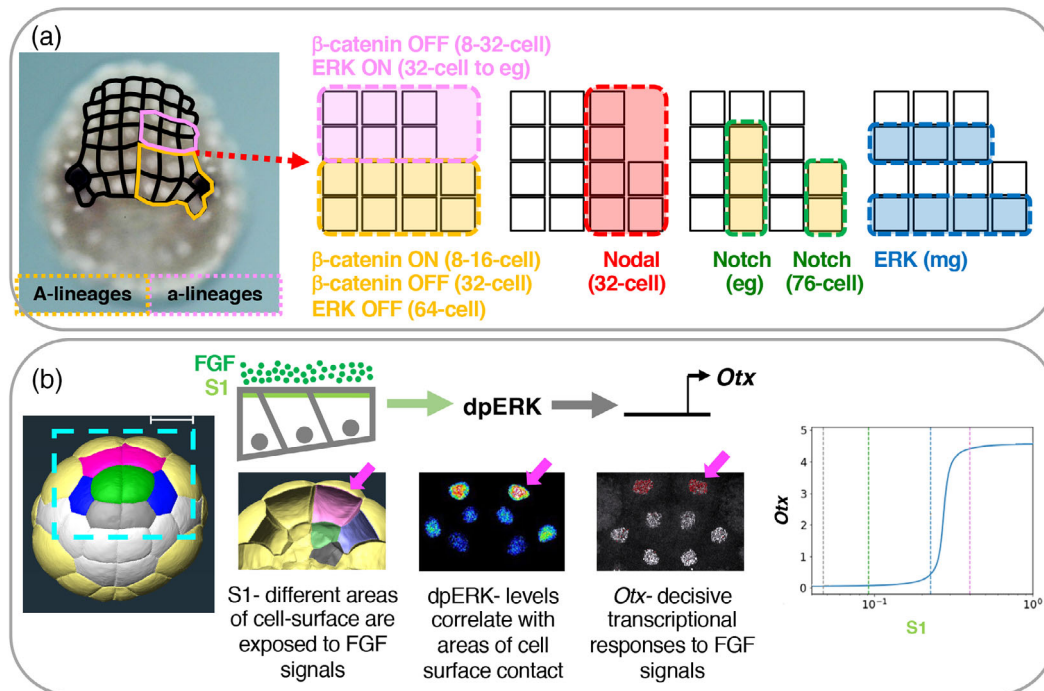


FIGURE 1 (a) Patterning and specification of the grid-like array of cells in the neural plate of the mid-gastrula stage embryo. From left to right. A composite image of a mid-gastrula stage embryo labeled for *Ebf/Coe* (*KH2012:KH.L24.10*) expression (dark brown) counter stained with DAPI (white). An overlay highlights the grid-like organization of the cells in the neural plate. At this stage, embryos are bilaterally symmetrical. On the right half of the embryo, orange bordered cells (A-lineage) are vegetal-hemisphere-derived central nervous system (CNS) precursors and pink-bordered cells (a-lineage) are animal-hemisphere derived CNS precursors. The four schematics composed of grids of squares represent the right-hand side neural plate CNS precursors and a summary of the specification/patterning mechanisms. Mechanisms of neural fate specification involve β -catenin and ERK signaling and are distinct between A- and a-lineage cells (reviewed in [Hudson & Yasuo, 2021]). Patterning across the medial-lateral axis of the neural plate involves Nodal and Delta/Notch signaling and patterning along the anterior-posterior axis of the neural plate depends upon differential ERK activation. The timing of specification/patterning is indicated with the cell stage; eg- early gastrula; mg- mid gastrula. (b) Early neural induction as a model for a switch-like response. From left to right. In silico reconstructed embryo with anterior ectoderm precursors colored pink (neural precursor), blue (mixed neural-epidermis precursor), green (ectoderm precursor), gray (ectoderm precursor); mesendoderm precursors are in yellow (source of FGF) and other ectoderm cells in white. The blue dashed box indicates the area shown in the photo panels, in which the neural precursors are indicated with a pink arrow. Top is a schematic representation of the FGF-mediated induction. Ectoderm cells (gray boxes) have different areas of their cell surface (pale green, S1) exposed to FGF-ligands (green dots). In the photo panel “S1” is shown in an in silico reconstructed embryo with the ectoderm cells computationally removed, revealing the surface area (colored) of each ectoderm cell that was in contact with the FGF expressing mesendoderm precursors. FGF signals lead to ERK activation, as shown in the pseudo color look up table image of nuclear dpERK signals. *Otx* activation is shown as segmented dots in the nucleus with a counter DAPI staining in white. The graph on the right shows a computer simulation of the relationship between the area of ectoderm cells that are in contact with FGF-expressing cells (S1) and the *Otx* activation response, showing a very steep, decisive relationship. Colored dashed lines represent the respective S1 values of the four anterior ectoderm cell types. ephrin signals arise from between the ectoderm cells themselves and for simplicity are not indicated here. Figure adapted from (Bettoni et al., 2023; Guillaume et al., 2021).

with both FGF-expressing mesendoderm cells and ephrin-expressing ectoderm cells (shown for FGF in Figure 1b). This rather gradual ERK activation response is converted into a steep transcriptional response of the immediate-early gene, *Otx*, so that its expression is restricted to neural precursors. A “dampening” effect by ephrin is critical to keep ERK levels below the threshold for *Otx* induction in non-neural ectoderm. We are now trying to understand mechanistically how the *Otx* transcriptional switch-like response to ERK is generated. We hope to continue with this collaborative approach, which has so far been both very challenging and a very exciting and rewarding experience, helped along by many states of bewilderment, scribbled explanations, and good humor.

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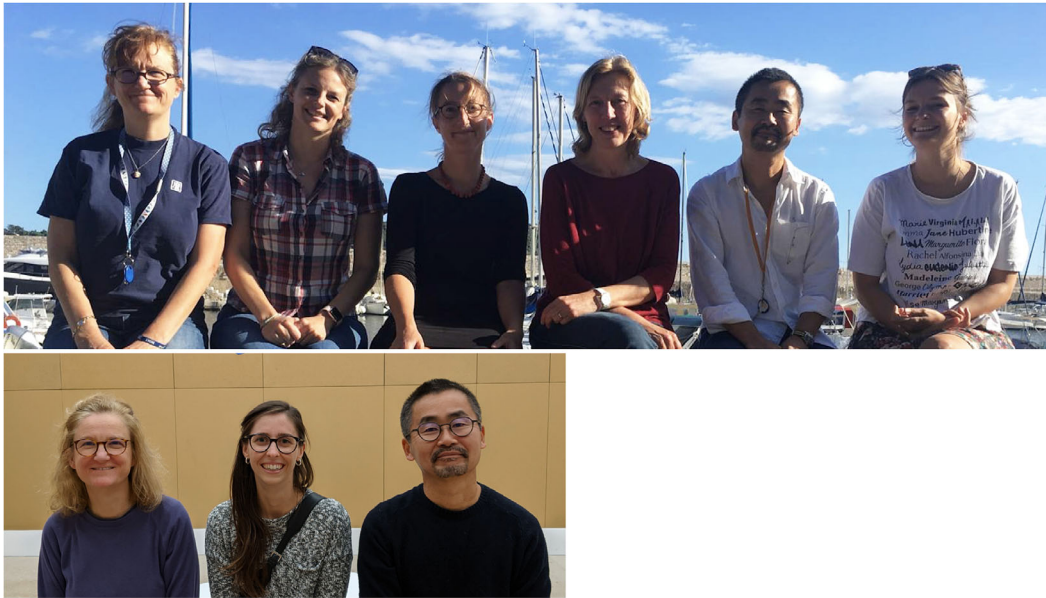


FIGURE 2 Top: “ERKtivation” team meeting in Villefranche-sur-mer, October 2019. From left: Clare Hudson, Cathy Sirour, Sophie de Buyl, Geneviève Dupont, Hitoyoshi Yasuo and Géraldine Williaume. Left: with Rossana Bettoni, during her visit to Villefranche-sur-mer, November 2022. Affiliations: CH, CS, HY, GW (LBDV, France); SdB, RB (Vrije Universiteit and Interuniversity Institute of Bioinformatics in Brussels, Brussels, Belgium); GD, RB (Université Libre de Bruxelles, Belgium).

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