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How animals get their skin patterns: fish pigment pattern as a live Turing wave

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ABSTRACT It is more than fifty years since Alan Turing first presented the reaction-diffusion (RD) model, to account for the mechanism of biological pattern formation. In the paper entitled "The chemical basis of morphogenesis", Turing concluded that spatial patterns autonomously made in the embryo are generated as the stationary wave of the chemical (cellular) reactions. Although this novel idea was paid little attention by experimental biologists, recent experimental data are suggesting that the RD mechanism really functions in some of the course of animal development. Among the phenomena in which involvement of the RD mechanism is suspected, the striped pigment pattern of zebrafish has been highlighted as an ideal model system for the following reasons: the stationary wave made by the RD mechanism stays alive and can be observed only in the fish skin; and in zebrafish, we can utilize genomic information and molecular genetic techniques to clarify the molecular basis of pattern formation. In this review, we summarize recent progresses in the study of zebrafish pigment pattern formation that is uncovering how the RD wave is made and maintained in the skin.

KEY WORDS: *pattern formation, reaction-diffusion system, zebrafish, pigment cell, Turing*

Mechanisms of biological pattern formation

One of the major issues in developmental biology is how positional information is laid down in the tissues and bodies of animals. Research in molecular genetics during the past three decades has proved that eggs already possess a substantial degree of positional information as evidenced by the localized distribution of key molecules proteins or ribonucleic acids (RNAs). (Gilbert, 2003; Wolpert, 2006) Cells in an embryo are able to read their position from the concentration of such molecules, and are thereby induced to undergo position-specific differentiation. The differentiated cell can produce signaling molecules that are used as secondary positional information. By repeating this induction cascade, it is theoretically possible to determine positional information in later stages.(Wolpert, 1969; Wolpert, 1989) This simple mechanism, generally called “pre-pattern theory” or “morphogen theory,” has been experimentally proved in many morphogenetic events in early development, and is widely accepted as a mechanistic principle that functions when spatial patterns are laid down in the embryos. However, this simple mechanism is apparently not fully capable of accounting for the complex structures of the adult body because its complexity far exceeds the positional information of the egg.

Moreover, many examples have shown that animal development is quite robust against the artificial disturbance of primary structures. For example, hydra can regenerate correct structures from an aggregate of dispersed cells.(Bode, 2003; Guder *et al.*, 2006; Wolpert *et al.*, 1971) When a planarian is cut into pieces, the complete structure is regenerated from each piece(Agata *et al.*, 2007; Best and Morita, 1982), suggesting that there is no fixed origin of a “morphogen.” This amazing robustness of animal development implies the existence of the second principle of spatial pattern formation, which is independent of the pre-existing

Abbreviations used in this paper: RD, reaction-diffusion; RNA, ribonucleic acid.

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positional information that is established in the egg.

RD mechanism: an autonomous mechanism that can generate the spatial pattern

There are several theoretical mechanisms that are able to generate spatial patterns autonomously without any pre-pattern (Meinhardt, 1982; Murray and Oster, 1984). Among them, one of the most plausible in biological systems is the reaction-diffusion (RD) mechanism which was first presented by A. Turing in 1952 (Gierer and Meinhardt, 1972; Turing, 1952), and mathematically refined by mathematical biologists (Meinhardt and Gierer, 2000a; Murray, 2003). In the model, the spatial pattern is made as stationary waves generated by the interactive RD of putative chemical substances. According to mathematical modelling using computer simulation, an RD system is able to generate stable and evenly-spaced patterns when the whole network satisfies a condition of “local activation and long range inhibition.”(Meinhardt and Gierer, 2000a) The spatial patterns made by the system (e.g.,”RD pattern” or “Turing pattern”) do not need any pre-pattern, and autonomously regenerate when artificially disturbed. In the 1970s, extensive computational studies showed that the RD model can reproduce a variety of morphogenetic phenomena of animal development, those that the pre-pattern model cannot explain. (Meinhardt, 2003; Murray, 2003)

However, in spite of its theoretical importance, until very recently, Turing's theory was not widely accepted by experimental biologists for two major reasons. First, the main concept of the theory, namely that the pattern is made by a wave, is quite unfamiliar to many experimental biologists. Second, it is difficult to prove the existence of such a wave by some experiment. In order to prove that the RD mechanism functions in a particular morphogenetic event, we need to show that the pattern possesses the dynamic nature of the RD wave.

Morphological phenomena in which the involvement of the RD mechanism is suspected

For about 40 years after Turing’s original work, studies of RD mechanisms were almost exclusively theoretical, and there was little convincing experimental evidence for Turing patterns in any system, biological or otherwise. The first clear experimental support for this mechanism came in chemical experiments in the early 1990s. Castets et.al. and Ouyang et. al. succeeded in making the Turing pattern using complex chemical reactions. (Castets *et al.*, 1990; Ouyang and Swinney, 1991) These works encouraged biologists to study the theoretical mechansim, and Kondo and Asai found that the pigmentation pattern on the skin of an angel fish moved exactly in the manner that Turing’s theory predicted (Kondo and Asai, 1995).

They recorded the pattern change of the pigment pattern of a marine angelfish, *Pomacanthus imperator*, and suggested that the time course of the pattern change is identical to that predicted by Turing’s theory. The involvement of the Turing mechanism is now seriously investigated experimentally in several morphological events; hair pattern of mammals (Jung *et al.*, 1998; Nagorcka, 1983; Sick *et al.*, 2006), feather patterns of birds (Harris *et al.*, 2005; Jiang *et al.*, 2004; Prum and Williamson, 2002), regeneration of hydra (Bode, 2003; Gierer *et al.*, 1972; Technau *et al.*, 2000) and right-left determination in the vertebrates (Hamada *et al.*, 2001; Hamada *et al.*, 2002; Nakamura *et al.*, 2006). In these cases, candidates for the core functional molecules of pattern formation were proposed.

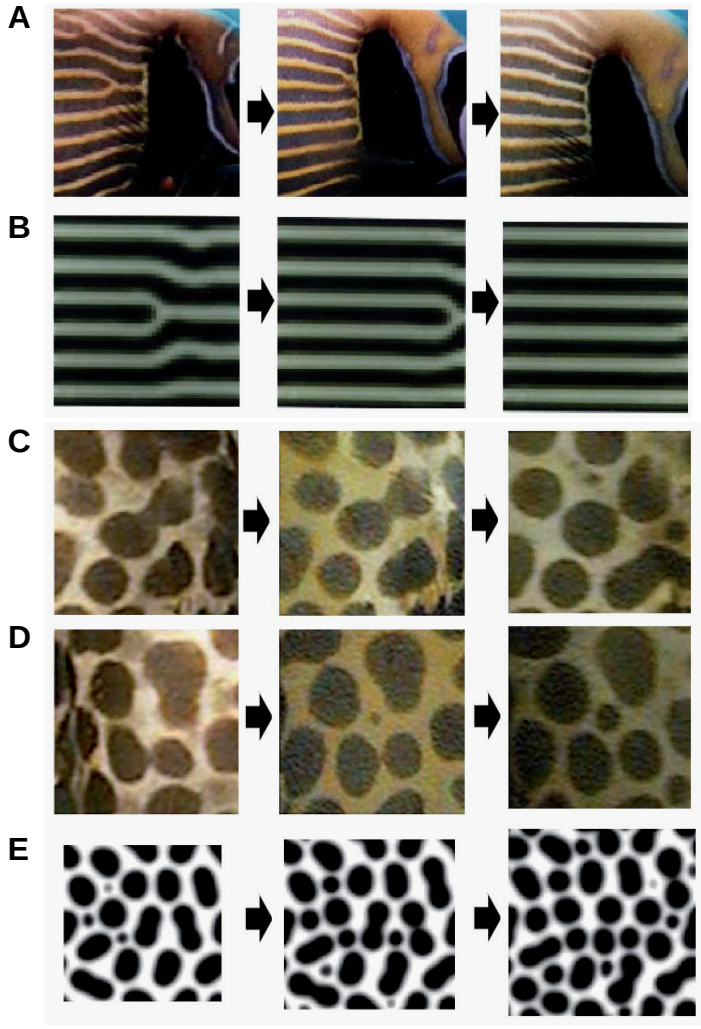

Fig. 1. Dynamic pattern change in the fish and simulation. (A) *Change of stripe pattern in the skin of* Pomacanthus *imperator during 90 days and* **(B)** *the prediction made by simulation of a reaction diffusion mechanism. Sliding of the branch point is observed in both systems. Change of spot pattern occurring in the skin of a catfish,* Plecostoms sp*., during 14 days* **(C,D)** *and the simulation* **(E)**. *Division (C) and insertion (D) of the spot are observed in both real fish and in the simulation based on the RD model. From (Kondo and Asai, 1995) and (Asai* et al.*, 1999).*

For example, in the case of the mouse hair pattern, Sick et. al. suggested that the WNT and DKK proteins play the role of the putative activator and inhibitor in the reaction-diffusion system (Sick *et al.*, 2006). Moreover, by artificially changing the parameters of the interactions, it is possible to induce the pattern change that is predicted from the simulation, suggesting that an RD mechanism underlies the determination of the hair distribution (Sick et al., 2006). However, most of these morphogenetic events are irreversible, and the patterns that we can observe are completed and fixed ones. Therefore, it is usually impossible to directly detect the existence of the ”wave” in the course of the

pattern-forming event.

Characteristic movement of the RD wave is visible in the animal skin

To date, pigmentation patterns in animal skins (Murray *et al.*, 1990; Murray and Oster, 1984), feathers of birds (Harris *et al.*, 2005; Prum and Williamson, 2002), and shells of the snails (Meinhardt, 2003) are the only examples in which we can detect the dynamic nature of Turing waves as a time course of the pattern change. Especially, the 2D skin pattern of the fish is quite convenient to study because waves are sometimes active even when the fish has reached adulthood.

For example, when a striped angel fish (*Pomacanthus imperator*) grows, the branching points of the stripes slide horizontally as the zip opens, and add a number of stripes; eventually the spacing between the stripes remains stable (Fig. 1A) (Kondo and Asai, 1995). In the case of spotted catfish (*Plecostoms sp.*), both division of the spots and insertion of the new spots occur to retain the density and size of the spots (Fig. 1B) (Asai *et al.*, 1999). Both stripes and the spots are the most typical 2D patterns generated by the RD mechanism, and the time course of the pattern change possesses the characteristics of the dynamics of RD waves, strongly suggesting that the RD mechanism underlies the process of pigment-pattern formation of fish.

Zebrafish as a model system for studying patterning mechanisms

In order to understand the principles of autonomous pattern formation controlled by the dynamic mechanism, it is important to identify the molecular-level network that functions in skin pattern formation of fish where the wave is active. Observation on the dynamics of the molecules related to the RD pattern formation would dramatically contribute to our understanding of how animals keep the stable structure under an environment that is full of disturbances. Fortunately, zebrafish, a small fish species with very clear stripes in their trunk and fins, was selected as a model animalÄfor biological studies, and for the use of the genomic information and molecular-genetic technologies that are available to identify the molecular mechanism of pigment-pattern formation.

The pigment pattern of zebrafish retains the dynamic nature of the RD wave during the post embryonic stage

The pattern of skin pigmentation in zebrafish is composed of three types of pigment cells distributed in the hypodermis: melanophores, the main component of dark stripes; xanthophores, the main component of light stripes; and iridophores (Hirata *et al.*, 2003; Kelsh, 2004). Although different from the stripes of *Pomacanthus imperator*, the stripes of zebrafish do not become rearranged during normal growth, artificial disturbance of the pattern can induce the characteristic pattern change that is specific to the RD mechanism. Kirschbaum (Kirschbaum, 1975a) cut a piece of skin from the trunk and re-planted it at an angle to its original orientation. The stripes on the graft were terminated at the edge of the transplant when the operation was completed. But, he observed that the ends of the stripes moved and rejoined the end of the stripes of the host skin. Parichy and Turner (Parichy and Turner, 2003) used a temperature sensitive mutant of *panther(c-fms)* gene, that is required to maintain both xanthophores and melanophores, to erase the pattern and observe the regeneration of the pigment pattern. They found that when the pigment cells were in the tail fins were'killed, development of pigment cells occurred to fill the vacant space, but the regenerated stripes often lost the original directionality. These experiments suggest that the stripes of the zebrafish stripes have the ability to repair themselves. and that the process is independent of the pre-pattern.

By using laser light to kill the pigment cells, it is possible to induce more dynamic movement of the stripes that is characteristic of the stationary wave of the RD mechanism. Yamaguchi *et al.* (Yamaguchi *et al.*, 2007) continuously killed the melanophores in the dorsal two black stripes of the young (40 to 80 day) and observed that the ventral black stripe bent and moved dorsally to fill the vacant space. (Fig. 2) This movement of the stripes strongly suggests that the pigment pattern of the zebrafish is made and maintained dynamically by the RD, or by a very similar mechanism.

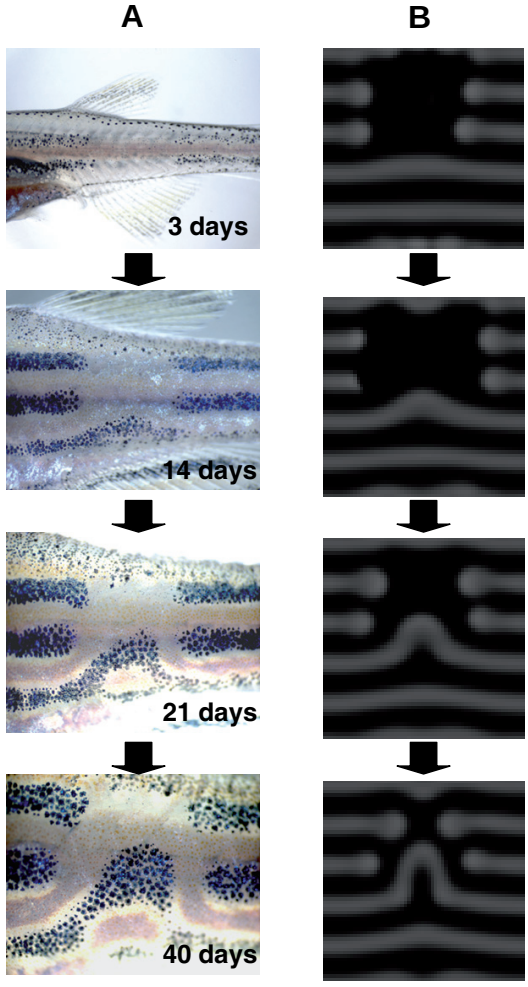

Fig. 2.Dynamic change of the zebrafish pigment pattern induced by laser experiment. (A) *Time course of the pattern change. Melanophores in upper two black stripes are killed by laser light.* **(B)** *Time-lapse captured images of the regeneration process produced by simulation of reaction-diffusion mechanisms. From Yamaguchi* et al. *(2007).*

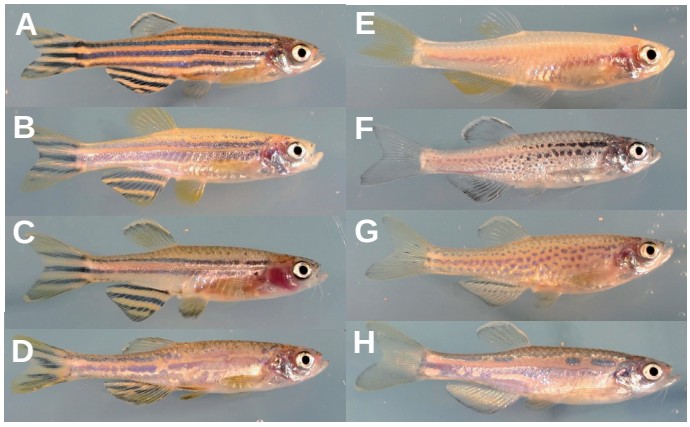

Fig. 3. Pigment patterns in zebrafish mutants. (A) *Wildtype;* **(B)** sparse*;* **(C)** nacre*;* **(D)** puma*;* **(E)** panther*;* **(F)** jaguar (obelix) *and* **(G)** leopard.

Another important suggestion which arises from these experiments is that the pigment cells do not simply make the hidden pattern visible, but are the major players in the pattern formation. Therefore, to uncover the mechanism, the most critical step should be the identification of the interactions between the two types of pigment cells (melanophores and xanthophores).

Mutants that affect both development of pigment cells and the resulting pattern

Several mutants that affect the skin pigment pattern have been isolated from large-scale screening ethylnitrosourea (enu) chemical mutagenesis and the selection of spontaneous mutations (Haffter *et al.*, 1996; Kelsh *et al.*, 1996; Odenthal *et al.*, 1996). Illustrations and summaries of the experimental data from these mutants are shown in Table 1 and Fig. 3. By gene cloning and functional analysis using a series of elegant chimera experiments, their functions in the pigment cell development is gradually becoming clear.

These mutants are classified into two categories: those with a defect in the development of pigment cells; and those with normal development of pigment cells at the embryonic stage, but with a disrupted pattern in the adult fish. Molecular genetic studies of the mutants in the first category have shown that *nacre* (Lister *et al.*, 1999), *sparse* (Parichy *et al.*, 1999), and *rose* (Parichy *et al.*, 2000a) are required for the development of melanophores, and that *panther* (Parichy *et al.*, 2000b) is required for the development of xanthophores. The *nacre* gene codes a transcription factor Mitf1 that is required by the cells to develop into melanophore precursor. *Sparse* and *panther* code the class II receptor tyrosine kinases, *c-kit* and *c-fms*, respectively. *rose* codes the endothelin receptor b1. *sparse* fish lack embryonic melanophores, but the adult melanophores are normally integrated in the stripes. The number of embryonic melanophores in *rose* fish is normal, but a reduced number of adult melanophores compose the disturbed stripe (Johnson *et al.*, 1995b). The double mutant of these genes loses almost all the melanophores, suggesting that there are two different populations in the melanophores, and only the adult type is required for the stripe pattern formation (Johnson *et al.,* 1995b).

Interestingly, when one of the pigment cell type failed to develop, other type of pigment cells fail to localize to their normal positions (Johnson *et al.*, 1995a; Lister *et al.*, 1999; Parichy *et al.*, 2000a; Parichy *et al.*, 2000b; Parichy *et al.*, 1999; Rawls *et al.*, 2001). *nacre* fish lack all melanophores and *panther* fish lack xanthophores. In both cases, the remaining pigment cells cannot form clear stripes but disperse randomly or form aggregates of uncertain shape. However, when a pigment cell type that is lost in the mutant is introduced, clear stripes are regenerated only in the region where both types of pigment cells exist. These experimental results show that mutual interaction between melanophores and xanthophores plays a critical role in the generation of skin pigmentation pattern (Kelsh, 2004; Maderspacher and Nusslein-Volhard, 2003; Parichy and Turner, 2003; Parichy *et al.*, 2003).

Mutants that affect the pigment pattern, but not the development of pigment cells

Mutants of *jaguar*/*obelix*(Maderspacher and Nusslein-Volhard, 2003) and */eopard* (Kirschbaum, 1975b; Maderspacher and Nusslein-Volhard, 2003) belong to this second category. In these mutants, development and distribution of the pigment cells is normal in embryos and young fish (~4weeks). In adult fish, although development of pigment cells is normal, their spatial arrangement (pattern) is changed, suggesting that these genes are specifically required for pattern formation. The *jaguar* mutant fish have wider stripes and the */eopard* fish have spotted patterns. Maderspacher *et al.* performed a series of chimera experiments with the mutants, and deduced the role of each gene in the pattern forming mechanism as follows. Jaguar/obelx is required in melanophores to promote their aggregation and to control boundary integuity. The */eopard* gene regulates homotypic interaction within both melanophores and xanthophores. Further, both are required

TABLE 1

SELECTED GENES INVOLVED IN PIGMENT PATTERN FORMATION IN FISH

Mutant	Gene	Pattern	Melanophore	Xanthophore	iridophore
sparse	kit /receptor tyrosine kinase	Stripe, boundary is slightly ambiguous	EM absent Present	Present	Present
rose	ednrb1/G-protein coupled receptor	Fewer stripes, but normal in fins	LM absent	Present	Absent
puma	not cloned	Purely formed	LM absent	Present	Present
nacre	mitf1/transcription factor	Clusters of xanthophores, but purely striped	Absent	Present	Present
panther	fms /receptor tyrosine kinase	Scatterd melanophores	Fewer	Absent	Present
jaguar(obelix)	kir7.1/potassium chnnel	Wider stripes	Present	Present	Present
leopard	connexin41.8/ gap junction	Spots	Present	Present	Present

Modified from (Kelsh, 2004)

to control the boundary shape (Maderspacher and Nusslein-Volhard, 2003). The positional cloning of the *jaguar* mutant revealed that this gene codes a inwardly rectifying potassium channel, Kir7.1 (Iwashita *et al*., 2006). Kir channels are a group of ion channels which transfer potassium ions unidirectionally from outside to inside the cell (Doring *et al*., 1998; Kim *et al*., 2000; Kusaka *et al*., 2001; Nakamura *et al*., 2000; Shimura *et al*., 2001). It is known from the study of cultured cells that this class of channels is responsible for the stability of membrane potential and sensitivity to the external signals (Suzuki *et al*., 2003; Wischmeyer *et al*., 2000; Yasuda *et al*., 2003). Recently Jantzi *et al.* reported that the kir channel (Kir2.2) facilitates cell-to-cell communication that propagates the contraction signal in hamster retractor muscle feed artery (Jantzi *et al*., 2006). In zebrafish, the *Kir7.1* gene is expressed in melanophores (Iwashita *et al*., 2006), suggesting that the channel controls the interaction of the melanophores. The gene responsible for the *leopard* mutant is cloned and identified to be a component of gap junctions, connexin41.8 (Watanabe *et al*., 2006). Connexin41.8 is expressed in many kinds of skin cells including melanophores and xanthophores. As the expression level of the *connexin41.8* gene is very low in cells of the zebrafish skin, little is known about the function and role of the molecule in pigment-pattern formation. However, Johnson *et al*. reported recently that another class of gap junction gene, connexin43, encodes the *shortfin (sof)* gene, which controls the length of the fins of the zebrafish (Iovine *et al*., 2005). This fact is quite interesting because it implies that a similar mechanism could control the size of limbs and the 2D patterns in the skin.

Future directions

Although molecular genetic studies have identified genes and molecules involved in pigment-pattern formation in fish, the questions as to how they are organized and how they generate the RD wave, remain largely unknown. To understand pigment-pattern formation, it is necessary to integrate all the molecular reactions and deduce how such complex systems behave. For this purpose, the framework of RD mechanism is useful. In most of the mathematical models of the RD systems, the putative molecular network is composed of chemicals that control the synthesis of molecules and their diffusion in the field. However, it is also possible to compose an equivalent network with the interaction of two types of cell (melanophores and xanthophores). Therefore there is no theoretical difficulty in applying the model to zebrafish pigment-pattern formation.

Mathematical studies on RD and related autonomous pattern-forming systems, revealed that the necessary conditions for the formation of a spatial pattern (spots and stripes) is the combination of "local activation" and "long range inhibition" (Meinhardt and Gierer, 2000b). Recentry, Nakamasu estimated the *in vivo* interactions between the pigment cells by observing regeneration in the area where the pigment cells in the surrounded region were killed by laser (Nakamasu *et al.,* 2009). They found that the effect of xanthophores on the melanophore is different depending on the distance of the cells, and the deduced cell-cell interaction network is consistent with the "local activation and long range inhibition" rule. Temporally, we have little experimental data which connects molecular data to the macroscopic observations which suggest the involvement of the Turing mechanism in pigment pattern formation. Use of advanced live-imaging techniques will help to assess whether or not the functioning molecules behave as the model predicts, and will also help to identify the molecular-level network. With the cooperation of advanced molecular genetics and mathematical modeling, the long unsettled question of how animal skin patterns are generated will be solved in the near future.

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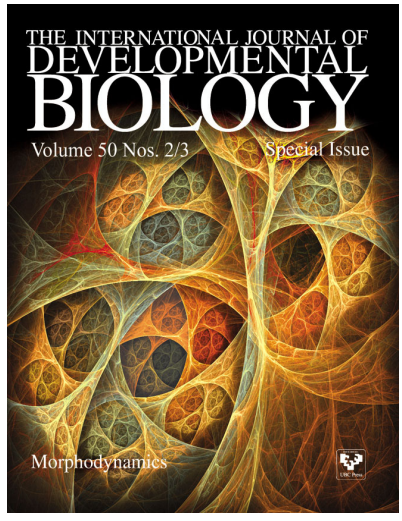

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