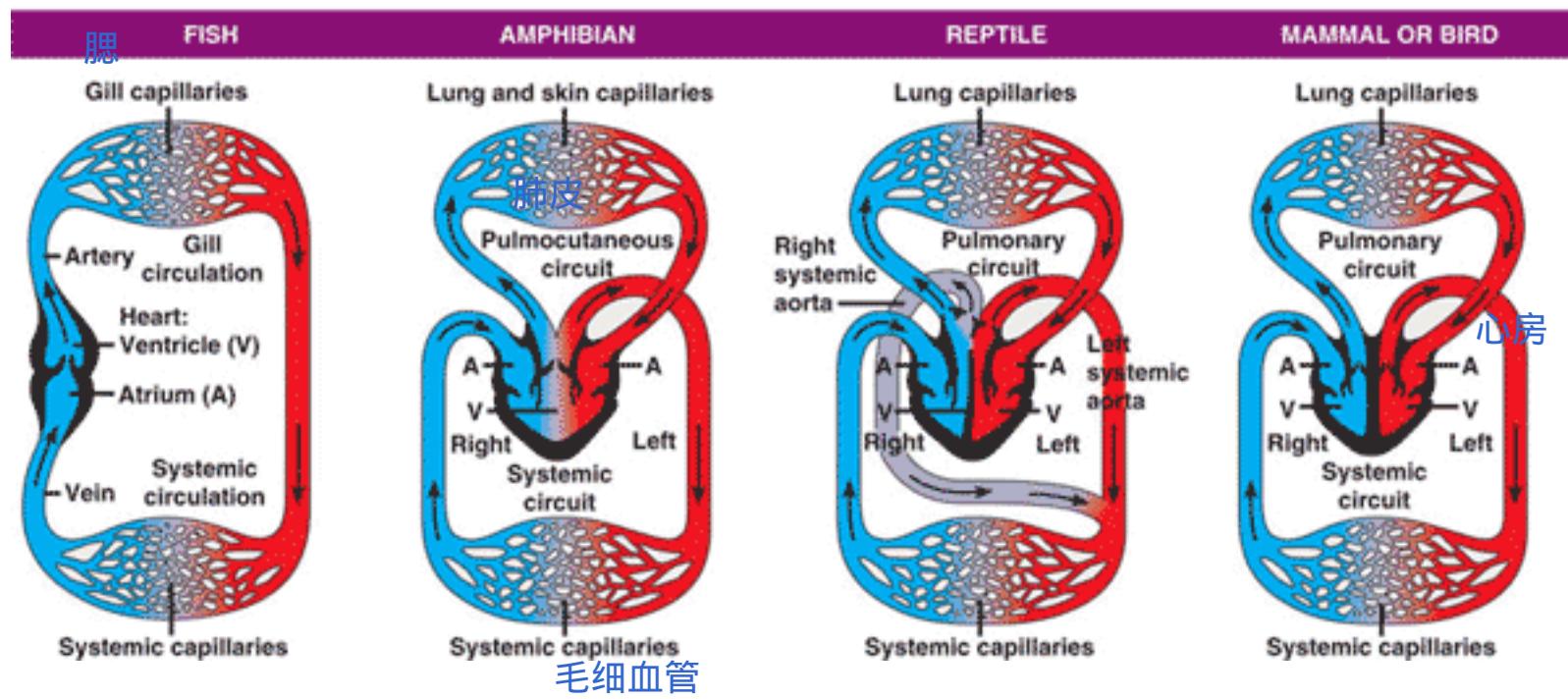
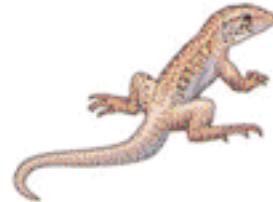


Model organisms and developmental biology

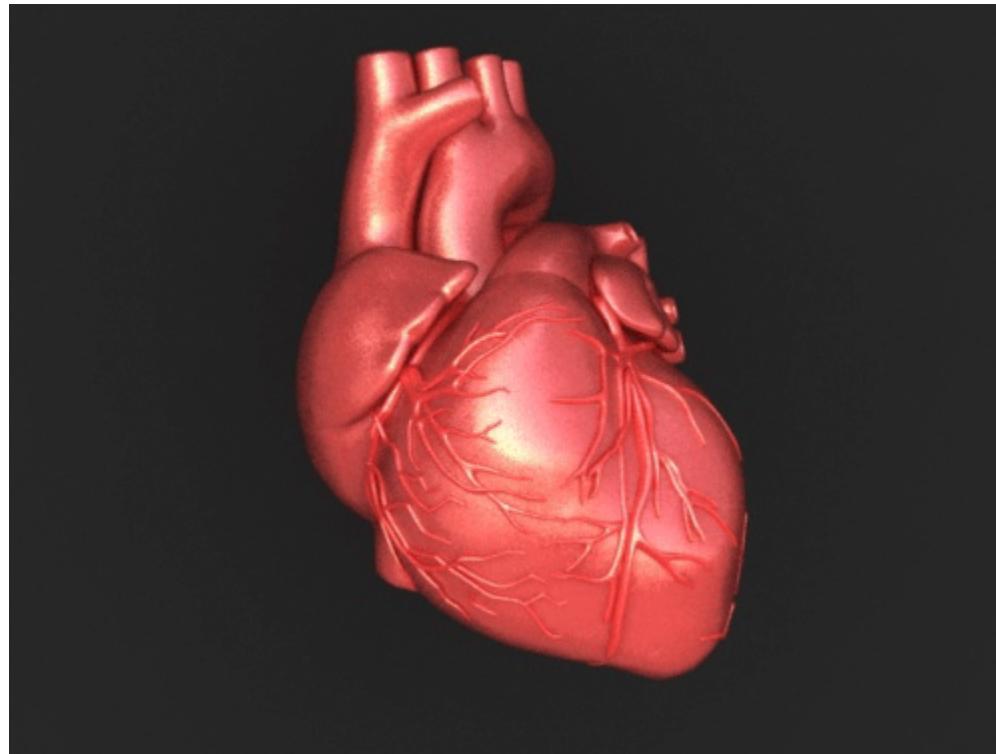
仲寒冰

zhong.hb@sustc.edu.cn

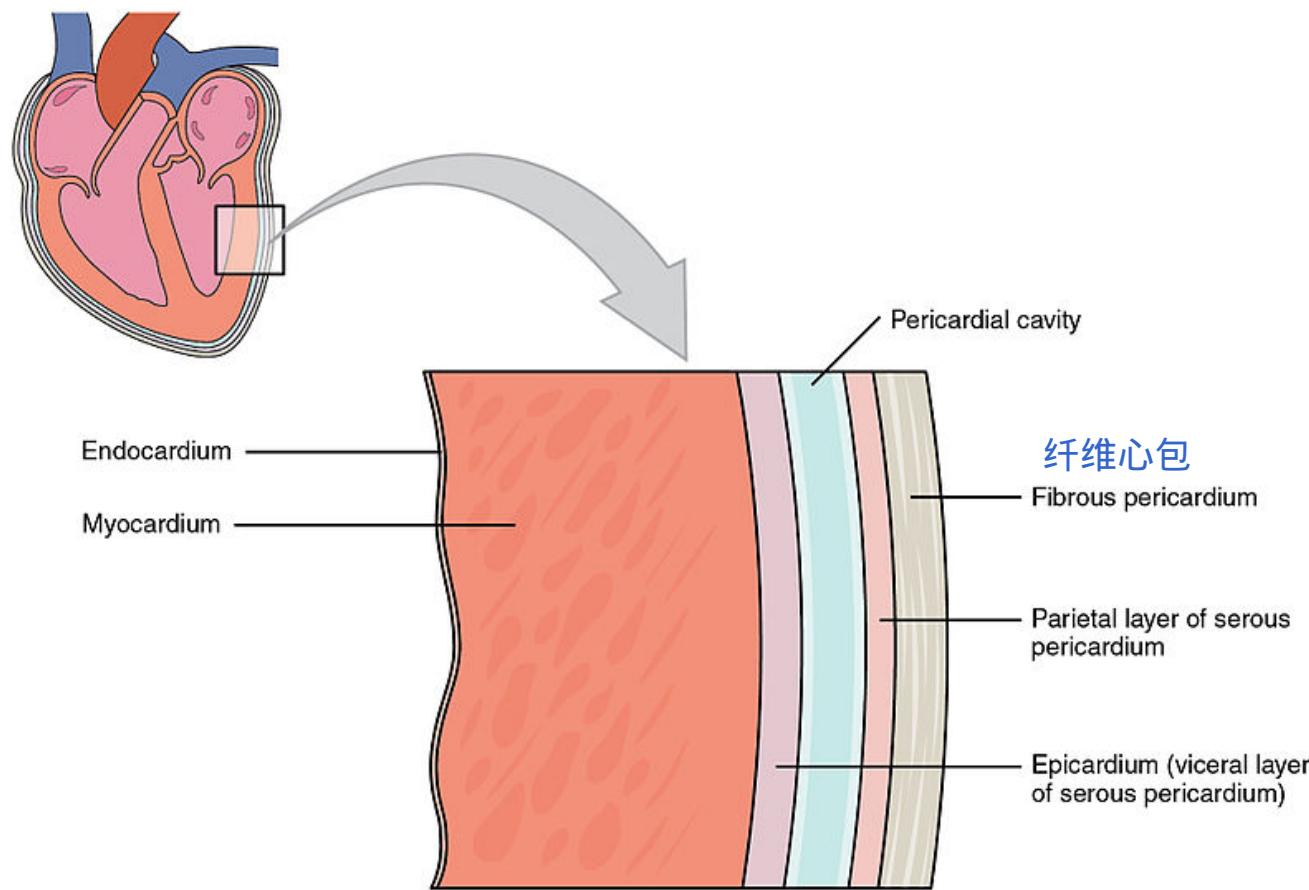
Vertebrate Circulatory Systems



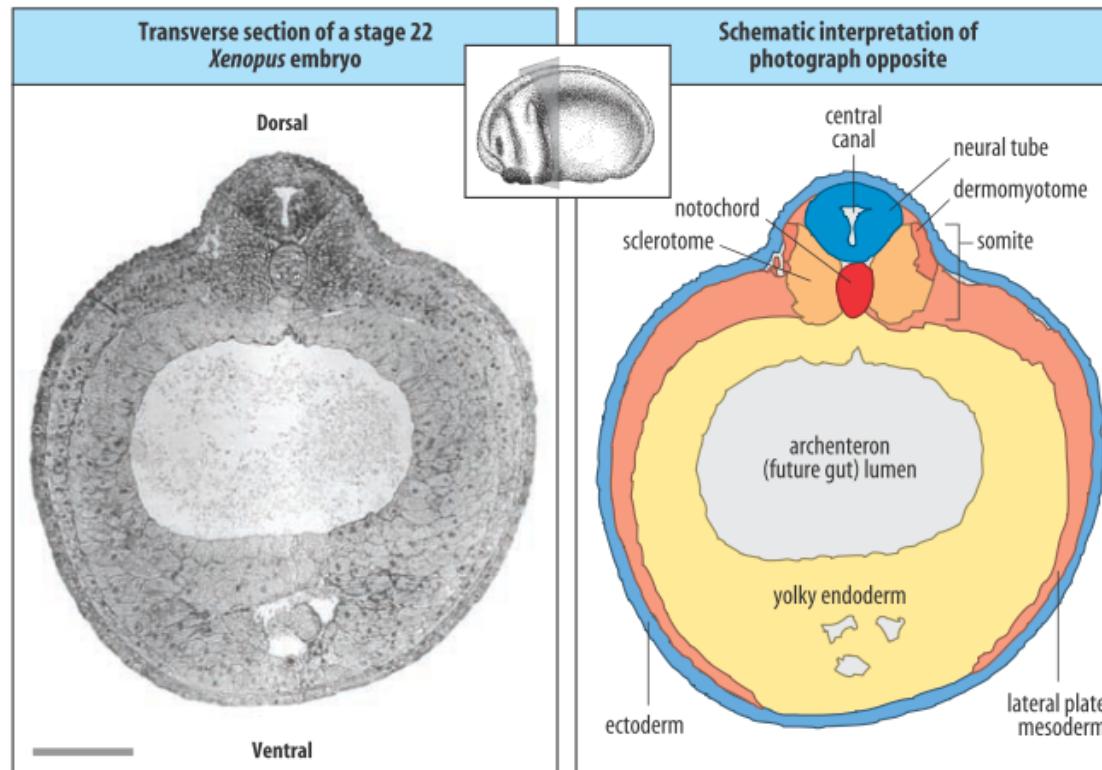
Human heart beating



Heart wall layers



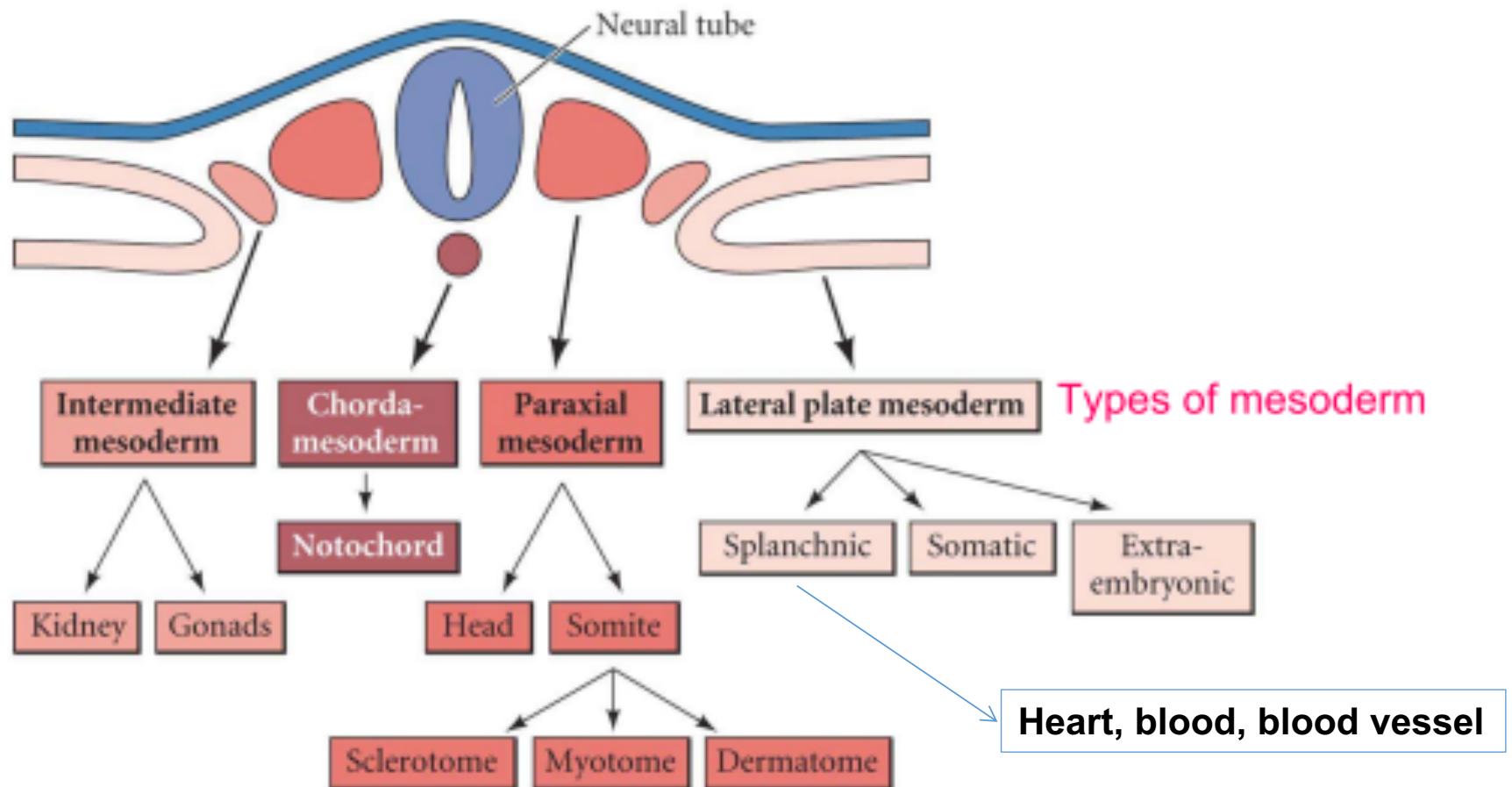
A cross-section through a *Xenopus* embryo



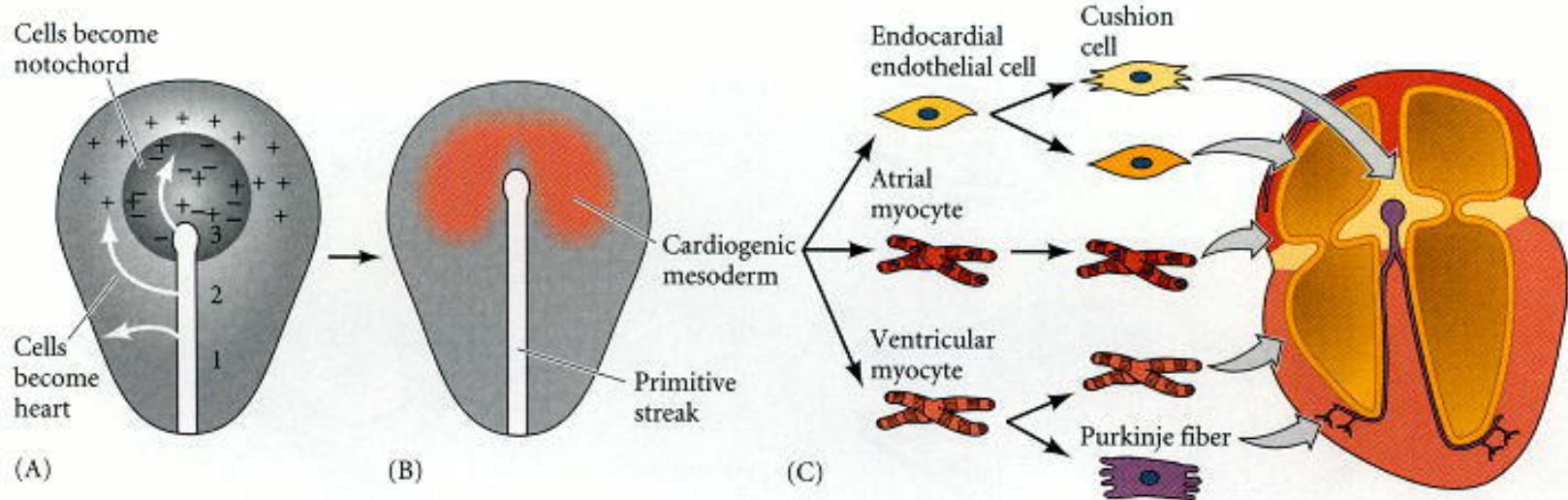
Sclerotome -> cartilage and bone.

Dermomyotome = dermo + myo -> dermis + muscle.

Heart origins from lateral plate mesoderm

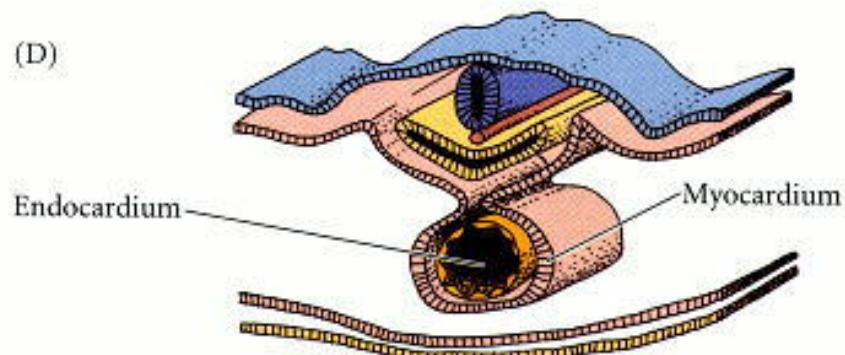
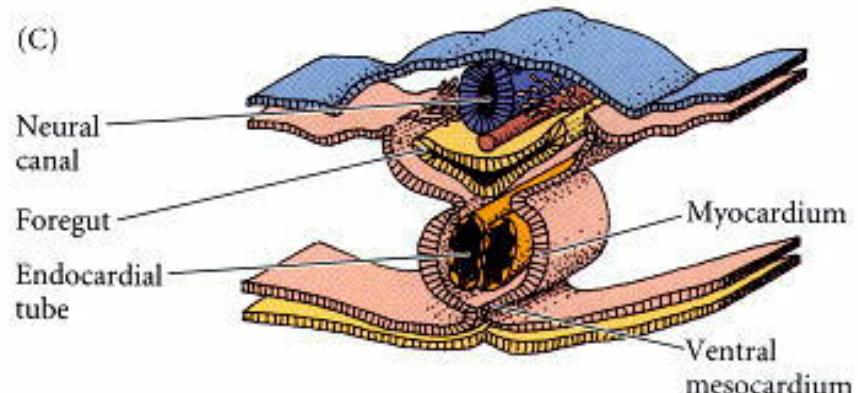
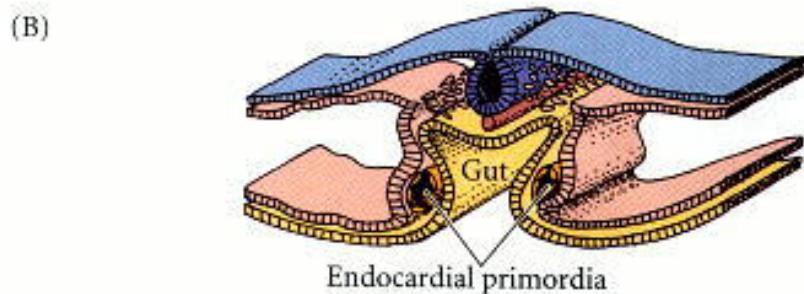
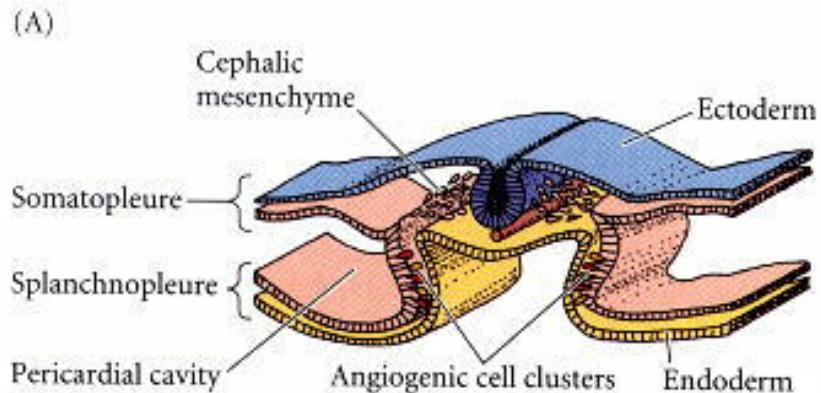


Cardiogenic mesoderm generates cells in heart



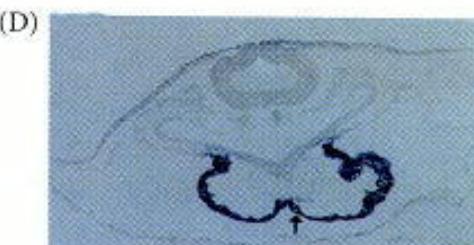
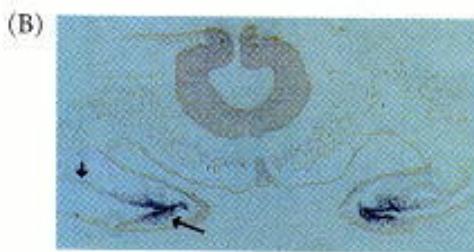
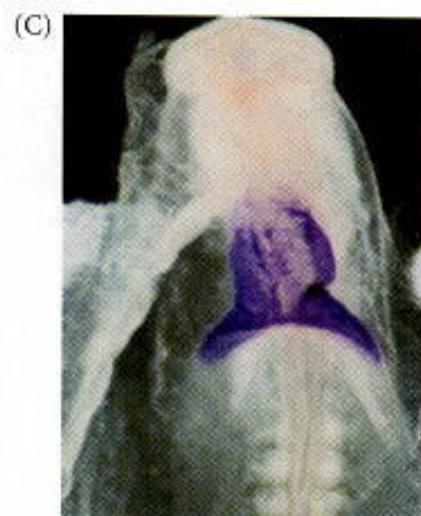
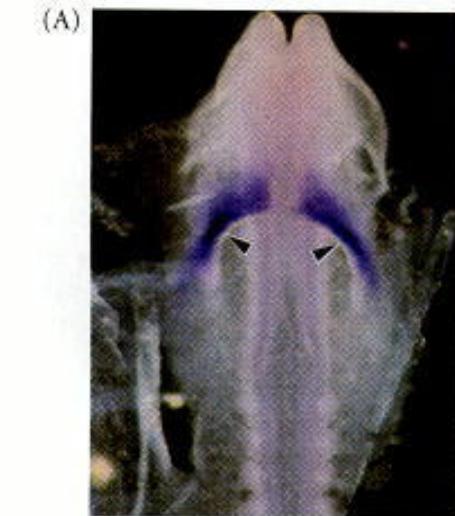
Formation of the chick heart from the splanchnic lateral plate mesoderm bilaterally

内脏的



Fusion of the right and left heart rudiments to form a single cardiac tube in chick

强心剂



Cardia bifida in zebrafish

The Sphingolipid Transporter Spns2 Functions in Migration of Zebrafish Myocardial Precursors

Atsuo Kawahara,^{1,2,*} Tsuyoshi Nishi,^{3,4} Yu Hisano,^{3,4} Hajime Fukui,¹
Akihito Yamaguchi,^{3,4} Naoki Mochizuki¹

Sphingosine-1-phosphate (S1P) is a secreted lipid mediator that functions in vascular development; however, it remains unclear how S1P secretion is regulated during embryogenesis. We identified a zebrafish mutant, *ko157*, that displays cardia bifida (two hearts) resembling that in the *S1P receptor-2* mutant. A migration defect of myocardial precursors in the *ko157* mutant is due to a mutation in a multipass transmembrane protein, Spns2, and can be rescued by S1P injection. We show that the export of S1P from cells requires Spns2. *spns2* is expressed in the extraembryonic tissue yolk syncytial layer (YSL), and the introduction of *spns2* mRNA in the YSL restored the cardiac defect in the *ko157* mutant. Thus, Spns2 in the YSL functions as a S1P transporter in S1P secretion, thereby regulating myocardial precursor migration.

During the late stages of zebrafish segmentation characterized by the formation of the somites, the myocardial precursors from both sides of the anterior lateral plate mesoderm migrate toward the midline to form the

tected in two separated domains (Fig. 1, C and G, and fig. S2); this finding suggests that the myocardial precursors failed to migrate but differen-

tiated into two chambers at the bilateral positions.

The migration of several mesodermal derivatives examined by the expression pattern of a vascular marker (*fli1*), an erythroid marker (*gata1*), a pronephric marker (*pax2*), and a lateral plate mesoderm marker (*hand2*) was not impaired in *ko157* mutants (figs. S2 and S3), which suggests that the migration of myocardial precursors is dominantly affected. Besides cardia bifida, there were abnormal blisters at the tip of the tail in the mutant (Fig. 1, D and H). These two characteristic phenotypes (cardia bifida and tail blisters) in the *ko157* mutant were similar to those in the *miles apart (mil)/S1P receptor-2 (SIP2)* mutant (4). Sphingosine-1-phosphate (S1P) is a lipid mediator involved in cell growth, death, migration, and differentiation (5–8). Both cardia bifida and tail blisters were observed in embryos injected with an antisense morpholino for *mil/SIP2 (mil MO; 15 ng)* (9) (fig. S4 and table S1), suggesting a genetic interaction between *ko157* and *mil/SIP2*.

Genetic mapping of the *ko157* mutation by means of simple sequence length polymorphism

Cadia bifida in zebrafish

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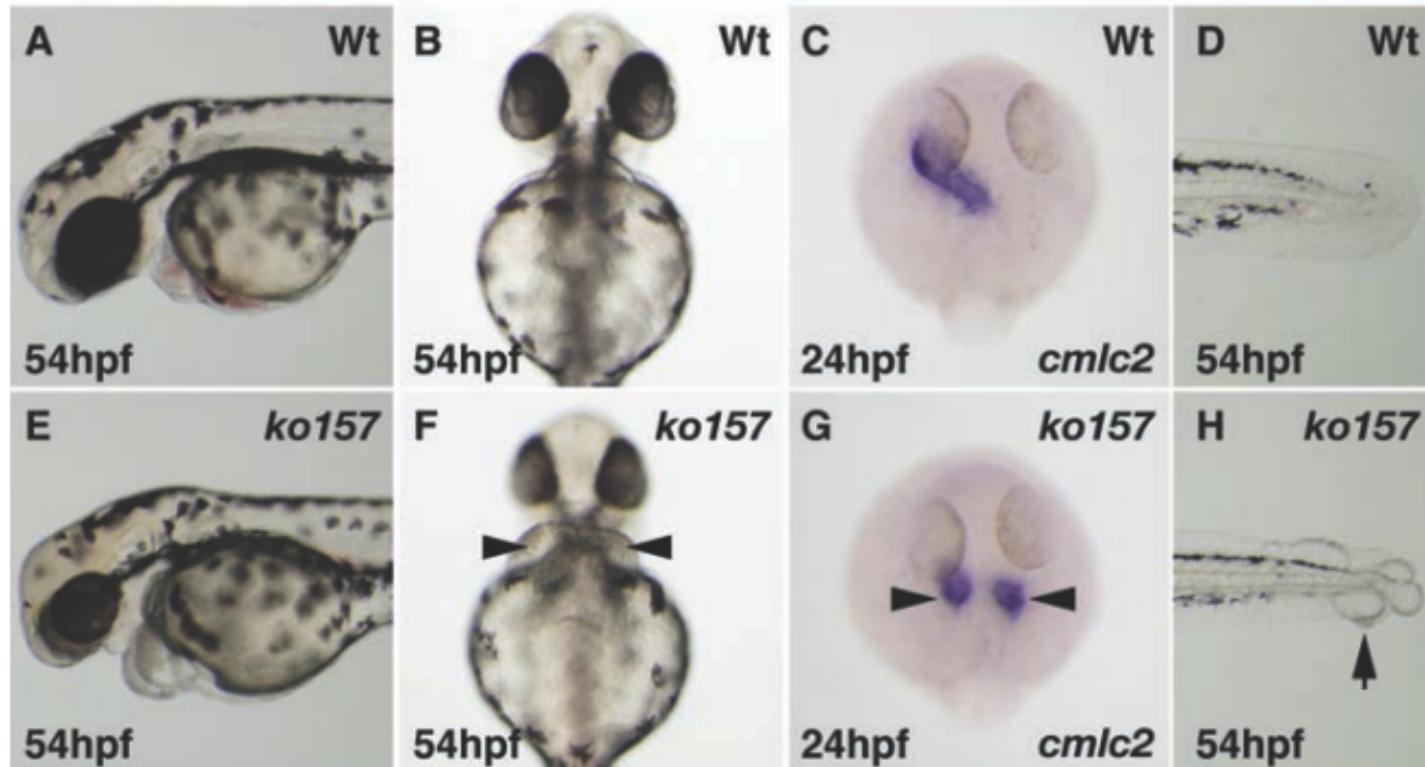
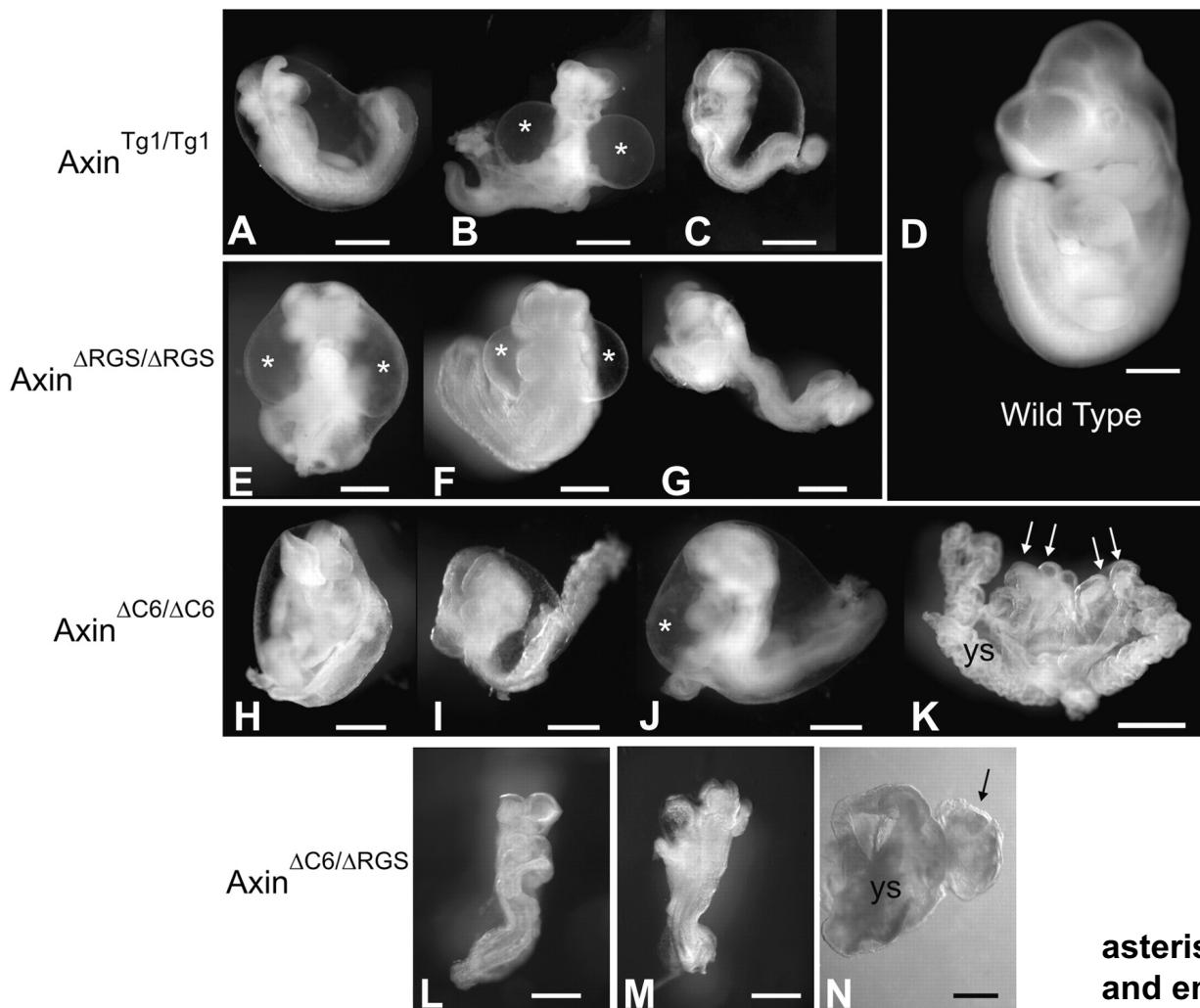


Fig. 1. Morphological phenotypes of *ko157* mutants. (A, B, D, E, F, and H) Stereomicroscopic views of wild-type (Wt) embryo [(A), (B), and (D)] and *ko157* mutant [(E), (F), and (H)]. Two swollen pericardial sacs (arrowheads) at 54 hours post-fertilization (hpf) were observed in *ko157* mutant [(E) and (F)] but not in Wt embryos [(A) and (B)]. (B) and (F) are ventral views. (C and G) Two hearts (arrowheads) in *ko157* mutants at 24 hpf were visualized (dorsal view) by whole-mount *in situ* hybridization with antisense *cmlc2* probe. *ko157* mutant (H), but not Wt embryos (D), exhibited tail blisters (arrow).

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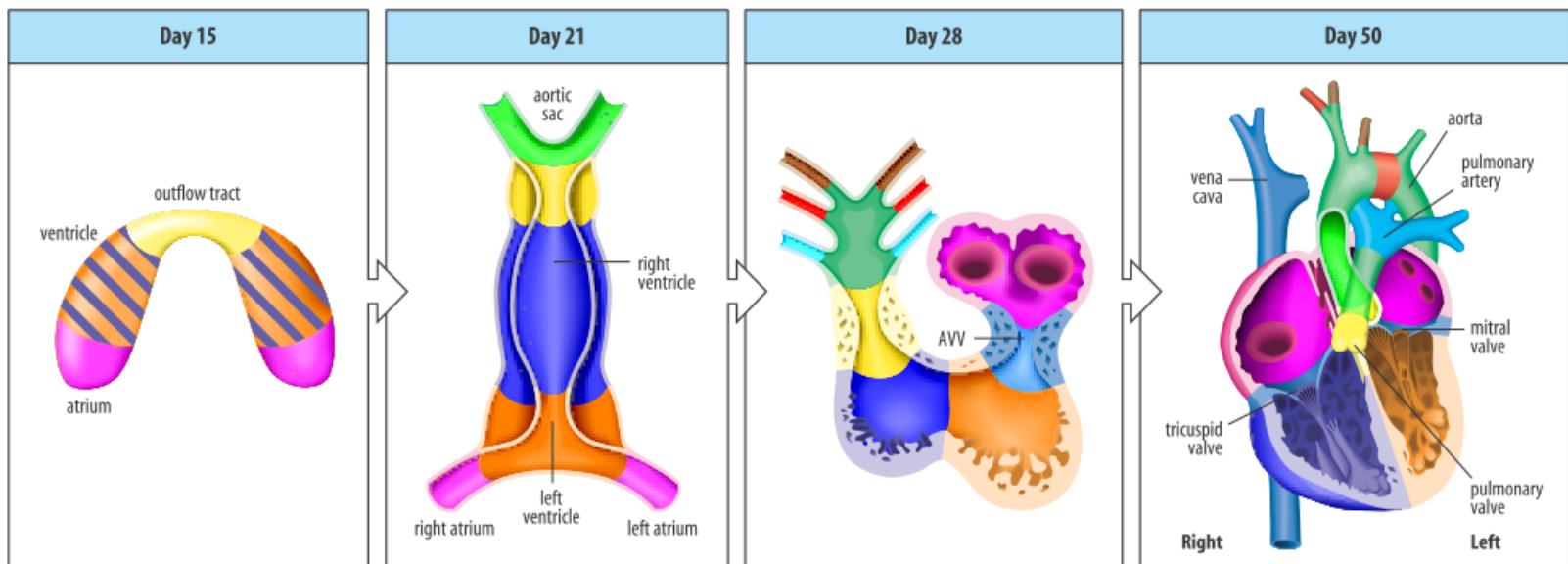
Axin Δ RGS or Axin Δ C6 homozygotes and Axin Δ C6/ Δ RGS compound heterozygotes display an embryonic lethal phenotype indistinguishable from that of the null allele AxinTg1.



Chia I V et al. Genetics 2009;181:1359-1368

GENETICS

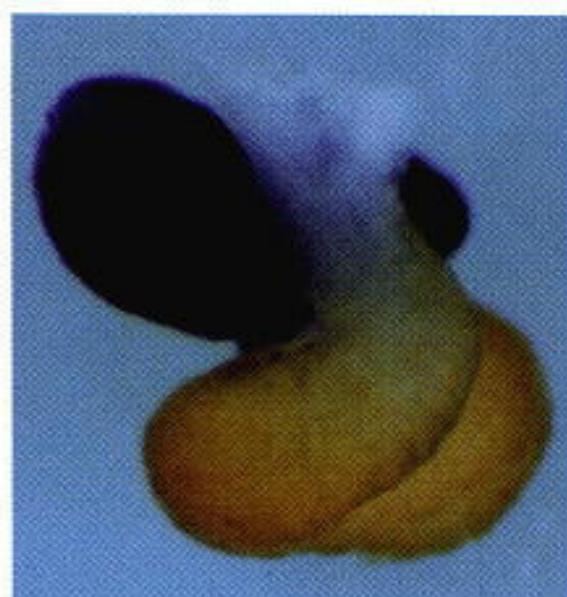
Schematic of human heart development



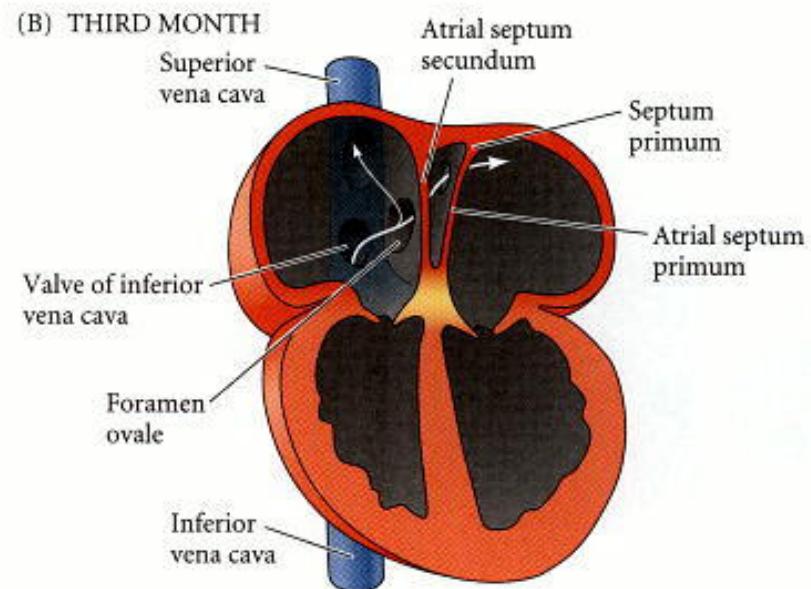
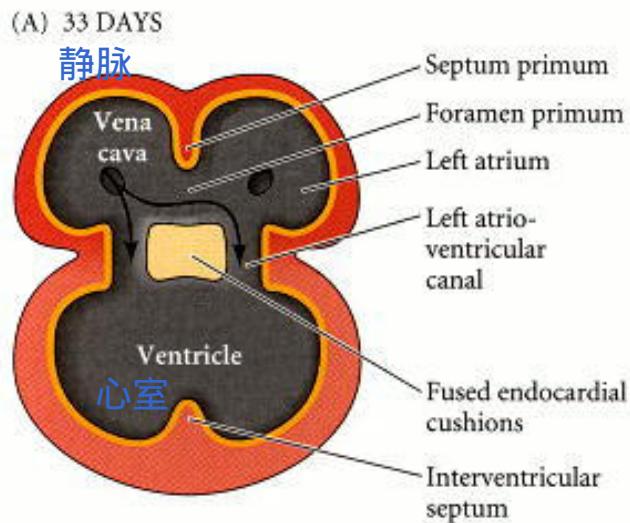
心房

心室

Specification of the atrium and ventricles
occurs even before heart looping

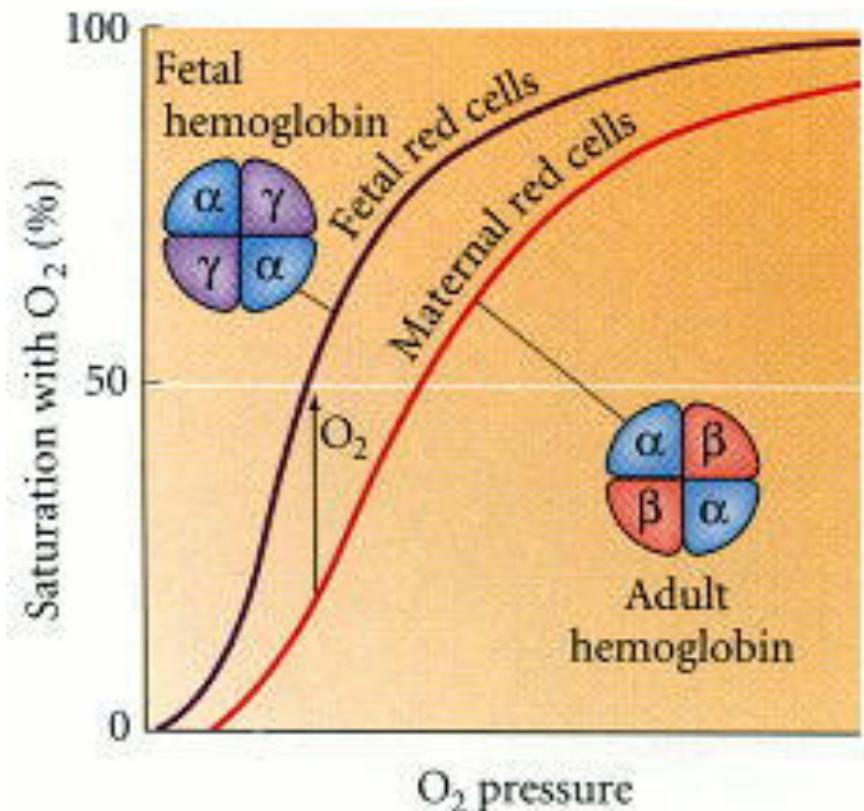


Formation of the chambers of the heart

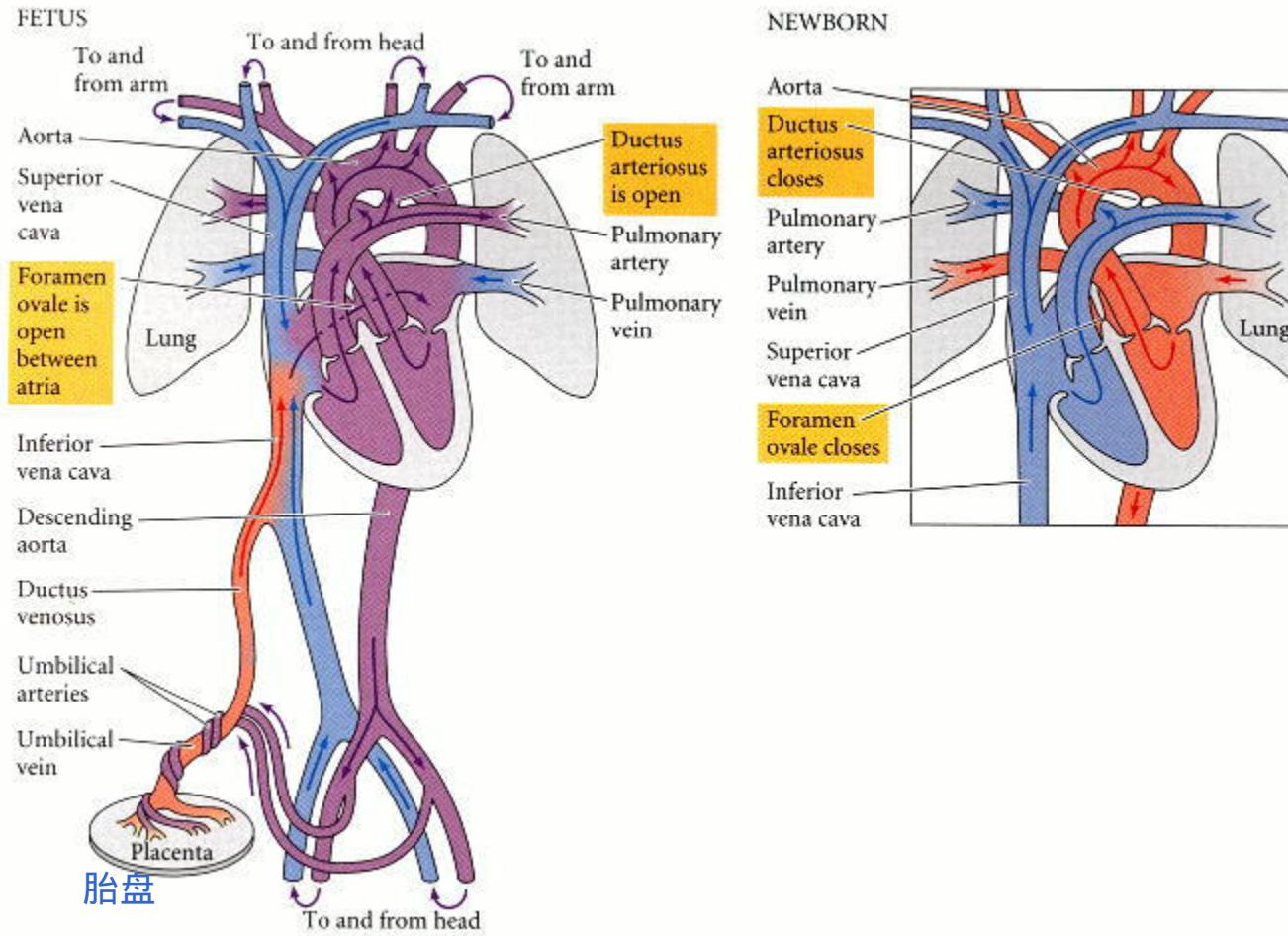


Transfer of oxygen from the mother to the fetus in human embryos

胎儿

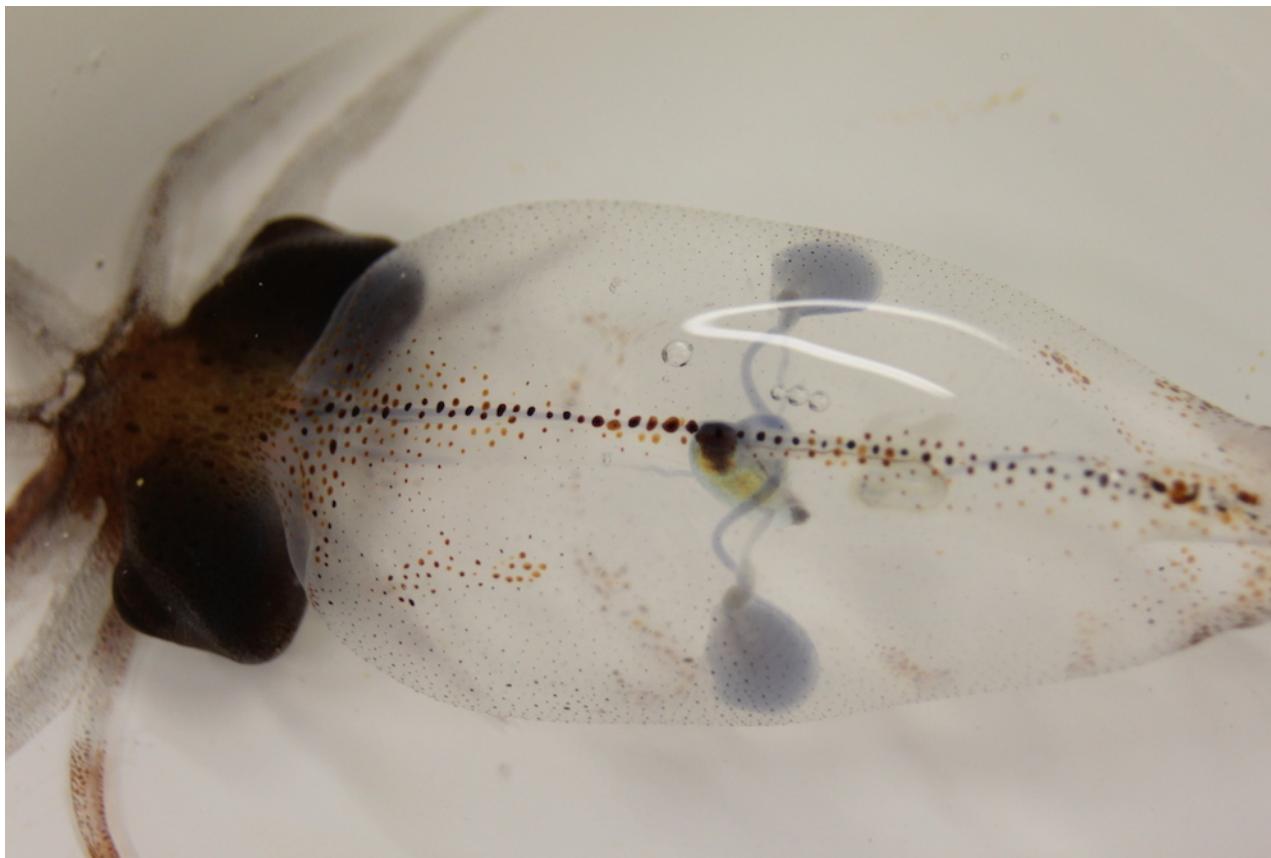


Redirection of human blood flow at birth



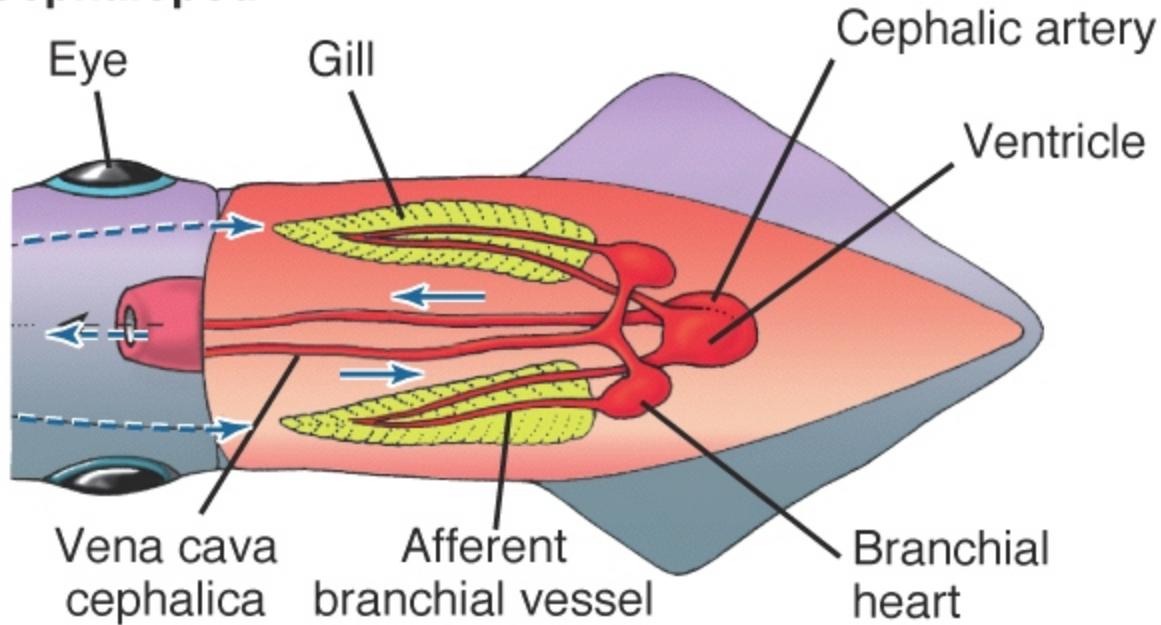
Three hearts for cephalopods

头足类动物



Three hearts for cephalopods

(c) Cephalopod





"A major advantage of this application is that although zebrafish may present a good model for developmental studies, the fact that zebrafish embryos, in contrast to those of chick and mouse (birds), are not dependent on a functional circulatory system makes it difficult to anticipate that similar molecular and cellular mechanisms are involved in the development of the heart in humans and zebrafish."

NBC reviewer 4/25/95

"The relevance of myocardial differentiation in the zebra fish to that in higher vertebrates has yet to be clearly established."

Akira Nakanishi Committee reviewer 9/1999

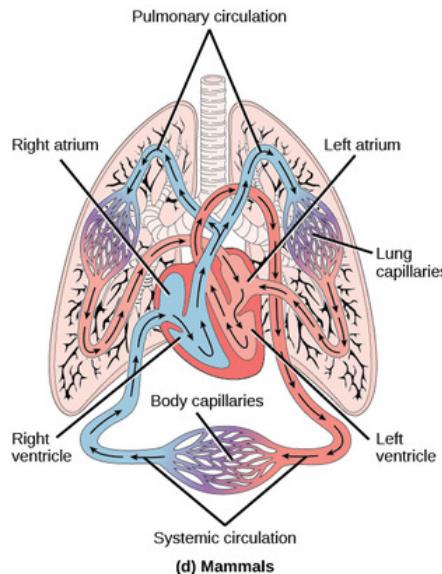
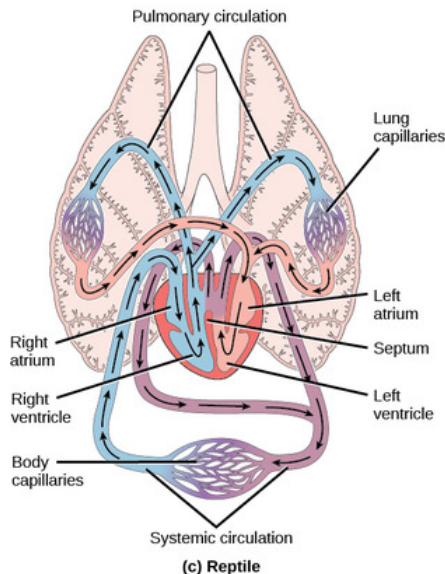
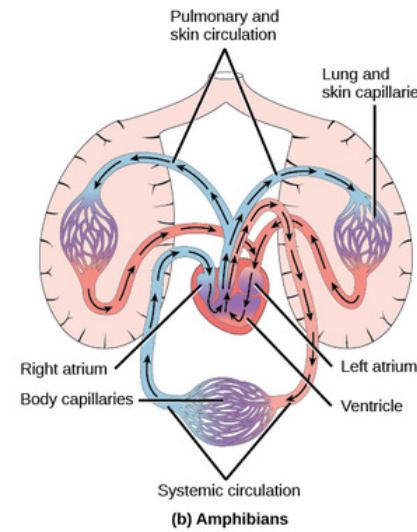
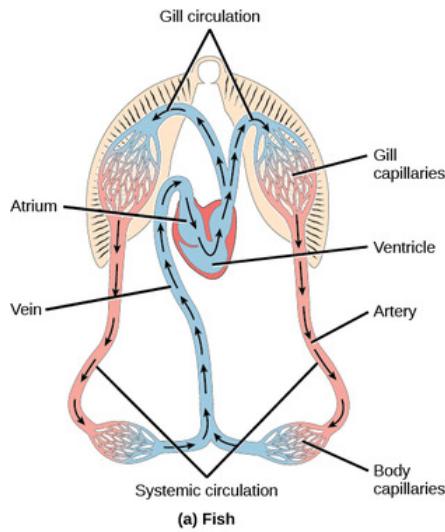
"A major weakness of this application is that although zebrafish may present a good model for developmental studies, the fact that zebrafish embryos, in contrast to those of chick and mammals (humans), are not dependent on a functional circulatory system makes it difficult to anticipate that similar molecular and cellular mechanisms are involved in the development of the heart in humans and zebrafish."

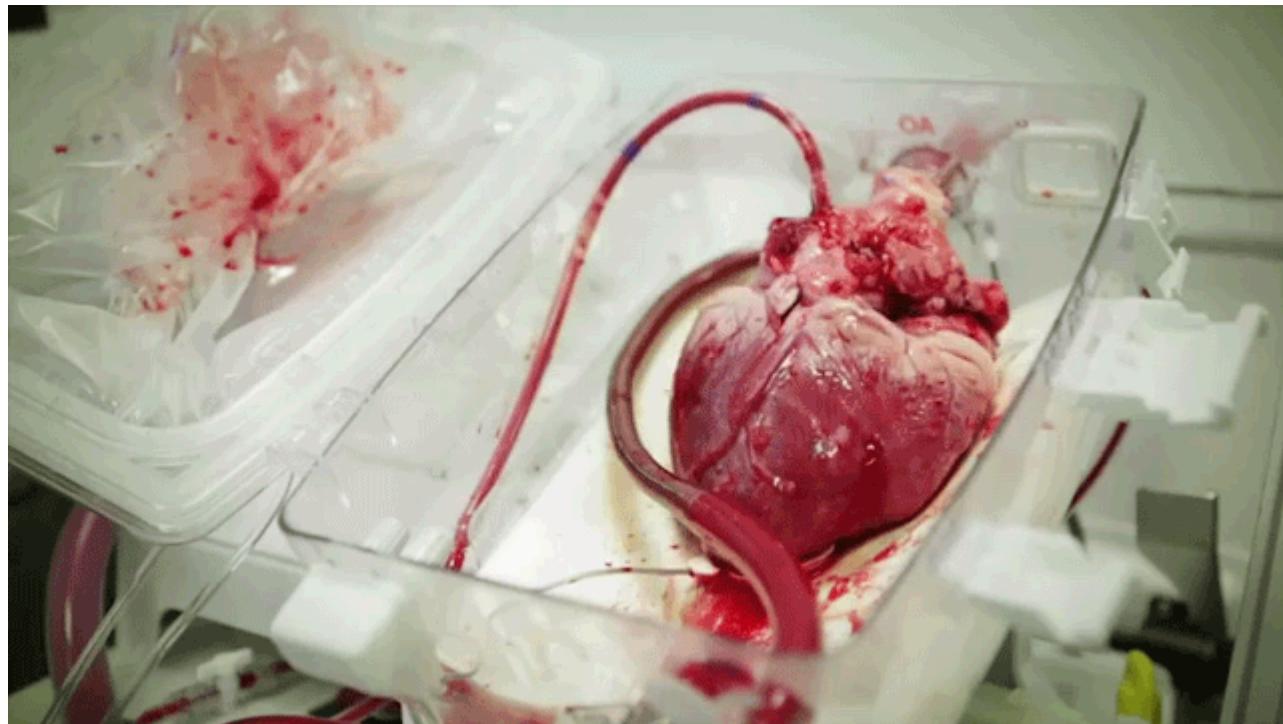
NIH reviewer 4/25/95

"The relevance of myocardial differentiation in the zebra fish to that seen in higher vertebrates has yet to be clearly established."

AHA National Committee reviewer 9/99

Thanks!







$$A = 4\pi x^2$$

$$V = \frac{4}{3}\pi x^3$$

$$J = kA \frac{dp}{dx} = k 4\pi x^2 \frac{dp}{dx}$$

P 氧分压

$$J = mV = m \frac{4}{3}\pi x^3$$

m 单位耗氧量

$$m \frac{4}{3}\pi x^3 = k 4\pi x^2 \frac{dp}{dx}$$

$$\frac{m}{3k} x dx = dp$$

$$\frac{dp}{x} = \frac{m}{3k} dx$$

$$\int dp = \int \frac{m}{3k} x dx$$

$$P_0 \geq 0$$

$$\therefore P_e \geq \frac{m}{6k} r^2$$

$$r \leq \sqrt{\frac{P_e 6k}{m}}$$

$$P_0 = 0.21$$

$$k = 8 \times 10^{-4} \text{ cm}^2$$

标准大气压

$$m = \underline{0.1}$$

$$\therefore r \leq 1 \text{ mm}$$

$$\int_0^r x dx = \frac{1}{2} r^2$$

附录二 球形动物的极限体型

若球形动物既没有呼吸系统也没有循环系统，仅依靠体表扩散氧的话，体型能变多大呢？

动物（球形）的半径为 r ，假定在距离球心 x 的地方有一个球面。



球面的面积 $A=4\pi r^2$ ，那么球的体积 $V=\frac{4}{3}\pi r^3$ 。

使用下面的公式求通过球面的氧的量。

$$J=-KA \frac{dp}{ds}$$

在这个公式里， J 是依据单位时间通过球表面（面积 A ）物质量获得的， $\frac{dp}{ds}$ 是物质（这是指氧）的浓度勾配。在这里， $s=r-x$ 。

这个氧的量是指球面内侧组织所使用的量，假如这个动物平均单位体积的耗氧量为 m ，那么仅仅需要流进 mV 的量。

因此公式的左边是：

$$J=mV=m \cdot \frac{4}{3} \pi r^3$$

165

166

公式的右边是：

$$-KA \left(\frac{dp}{ds} \right) = 4K\pi r^2 \left(\frac{dp}{dx} \right)$$

去掉两边相同的部分整理后就成为：

$$dp = \left(\frac{m}{3K} \right) x dx$$

x 从 0 到 r 积分。

如果动物体外的氧压为 P_e ，而动物的中心的氧压为 P_0 ，那么

$$P_e - P_0 = \left(\frac{m}{6K} \right) r^2$$

因为 P_0 不会变为负数，所以，

$$P_e \geq \left(\frac{m}{6K} \right) r^2$$

因此，

$$r \leq \sqrt{\frac{6P_e K}{m}}$$

在此，

$$P_e = 0.21 \text{ 标准大气压 (大气中的氧压)}$$

$$K = \frac{8 \times 10^{-4}}{\text{标准大气压} \cdot \text{时}} \text{ (动物组织的实测值)}$$

$$m = \frac{0.1 \text{ 厘米}^3 \text{O}_2}{\text{厘米}^3 \cdot \text{时}} \text{ (无脊椎动物的实测值)}$$

代入这些值， $r \leq 1$ 毫米。

对于扁虫那样的生物，氧会从身体上方进入，利用和上面相同的方法计算出它的最大厚度。结果如下

$$r \leq \sqrt{\frac{2P_e K}{m}}$$

代入上面 P_e 、 K 、 m 的值，得出 $r \leq 0.6$ 毫米。

圆柱形的生物，氧从表面进入，利用下面的公式计算：

$$r \leq \sqrt{\frac{4P_e K}{m}}$$

代入上面 P_e 、 K 、 m 的值，得出 $r \leq 0.8$ 毫米。

1. 自供血

心房 (Atrium)

2. 2 chambers \rightarrow 4 Chambers

心室 (Ventricle)

3. 能量

4. 自律



5. 血管 \leftrightarrow 肌肉

9. 先天 or

6. 血流方向 + 血量.

后天改变

7. 心房 / 室 的决定 / 分化

10. 心脏
修复

8. 心脏对称.

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