NEWS & VIEWS

EVOLUTIONARY BIOLOGY

Born-again hagfishes

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The strange, slimy creatures called hagfishes are of abiding interest to students of vertebrate evolution: just where do they fit in? Investigations of hagfish development take the story forward.

Hagfishes are almost blind, cartilaginous, eel-shaped, marine vertebrates and, most notably, they lack jaws. Their relationships to other major living vertebrate groups — the similarly jawless lampreys, and the jawed vertebrates — remain contentious, and one avenue of investigation is to look to embryonic development for further information. Alas, hagfish embryos that are suitable for such studies have been desperately rare. In a paper published on *Nature*'s website today[1], however, Ota and colleagues describe the first early embryos from hagfishes to have been found since 1930, and report their studies on gene-expression patterns in them.

Hagfishes (Fig. 1) are occasional scavengers, and are frequently found inside dead fish. So Linnaeus[2] classified them among the 'intestinal worms', although he noticed that they share some characteristics with lampreys, and thus with vertebrates. They then became classified with lampreys as cyclostomes ('rounded mouth') because both possess a jawless mouth armed with retractable horny teeth, and gills enclosed in pouches. Living vertebrates thus fell into two major groups, the cyclostomes and the jawed vertebrates (or gnathostomes), which remained the received view for more than 170 years.

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Figure 1 | Fresh and slimy hagfishes. These are specimens of *Eptatretus burgeri*, the species studied by Ota *et al.*[1], caught by fishermen in the sea off Shimane prefecture, Japan.

However, biologists progressively noticed that hagfish anatomy and physiology were in many respects more 'simple' or 'primitive' than those of lampreys and jawed vertebrates. Unlike these two groups, hagfishes lack vertebrae, heart innervation, eye lenses, lymphoid tissues, a perfected adaptive immune response, and many other classical vertebrate characters. In these respects, then, they resemble non-vertebrate chordates such as amphioxus or sea-squirts. That meant that there are two possibilities (Fig. 2). First, that hagfishes are 'degenerate' cyclostomes — that is, they have lost several vertebrate characters that lampreys and jawed vertebrates retain (unless independently acquired, which is unlikely). Second, that they are actually the most primitive vertebrates, and so are the 'sister group' of all other vertebrates[3]. Phylogenies based on DNA and RNA sequencing generally support the first hypothesis, but remain ambiguous[4,5].

Palaeontology sometimes settles such conflicts. But it is powerless in this case, because the earliest (300-million-year-old) hagfishes, preserved as soft-tissue imprints, are very similar to living ones. Moreover, the distribution of lampreys and gnathostomes through time suggests that hagfishes had a 'ghost range' of between 50 million and 170 million years during which they were apparently present, but are unrecorded[6]. In such cases, embryonic development may provide clues, on the assumption that early embryos may mirror ancestral conditions. But hagfish eggs found on the sea floor generally contain no visible embryo, probably because their development is very slow and early embryos may be missed[1]. Out of the 150 fertilized eggs found between 1896 and 1930, only a few embryos could be studied, but the techniques then in use did not allow detailed description.

However, among the embryonic hagfish features described 65 years ago[7] was the odd development of the 'neural crest', a unique vertebrate structure that has possible precursors in other chordates[8,9]. During the embryonic development of lampreys and gnathostomes, the brain and spinal cord form from a dorsal infolding of the ectoderm (the future epidermis of the skin), which then closes into a 'neural tube'.

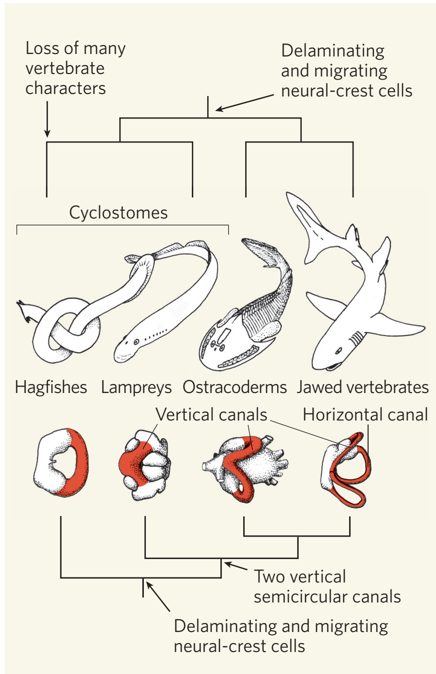

Figure 2 | The hagfish puzzle. Ota *et al.*[1] show that hagfishes have delaminating and migrating neural-crest cells, a feature of vertebrate head development. But it is still not clear whether hagfishes are 'degenerate' cyclostomes (top tree), or are 'primitive' and are the sister group of all other vertebrates (bottom tree). This second hypothesis is supported by many characters shared only by lampreys, jawed vertebrates and jawed-vertebrate precursors, the 480–365-million-year-old jawless ostracoderms. Notably, there are differences in the canals (red) of the inner ear (labyrinth): the hagfish labyrinth possesses a single semicircular canal for balance, whereas all other vertebrates have at least two, vertical, canals.

Where the two lips (or crests) of this infolding meet to close the neural tube, some cells of the ectoderm delaminate, becoming free, and then migrate to contribute to essential organs of the vertebrate body, such as the branchial apparatus, part of the braincase, and the dermal bones, scales, teeth, nerve ganglia and pigment cells. The neural crest thus generates a 'new head', which possibly made vertebrates more competitive in the early stage of their

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evolution[10]. Early studies of hagfish embryos suggested that their neural crests remained in the form of a simple epithelial 'pocket' that did not delaminate and migrate in the same way as in other vertebrates.

Ota *et al.*[1] have been both lucky and ingenious in finding the right style of aquarium where the shy and capricious hagfishes can thrive and spawn. But they were also helped by local fishermen, who knew of the secret and seasonal behaviour of their subjects. Thanks to these efforts, Ota *et al.* can now show that the epithelial pocket is a mere artefact, and that the neural-crest cells of hagfishes delaminate and migrate like those of all other living vertebrates. With this discovery, hagfishes become more 'conventional' vertebrates. And the increased understanding of hagfish spawning habits will make access to their embryos much easier, and thereby help in understanding why certain features of their anatomy and physiology are so odd and apparently primitive.

For example, the labyrinth (inner ear) of vertebrates comprises bow-shaped semicircular canals that ensure balance (Fig. 2). Hagfishes have only one such canal, with sensory ampullae forming a swelling at each end, hence the doughnut shape of their labyrinth that is already visible in early embryos[1] and has long been regarded as primitive. Lampreys and gnathostomes have two vertical canals, each with one ampulla, and gnathostomes have an additional horizontal canal. There is no intermediate between these three conditions, even among fossil 'stem' gnathostomes, the jawless ostracoderms, whose labyrinth is lamprey-like.

Which of these conditions is primitive for vertebrates? Is the hagfish condition derived from that of lampreys by fusion of the two vertical canals? Two genes, *Otx1* and *BMP2*, have proved to be involved in the development of semicircular canals[11,12]. But the morphogenetic control of such remarkably conserved anatomical features also involves complex pathways that regulate their development. Further analyses of the developmental genetics of hagfish embryos might enable us to discover whether hagfish anatomy is primitive or degenerate, and may help in reconstructing the theoretical common ancestor to all vertebrates. ■

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