Study shows developing organisms can identify and fix abnormalities in head and face

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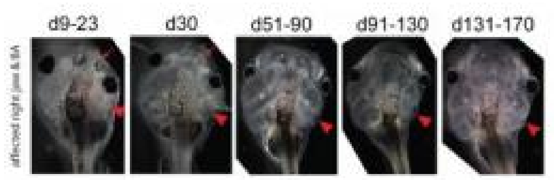

Developmental biologists at Tufts University have identified a "self-correcting" mechanism by which developing organisms recognize and repair head and facial abnormalities. The research, reported in the May 2012 issue of the journal *Developmental Dynamics*, used a tadpole model to show that developing organisms are not genetically "hard-wired" with a set of pre-determined cell movements that result in normal facial features. Instead, the study shows that cell groups are able to measure their shape and position relative to other organs and perform the movements and remodeling needed to compensate for significant patterning abnormalities. Here three abnormal facial structures on the right side of a tadpole self-repair over time. On days 9 to 23, the branchial arch, or gill, (arrowhead) is almost flat rather than displaying the expected curvature, the right side of the jaw (arrow) is deformed, and the right eye is out of position and displays a "chocolate kiss" shape. By day 131-170, the branchial arch has become curved, the jaw displays the expected "U" shape and the right eye has moved up to align with the left eye and has a more rounded shape. Credit: Tufts Center for Regenerative and Developmental Biology

Developmental biologists at Tufts University have identified a "self-correcting" mechanism by which developing organisms recognize and repair head and facial abnormalities. This is the first time that such a mechanism has been reported for the face and the first time that this kind of flexible, corrective process has been rigorously analyzed through mathematical modeling.

The research, reported in the May 2012 issue of the journal *Developmental Dynamics*, used a tadpole model to show that developing organisms are not genetically "hard-wired" with a set of pre-determined cell movements that result in normal facial features. Instead, the process of development is more adaptive and robust. Cell groups are able to measure their shape and position relative to other organs and perform the movements and remodeling needed to compensate for significant patterning abnormalities, the study shows.

"A big question has always been, how do complex shapes like the face or the whole embryo put themselves together? We have found that when we created defects in the face experimentally, facial structures move around in various ways and mostly end up in their correct positions," said Michael Levin, Ph.D., senior author on the paper and director of the Center for Regenerative and Developmental Biology in Tufts University's School of Arts and Sciences. "This suggests that what the genome encodes ultimately is a set of dynamic, flexible behaviors by which the cells are able to make adjustments to build specific complex structures. If we could learn how to bioengineer systems that reliably self-assembled and repaired deviations from the desired target shape, regenerative medicine, robotics, and even space exploration would be transformed."

Previous research had found self-correcting mechanisms in other embryonic processes — though never in the face — but such mechanisms had not been mathematically analyzed to understand the precise dynamics of the corrective process.

"What was missing from previous studies — and to our knowledge had never been done in an animal model — was to precisely track those changes over time and quantitatively compare them," said first author Laura Vandenberg, Ph.D., post-doctoral associate at the Center for Regenerative and Developmental Biology. Such an analysis is crucial in order to begin to understand what information is being generated and manipulated in order for a complex structure to rearrange and repair itself.

Co-author with Levin and Vandenberg was Dany S. Adams, Ph.D. Adams is a research associate professor in the Department of Biology and a member of the center.

The Tufts biologists induced craniofacial defects in *Xenopus* frog embryos by injecting specific mRNA into one cell at the two-cell stage of development; this resulted in abnormal structures on one side of the embryos. They then characterized changes in the shape and position of the craniofacial structures, such as jaws, branchial arches, eyes, otic capsules and olfactory pits, through "geometric morphometric analysis," which measured positioning of a total of 32 landmarks on the top and bottom sides of the tadpoles.

Images of tadpoles taken at precise intervals showed that as they aged, the craniofacial abnormalities, or perturbations, became less apparent. This was particularly true for the jaws and branchial arches. Eye and nose tissue became more normal over time but varied in ability to achieve a completely expected shape and position.

Changes in the shape and position of facial features are a normal part of development, as any baby animal shows. With age, faces elongate and eyes, nose and jaws move relative to each other. But the movement is normally slight.

In contrast, the Tufts research team found that in tadpoles with severe malformations, the facial structures shifted dramatically in order to repair those malformations. It was, the researchers said, as if the system were able to recognize departures from the normal state and undertake corrective action that would not typically take place.

"We were quite astounded to see that, long before they underwent metamorphosis and became frogs, these tadpoles had normal looking faces. Imagine the implications of an animal with a severe 'birth defect' that, with time alone, can correct that defect," said Vandenberg.

Information Exchange Process

These results, say the Tufts biologists, are consistent with an information exchange process in which a structure triangulates its distance and angle from a stable reference point. While further study is needed, the researchers propose that "pings" (information-containing signals) are exchanged between an "organizing center" — such as the brain and neural network — and individual craniofacial structures.

The article points out that congenital malformations of craniofacial structures comprise a significant class of birth defects such as cleft lip, cleft palate and microphthalmia, affecting more than 1 in every 600 births. Demystifying the "face-fixing" mechanism by further research at the molecular level could inspire new approaches to correcting birth defects in humans.

"Such understanding would have huge implications not only for repairing birth defects, but also for other areas of systems biology and complexity science. It could help us build hybrid bioengineered systems, for synthetic or regenerative biology, or entirely artificial robotic systems that can repair themselves after damage or reconfigure their own structure to match changing needs in a complex environment," said

Levin.

More information: Vandenberg, L. N., Adams, D. S. and Levin, M. (2012), Normalized shape and location of perturbed craniofacial structures in the Xenopus tadpole reveal an innate ability to achieve correct morphology. *Dev. Dyn.*, 241: 863-878. doi: 10.1002/dvdy.23770

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