

Fallen arches, or how the vertebrate got its head.

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Editorial

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The pharyngeal arches are embryonic structures, roughly in the position of gills, that contain most of the progenitors needed to assemble the evolutionarily “new head,” i.e., the face, neck, and major vascular structures added by vertebrates to our headless chordate ancestor (1). The sausage-like links of the six arches are generated by the outpouching of endoderm and the infolding of ectoderm, and are filled with cells migrating from the neural crest and lateral plate mesoderm (Fig. 1). Endothelial channels emerge from this mesodermal core, carrying blood from the heart to dorsal aortae. The arches give rise to bones, muscles, and other tissues of the face and neck, and the vessels undergo remodeling to form the major arteries of the thorax, i.e., brachiocephalic, carotids, aortic arch, and ductus arteriosus (Fig. 2). But what are the signals for arch design and remodeling? Are they orchestrated from a localized epithelial signaling center, as is the other great appendage, the limb bud? The answer is still unknown, but there are tantalizing clues to suggest that it is so.

During development, a special population of neural crest cells migrates from the length of the developing hindbrain to populate all of the arches. In birds and mammals, there are four true arches (numbered 1–4) and one pseudo-arch (No. 6). Arches 1 and 2, the most cranial of the arches, contribute largely to skeletal structures of the lower face, while the more caudal arches, 3, 4, and 6, support arterial development and do not play a significant role in skeleton formation. The crest-derived mesenchyme is organized somewhat differently in more cranial as opposed to more caudal arches (Fig. 1). In pharyngeal arches 1 and 2, where crest participates in formation of skeletal components, it condenses in the lateral portion of the arches beneath the ectoderm (2). In the caudal arches, the crest cells invest the endothelial cell precursors of the arch arteries, and hence occupy a more central position (3). This is most likely to have been the original crest position in the cranial arches before they were conscripted for service in building the lower face.

The presence of crest in the arches is not necessary for the arch arteries to open in a bilaterally symmetrical pattern. However, in the absence of their neural crest-derived sheaths, the caudal arch arteries are not stable and do not repattern themselves into the normal great arteries (4). The arch arteries in pharyngeal arches 1 and 2 never persist under normal circumstances, while those in 3, 4, and 6 remain and undergo remodeling. Until recently, the molecular information required for these repatterning steps has been largely unknown. However, targeted gene mutations in mice suggest roles for *hoxa-3*, *RAR α* and β , and for some of the components of the endothelin system.

In fact, endothelin 1 (ET-1)¹ now appears to be a good candidate for an arch signal needed for vascular remodeling (5–7).

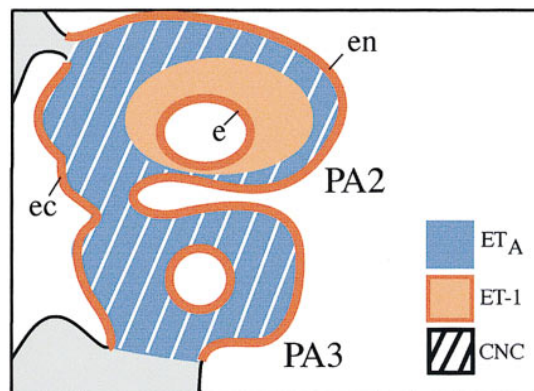


Figure 1. One side of pharyngeal arches 2 (PA2) and 3 (PA3). The arches are covered externally by ectoderm (ec) and lined by pharyngeal endoderm (en). Each pharyngeal arch contains endothelium of an aortic arch artery (e), surrounded by mesenchyme. The arch arteries in PA1 and 2 regress while those in PA3, 4, and 6 are remodeled into the great arteries as shown in Fig. 2. The central core of mesenchyme in pharyngeal arches 1 and 2 (light orange) is not derived from neural crest, while in 3, 4, and 6 the central core is from neural crest (hatched blue). In arches 1 and 2 the neural crest–derived mesenchyme is displaced circumferentially by the noncrest mesenchyme. The sites of ET_A and ET-1 expression are indicated.

ET-1 is best known for its role in the adult, where it serves as an endothelin-derived peptide with extraordinarily potent vasoconstrictor properties (8). Active ET-1 (21 amino acids long) is generated by endothelin-converting enzyme (ECE-1) cleavage of the precursor, and signals via the ET_A receptor to trigger contraction and proliferation of smooth muscle cells.

As shown in Fig. 1, *ET-1* is expressed in the epithelial layer and in the inner lateral plate mesoderm-derived core of pharyngeal arches 1 and 2 in the mouse embryo (5, 6). *ECE-1* is expressed in both the surface epithelium and mesenchyme. ET_A is in the migrating neural crest cells and in the neural-crest-derived mesenchyme in the arches (6, 7). (This is a bit of an oversimplification. Precise stage and arch-specific variations still need clarification.)

Targeted ablation of each component of the cascade, *ET-1*, *ECE-1*, or ET_A, disrupts arch development, with grossly similar phenotypes (5–7). The essential morphological underpinning is an anomalous loss of some arch arteries and retention of others, as discussed in the paper by Yanagisawa et al. in this issue of *The Journal* (9). The phenotype is variable and complex, even in genetically homogeneous backgrounds, perhaps because other factors, including hemodynamics, also modify arch development. Neural crest cells appear to migrate normally to the arches, suggesting that it is deficiency in signaling within the arches that is responsible for the defects.

Therefore, it seems most likely that the surface epithelia of

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1. Abbreviations used in this paper: ECE-1, endothelin-converting enzyme; ET-1, endothelin 1.

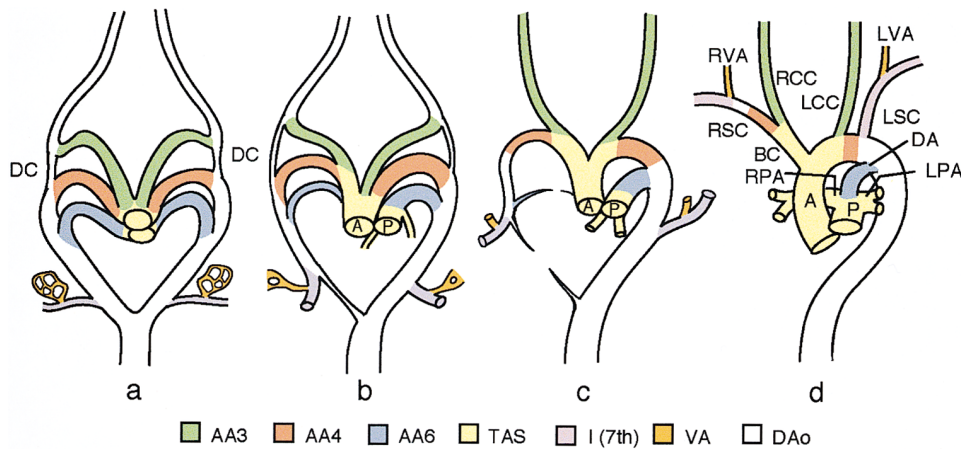


Figure 2. Remodeling the persisting aortic arch arteries, 3 (AA3), 4 (AA4), and 6 (AA6) from their initially bilaterally symmetrical configuration to the normal adult pattern. The aorta (A) and pulmonary trunk (P) are remodeled from the aortic sac and give rise to the brachiocephalic (BC) which branches into right common carotid (RCC) and right subclavian (RSC). The second major branch is the left common carotid (LCC). The ductus arteriosus (DA) connects the left pulmonary trunk with the dorsal aorta (not labeled).

the arches secrete ET-1, which is locally converted by ECE-1 into active ET-1, which then acts upon neural crest cells to dictate their fate.

What are the downstream effectors of the ET-1 signal? Some candidates include the transcription factors goosecooid (6), dHAND, and eHAND (10, 11), all of which are expressed in the arch mesenchyme. *goosecooid* and *dHAND* (10) mutant mice evidence arch defects, and *goosecooid* expression is absent in *ET_A* mutant mice (6). It will be of interest to determine the effectors of this pathway, not least because it may include culprit genes for presumptive aortic arch anomalies in humans, such as the DiGeorge syndrome (12).

Similarly, the cellular mechanism of arch and vessel remodeling needs exploration. In general, stabilization of embryonic endothelial tubes is believed to be due to signaling from surrounding cells, including pericytes in small and smooth muscle in large vessels. Some signals, such as angiopoietin 1 and 2 and their tie 2 receptor, have been identified as crucial to this process, at least in other vessels (13). Vessel regression in at least one site is believed to be a result of local vascular occlusion and a consequent apoptotic loss of endothelial cells (14). Could ET-1 recruit or cause differentiation of certain types of perivascular cells? Could local constriction in certain arches lead to cell death, and, if so, what cells would mediate the constriction and why would it be localized to particular arches? Does the arch expression of smooth muscle gene *SM22 α* (15) suggest that arch mesenchyme is contractile?

This is an exciting beginning. Like the limb bud, there are likely to be many coordinates to patterning information. If the limb bud is any guide, such signals may originate from a local signaling center, and the surface epithelium is a good candidate. In the limb bud this region, the apical ectodermal ridge, maintains mesodermal growth by signals such as FGF 8 (16), and establishes the antero-posterior and dorso-ventral axes by secretion of localized signals such as sonic hedgehog in the posterior mesoderm and Wnt-7a in the dorsal ectoderm. Aortic arch arteries also develop a marked right-left asymmetry, orchestrated by signals from the neural crest.

Considering how much research into the limb bud has taught us about developmental biology, it follows that a similar effort is warranted for the arches. After all, they are the basis of our "new head."

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