



Figure 1 | Blood flow shapes the great arteries. **a**, The heart of a 10.5-day-old mouse embryo (the equivalent of 30-day-old human embryo) shows symmetrical development of branchial arch arteries (1–4 and 6); at this stage, equivalent amounts of blood flow through all of these arteries. **b**, By embryonic day 11.5 (the equivalent of day 35 in human embryos), these arch arteries have undergone asymmetrical remodelling. Consequently, the right fourth and sixth arch arteries regress, and the left fourth and sixth arch arteries persist to become the aortic artery and pulmonary trunk. At this stage, blood predominantly flows through the left arch arteries; this follows the rotation and realignment of the outflow tract (green arrow), and is concomitant with increased expression of the growth factors PDGF and VEGF. **c**, To test whether blood flow determines asymmetrical remodelling of the branchial arch arteries, Yashiro *et al.*⁴ surgically ligated the left arch arteries in 11.5-day-old mouse embryos, thereby preventing normal blood flow through them. This led to abnormal regression of the left sixth arch artery and the parallel development of the right arteries, into which blood flow was not obstructed. The anterior-heart-derived cells⁵ are shown in red and blood flow is indicated by pink arrows. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

Yashiro *et al.* found to their surprise that *Pitx2* is not expressed in any of the cells that surround these arteries. Instead, this transcription factor is known¹⁰ to be expressed in the anterior heart, where it orchestrates rotation of the outflow tract^{8,9}. Given that the anterior heart requires the action of the growth factor *Fgf8* (ref. 10), and that mouse embryos lacking *Pitx2* express abnormal levels of *Fgf8* (ref. 11), it will be interesting to determine whether *Fgf8* is another mediator of arch-artery regression.

Earlier work has demonstrated that several other mouse mutants that show defects in arch-artery laterality do not have either a deficiency in the Nodal–*Pitx2* signalling pathway or abnormal rotation of the outflow tract⁵. To reconcile these observations with those of Yashiro and colleagues, it is necessary to find out what other mechanisms underlie abnormal remodelling of the arch arteries and whether there is a common molecular pathway responsible for causing these congenital heart defects.

It also remains to be seen whether the cardiovascular abnormalities in the mutant mice studied by Yashiro *et al.* are due to a direct effect of haemodynamics. This is because a general reduction in cardiac output and blood flow could cause an overall decrease in shear-stress-responsive vascular growth factors, which might, in turn, result in the regression of certain vessels. Other questions that need to be addressed include whether direct manipulation of the outflow-tract rotation would affect arch-artery remodelling, and why the sixth arch artery is particularly sensitive to haemodynamics.

Nonetheless, Yashiro and colleagues' results provide a useful model for converting physical forces into genetic information — that is, the maintenance by haemodynamics of the expression of vessel-stabilization factors (such as PDGF and VEGF) that shape the asymmetrical cardiovascular system of mammals. It is also exciting that these researchers have successfully manipulated embryonic blood flow — a technically challenging task — to carry out genetic analysis. ■

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50 YEARS AGO

On the morning of November 3, the U.S.S.R. announced from Moscow the launching of the second artificial Earth satellite — about a month after the launching, on October 4, of the first ... For the first time in history, a living mammal from the Earth is travelling in an Earth satellite, for the second one is carrying a dog: at the time of writing it was “calm and behaving normally” according to Russian reports ... The launching of the second satellite is staggering enough in itself; but some Russian scientists have stated that it is hoped that the dog will return alive. They claim to have solved the immensely difficult ‘re-entry’ problem; that is, the safe passage through the atmosphere in spite of the great heat generated through friction. This possibility will be watched with the keenest interest. The greatest peril which the animal is facing is the absence, or considerable reduction in strength, of gravity; also it is conceivable that cosmic rays at that height may have a fatal effect on the nervous system.

From *Nature* 9 November 1957.

100 YEARS AGO

No-one more fully understands the danger of indiscriminately using a questionnaire than Dr. J. G. Frazer, who is publishing through the Cambridge University Press his “Questions on the Customs, Beliefs, and Languages of Savages” ... They are intended, not so much to be put directly to the savage, as to indicate to the inquirer in the field those subjects upon which students at home desire information. Leading questions should be avoided, as they tempt the savage to give answers which he thinks will be acceptable. The savage should be encouraged to talk in his usual vague way until he has exhausted his information for the time, when a question judiciously asked may jog his memory.

From *Nature* 7 November 1907.

50 & 100 YEARS AGO