

Roczniak-Ferguson, 2004), but it is not known how these changes influence p120-catenin/Kaiso signaling. Even in the case of β -catenin, the role of cadherins in β -catenin nuclear signaling is regulated and not just a simple matter of binding competition; posttranslational modifications of β -catenin control the relative selectivity of its interactions with cadherins or TCF (Brembeck et al., 2004; Gottardi and Gumbiner, 2004). It would not be surprising, therefore, if the regulation of p120-catenin/Kaiso signaling by cadherins depends similarly on posttranslational modifications of p120-catenin or on the type of cadherin expressed in the cell.

Finally, what is the developmental or physiological significance of coordinate regulation of canonical Wnt target genes by β -catenin and p120-catenin? Dual regulation of p120-catenin and β -catenin signaling by cadherins could translate into cooperative regulation of canonical Wnt target genes by these two effectors. Perhaps in this way cadherins could regulate target genes differently from the Wnt pathway, whose target-gene regulation might be mediated by β -catenin alone. Alternatively, p120-catenin/Kaiso signaling might be regulated by a completely separate pathway, such as one mediated by src-family tyrosine kinases, and in this way serve to integrate the regulation of target genes by the two pathways. These possibilities have important implications for both developmental biology and cancer research and are sure to be aggressively addressed by investigators in these fields.

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Selected Readings

- Brembeck, F.H., Schwarz-Romond, T., Bakkers, J., Wilhelm, S., Hammerschmidt, M., and Birchmeier, W. (2004). *Genes Dev.* **18**, 2225–2230.
- Gottardi, C.J., and Gumbiner, B.M. (2004). *J. Cell Biol.* **167**, 339–349.
- Gottardi, C.J., Wong, E., and Gumbiner, B.M. (2001). *J. Cell Biol.* **153**, 1049–1059.
- Gumbiner, B.M., (2005). *Nat. Rev. Mol. Cell Biol.* **6**, in press.
- Kelly, K.F., Spring, C.M., Otchere, A.A., and Daniel, J.M. (2004). *J. Cell Sci.* **117**, 2675–2686.
- Kim, S.W., Park, J.I., Spring, C.M., Sater, A.K., Ji, H., Otchere, A.A., Daniel, J.M., and McCrea, P.D. (2004). *Nat. Cell Biol.* **6**, 1212–1220.
- Moon, R.T., Bowerman, B., Boutros, M., and Perrimon, N. (2002). *Science* **296**, 1644–1646.
- Park, J., Kim, S.W., Lyons, J.P., Ji, H., Nguyen, T.T., Cho, K., Barton, M.C., Deroo, T., Vleminckx, K., and McCrea, P.D. (2005). *Dev. Cell* **8**, this issue, 843–854.
- Reynolds, A.B., and Roczniak-Ferguson, A. (2004). *Oncogene* **23**, 7947–7956.
- Yoon, H.G., Chan, D.W., Reynolds, A.B., Qin, J., and Wong, J. (2003). *Mol. Cell* **12**, 723–734.

Reversed Bodies, Reversed Brains, and (Some) Reversed Behaviors: Of Zebrafish and Men

Although zebrafish with *situs inversus* show complete reversal of normal visceral and cerebral asymmetries, they show left-right reversal of only *some* behaviors, with others continuing to show species-typical lateralization. The implication is that, as in humans, there are at least two independent mechanisms for generating asymmetry.

Despite the eternal desires of theoretical physicists to create a world replete with symmetries, the natural world insists on being asymmetric at every level from the subatomic to the symbolic (McManus, 2002). Although studies at particular levels of analysis are common, links across levels are rare. The past decade has seen major advances in the understanding of the embryology of anatomical lateralization and the biology of behavioral lateralizations. An important and interesting paper in *Current Biology* now brings together these two areas of work, with unexpected results (Barth et al., 2005).

An obvious anatomical fact, for mice and for men, as well as for other vertebrates, is that the heart is almost always on the left (so called *situs solitus*). The developmental biology of this process is increasingly well understood, although the fundamental symmetry-breaking step is in some doubt (Levin, 2005). Of particular interest are mutations known to result in *situs inversus*, the complete left-right reversal of body organs.

Understanding of *situs* was revolutionized by the work of Hirokawa and colleagues (Nonaka et al., 1998), who suggested that the flow resulting from rotation of nodal cilia caused the development of normal *situs* in mice, a hypothesis supported by finding that *situs inversus* occurred in 50% of cases in the *iv* and *kif3a/b* mutations, which had defective nodal cilia, and by the finding that *situs inversus* resulted when the nodal flow direction was artificially reversed. The theory does, however, have problems, particularly with finding the cilia and the flow in other species (Hornstein and Tabin, 2005), although directional flow does seem to be important in zebrafish (Essner et al., 2005).

Another very obvious laterality, staring humans in the face as they write, is right-handedness. Conventional wisdom has seen such strong directional lateralization, with only 10% showing a reversed pattern, as unique to humans, but that position is now controversial, with

many vertebrate species being shown to have behavioral asymmetries (Rogers and Andrew, 2002). Whether these behaviors are homologous or merely analogous to human handedness is very contentious, with some researchers arguing strongly for human exceptionalism, and Crow suggesting that cerebral lateralization was the unique human “speciation event” (Crow, 2003).

Until recently the only behavioral data in individuals with *situs inversus* were from humans. Sir Thomas Watson’s early 19th century review identified the key fact that individuals with *situs inversus* are no more left-handed than the rest of the population (Watson, 1836), a finding replicated in later studies, although it long remained a mere curiosity. Studies of human *situs inversus* often suffer from poor behavioral description of handedness, small sample sizes, or poor characterization of the etiology of *situs inversus*. In particular, proper neural imaging studies are woefully scarce.

Primary ciliary dyskinesia (PCD), the Siewert-Kartagener syndrome, is a human condition in which ciliary dysfunction causes bronchiectasis, sinusitis, and (in males) infertility. 50% of individuals with PCD also show *situs inversus*, strongly suggesting that nodal cilia are affected. However, our study of 88 individuals with PCD found normal rates of left-handedness and other lateralities in both *situs solitus* and *situs inversus* (McManus et al., 2004), the only behavior associated with *situs* being the obscure laterality of the side of wearing a wristwatch. The lack of an association of handedness with *situs* poses severe problems for theories suggesting that nodal cilia alone define the left-right axis of the body, for in PCD the prediction has to be either that handedness is reversed in *situs inversus* (if cerebral asymmetry is secondary to visceral asymmetry) or that there is a 50% rate of left-handedness in both *situs inversus* and *situs solitus* (if visceral and cerebral asymmetry are random and uncoupled). Nodal flow alone cannot explain normal cerebral lateralization in the presence of random visceral asymmetry.

A practical problem for studying these matters has been the absence of a good animal model. The recent collaboration between teams of animal behaviorists and zebrafish developmental biologists suggests that a useful solution has now been found (Barth et al., 2005).

The *fsi* (frequent *situs inversus*) line of zebrafish show *situs inversus* in 5% to 25% of offspring. The fish with defects show complete *situs inversus*, with reversal not only of viscera but of neural structures such as the habenula and parapineal nuclei, which are often asymmetric in amphibia and other organisms (Concha and Wilson, 2001). Because brain asymmetry was reversed, the researchers’ expectation was of reversal also of the characteristic behavioral asymmetries of fish (Vallortigara et al., 1999). Indeed, that was the case for two behaviors, mirror-viewing and approaching a target to bite, which were left-right reversed in *situs inversus*. However, “surprisingly,” as the authors put it, behavior was not reversed for two similar tests in which fish swim from a dark chamber into a novel environment (Barth et al., 2005). *Situs inversus* zebrafish may also be less well adapted, showing a reduced emergence

latency after confronting a novel object, which the authors speculate might result from atypical cross-lateralization of behavioral functions.

Although it seems natural that a viscerally reversed organism should also be behaviorally reversed, human cases of *situs inversus* show it is not so. The assumption must have seemed stronger still for zebrafish whose visceral *and* cerebral asymmetry were reversed. However, here also one must be careful. In a study of three human cases of *situs inversus*, there were anatomical left-right reversals of occipital and frontal brain petalias. However—and here is the crunch—neither handedness nor language dominance were reversed in these cases (Kennedy et al., 1999). Anatomical asymmetries are not the same as functional asymmetries. Just as a computer does not function differently when it is packed in a differently shaped box, so neither are human functional brain asymmetries reversed when the packaging is changed. The same seems also to be the case for at least two zebrafish behaviors.

The reasons why some zebrafish behaviors are not reversed in animals with *situs inversus* are mysterious and fascinating. The parallel with human handedness, and the possibility of two or perhaps more independent mechanisms by which vertebrates set up the left-right axis, means that further work will be of great interest.

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Selected Reading

- Barth, K.A., Miklosi, A., Watkins, J., Bianco, I.H., Wilson, S.W., and Andrew, R.J. (2005). *Curr. Biol.* 15, 844–850.
- Concha, M.L., and Wilson, S.W. (2001). *J. Anat.* 199, 63–84.
- Crow, T.J. (2003). *The Speciation of Homo sapiens* (London: British Academy).
- Essner, J.J., Amack, J.D., Nyholm, M.K., Harris, E.B., and Yost, H.J. (2005). *Development* 132, 1247–1260.
- Hornstein, E., and Tabin, C.J. (2005). *Nature* 435, 155–156.
- Kennedy, D.N., O’Craven, K.M., Ticho, B.S., Goldstein, A.M., Makris, N., and Henson, J.W. (1999). *Neurology* 53, 1260–1265.
- Levin, M. (2005). *Mech. Dev.* 122, 3–25.
- McManus, I.C. (2002). *Right Hand, Left Hand: The Origins of Asymmetry in Brains, Bodies, Atoms and Cultures* (London: Weidenfeld and Nicolson).
- McManus, I.C., Martin, N., Stubbings, G.F., Chung, E.M.K., and Mitchison, H.M. (2004). *Proc. R. Soc. Lond. B. Biol. Sci.* 271, 2579–2582.
- Nonaka, S., Tanaka, Y., Okada, Y., Takeda, S., Harada, A., Kanai, Y., Kido, M., and Hirokawa, N. (1998). *Cell* 95, 829–837.
- Rogers, L.J., and Andrew R.J., eds. (2002). *Comparative Vertebrate Lateralization* (Cambridge: Cambridge University Press).
- Vallortigara, G., Rogers, L.J., and Bisazza, A. (1999). *Brain Res. Brain Res. Rev.* 30, 164–175.
- Watson, T. (1836). *London Medical Gazette* 18, 393–403.