What are the underlying principles in the evolution of animal embryonic development?

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Q. What is the one thing you want to know the most right now?

That's a difficult question because I'm interested in various things. For example, I'm curious about why physical laws exist. Are they just mathematical approximations? I'm also interested in neuroscience and have a lot of questions. But the main thing I want to explore in my research is **whether the process of animal development (embryogenesis) changes according to certain laws throughout evolution**. If it does, what are those laws? In simple terms, I'm looking into the laws of evolutionary embryology. For instance, how likely is it that primates, like humans, could evolve into creatures with multiple faces or arms, kind of like the Ashura statue? It's a pretty simple question, but it's actually quite complex.

While evolutionary biology has done a great job studying events in the past, including those from millions or even billions of years ago, predicting how species might evolve in the future is a much tougher challenge. The farther into the future we try to predict, the less certain we become. Of course, we can make some predictions under certain conditions—like with the Red Queen hypothesis, viral evolution, symbiotic relationships, microevolution within species over short generations, and so on. But when it comes to finding universal evolutionary laws that apply to various traits across different organisms, there's still very little research being done.

Q. What do you consider to be a challenge at the moment?

When it comes to challenges in my research, if I had to sum it up in one sentence, it would be: **"There are quite limited research approaches to clarify the mechanisms that restrict or constrain the evolutionary diversification of phenotypes."** As I mentioned earlier, what I want to understand is how the process of animal development (embryogenesis) changes according to certain laws throughout evolution. This is actually a question that the scholar Ernst Haeckel began discussing in the early 19th century, and we're slowly starting to gather hints about it.

From a phenomenological perspective, one of the findings is that during embryogenesis—the process where a single fertilized egg develops into a complex organism with various tissues and organs—the period when the basic body pattern is formed is one where diversity is least pronounced. This is referred to as the "developmental hourglass model." Actually, as we compare the embryogenesis of various animals at molecular level, there seems to be a trend where the evolutionary diversity (divergence) decreases during specific stages.

In our research, we've seen this trend in vertebrates like chickens, mice, turtles, frogs, fish, and lampreys, as well as in echinoderms like sea urchins, sea cucumbers, and sea lilies. There have also been reports from overseas groups suggesting similar trends in insects, nematodes, annelids, and even plants.

However, this observation only indicates that evolutionary diversity is low during mid-embryonic stages (around organogenesis stages in vertebrates). The question of why this happens and the underlying evolutionary mechanisms still require significant exploration. At the gene expression level, however, we've found that the conserved mid-embryonic phase shows fewer transcriptomic variations. In evolutionary biology, if different variations don't arise within species, then diversification simply can't occur. Thus, one could argue that the evolutionary potential for diversification is lower during these mid-embryonic stages.

Getting back to the main point, the major challenge lies in the limited research approaches available to examine how evolutionary potential becomes limited. We do have several hypotheses about this. For instance, concepts like developmental constraints, developmental burden, and pleiotropic constraints have been proposed and argued for decades. However, the challenge remains in effectively testing whether these hypotheses stand or not. Our experimental data, for example, supported the idea of pleiotropic constraints. Just like other biological activities, the developmental process relies on the activity of various cells, which involves a multitude of genes and their products. Simply put, these genes can be regarded as molecular-level components, which make up our body. In vertebrates, including humans, there are tens of thousands of different genes in the genome, however, these genes aren't evenly utilized. It turns out that a very small number of protein-coding genes are reused at various developmental stages. This is referred to as "pleiotropic expression." These pleiotropically expressed genes play a critical role in constructing various organs, so if there's an issue with these genes, it can have catastrophic effects on the entire developmental process. It's like imagining a machine that relies on specific parts used in multiple places—if this type of specific parts runs out, it poses a significant problem.

Although the exact mechanism of pleiotropic constraint requires further investigations, **it's possible that these pleiotropically expressed genes have robust regulatory systems to ensure consistency in how they're used, which leads to evolutionary conservation of their expression patterns.** This discovery was based on large-scale information analyses, and there's still a lot we need to figure out experimentally regarding what other mechanisms might contribute to lower evolutionary potential. From a data processing perspective, I believe that information analysis technologies, including AI, could play a role, but what's even more crucial is what kind of experimental data we can obtain and analyze.

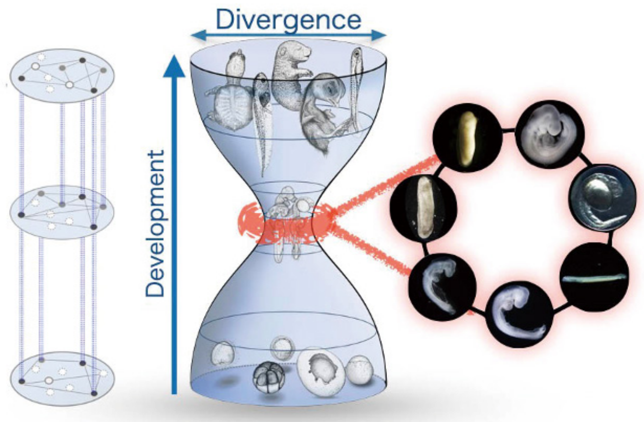

Figure: Developmental Hourglass Model
The hourglass at the center represents the relationship between the process of animal embryogenesis (vertical axis) and evolutionary diversity (horizontal axis). This hypothesis was proposed by Denis Duboule in 1994 and has been supported by research from Professor Irie and colleagues. On the right side of the figure, we see the embryonic stages where evolutionary diversity is at its lowest. Starting from the top right and moving clockwise, the species shown are mouse, zebrafish, lamprey, chicken, turtle, African clawed frog, and fat-tailed dwarf gecko. On the left side of the figure, there's a conceptual diagram of the gene networks observed during the early, mid, and late stages of development. In the evolutionary conserved mid-development stages, hub genes that interact with various other genes were enriched. This finding, from the research conducted by Professor Irie and others, suggests a potential link to the lack of evolutionary diversity.

Q. Could you share your thoughts on the future prospects of this field?

I'm really hopeful that we'll be able to start tackling questions about how different organisms might evolve in appearance and form. For example, birds can fly because they have transformed their forelimbs into wings. But **could a horse gain new wings (without sacrificing its front legs) and become something like a Pegasus?** It's a simple question, but not easy to answer. I'm secretly hoping we'll find answers to this kind of questions that have not been addressed yet. In fields outside of biology, like astronomy and theoretical physics, a lot of progress has been made in understanding how the universe might change over time. There are reports suggesting that our active universe could last for about 100 billion more years. But when it comes to biology, even though we're talking about life that originated on just one planet in the vast galaxy, we don't have much to say about how these life forms will evolve in the future. For just a few generations, yes, we can say that "their appearance probably won't change much," where genetics and/or machine learning can help us make some predictions. However, when we try to predict over scales of millions or even billions of years, we really hit a dead end. The reason we struggle to make these predictions is that we don't fully understand the mechanisms of evolution. You might think, 'Isn't it just about the natural selection of organisms with various traits arising from mutations?' But unfortunately, that is just a part of evolutionary mechanisms. We still don't have a clear grasp of the general principles behind what kinds of traits are likely to emerge in situations where there are mutations or where there aren't. For example, what variations are more likely to occur? **What common laws might limit evolutionary diversity?** If we could figure these out, we'd be able to identify traits that are less prone to diversification—traits that exhibit strong evolutionary inertia. By integrating that understanding with existing evolutionary theories, we might even be able to solve the Pegasus problem. That's what I'm hoping for!

Q. What was the most enjoyable moment and the most challenging moment during your research?

Well, there are a lot of memorable moments, but I think the one that stands out the most is when I first started obtaining results on the current research topic, search for the laws of evolution and development. It was during my graduate studies, and I got results that supported the hourglass model for the first time. Back then, there were hardly any researchers in this field, and I faced a lot of ridicule in the lab while I was pushing through my analysis on my own. People kept telling me **I might as well give up on getting my PhD, so it was a pretty hopeless situation. But when I finally got those results that supported the hourglass model,** I was super excited. Of course, it felt great to publish papers and have my work recognized and included in textbooks, but the moment when I felt that I might have discovered a truth that humanity had never grasped was truly the most enjoyable moment for me. If I'm allowed to mention another highlight, it would be spending time with colleagues from around the world and engaging in various discussions in different countries. Just the other day, I had dinner and talked with friends from Germany, Russia, Italy, the U.S., and Japan. We laughed together, reflecting on how, in another time, we might have considered each other as enemies and fought against each other. It really felt like a miraculous moment. On the flip side, I can't really point to a single moment when I felt it was particularly difficult. There are always challenges, like experiments not going well, worrying about whether I'll find my next job, or dealing with insufficient budgets and equipment. Those struggles are quite ordinary. However, I try not to dwell on them because I'm still fortunate enough to have the opportunity to take on challenges that expand human knowledge. That's probably why I might not even remember the specifics of the hardships.

Q. Do you have a message for undergraduate and graduate students who are interested in joining your lab?

So, this is meant as a message to undergraduate students who are interested in joining my lab, right? If so, I'd say, **'You only live once, so make sure to enjoy it to the fullest!'** A PhD is a globally recognized credential, so I want to encourage you to earn it and take on big challenges while enjoying everything that comes your way.