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Editorial

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Vette to Volt: Evolution of Cardiac System

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Automobiles of these days are under constant pressure to become more environment friendly and fuel efficient. Conventional cars are constantly replaced by hybrid vehicles. Chevy Volt, a solution presented by General Motors Cooperation, has a gasoline engine which works mostly as a generator to charge battery that supplies energy for electric motors. Therefore, the engine provides motive power only indirectly by means of electric energy instead of directly through transmission as with Chevy Corvette (nicknamed Vette). Overviewing the process of evolution of cardiac system in multicellular organisms based on both published sources and preliminary information, we find that the evolution of cardiac system shares common features with the evolution of automobiles.

Former research on the evolution of cardiac system or cardiovascular system has dealt with the heart in lower vertebrates or primitive invertebrates, e.g. fishes, chordates (tunicate), molluscs (Aplysia), arthropods (Drosophila) as model systems. Strangely, however, extensive discussion has not been made about how the cardiac system started in evolution, from one origin or from multiple origins.

The first breakthrough for this problem came from the identification of a non-hox type homeobox gene *Nkx-2.5* [1]. This gene originally identified as *tinman* in Drosophila [2] as the gene expressed in dorsal vessels (flies' heart) mesodermal muscle has now been recognized as a heart progenitor gene, namely the genetic switch for heart formation. What is interesting about this gene is that it is expressed not only in the mesodermal tissue of the heart progenitor, but also in the tissue of primitive invertebrates that has no heart, no vascular system, or even no mesoderm. A typical example is found in hydra, a member of class hydrozoa of phylum Cnidaria. Cnidaria diverged from Eumetazoa (metazoan common ancestor) before it split into Protostomia and Deuterostomia [3]. Cnidaria consists of four classes, Anthozoa (most ancestral, includes corals and sea anemone), Scyphozoa, Cubozoa and Hydrozoa (most descendent, includes hydra). Hydra is made up of a cylindrical body column with a head at one end and a foot at the other end. Hydra's orthologue of *Nkx-2.5* was cloned by Grens et al. [4] as *CnNk-2*. *CnNk-2* is expressed in the endodermal tissue of the peduncle which is located adjacent to the foot end. Although initially interpreted as a gene that specifies the area of peduncle formation, later physiological analysis by Shimizu and Fujisawa [5] provided an entirely different view. The internal cavity of hydra body column termed gastrovascular cavity has been thought to be an open space where diffusion of materials takes place and this diffusion has been considered a primitive but efficient way of material transport in primitive metazoans that have no circulatory system. Shimizu and Fujisawa [5] showed that the gastrovascular cavity of hydra is normally closed unlike previously thought and contraction of the animal that takes place as irregular events makes the cavity open that enabling the circulation of fluid in the cavity (Figure 1). They also showed that the peduncle behaves as a pump to circulate the fluid throughout the cavity. To add to it, a type of neuropeptide termed Hydra RFamide III [6] had an effect to elevate the frequency of contraction and pumping whilst in flies, some RFamides have an effect to elevate heart rate [7]. These observations implied that the peduncle of hydra shares several features in common with the heart of higher organisms, showing pumping movement, involving *Nkx-2.5* orthologue in specification of the pumping tissue, and involving potential cardioactive neuropeptides. Meanwhile, a difference from the heart was that the pumping takes place not in the coelomic space as in vertebrates but in the gut of hydra. Notice here that Cnidarians are called acoelomate that has no coelom and the only space in the animal is the gut. These considerations suggest a possibility that hydra did not depend upon diffusion in the gastrovascular cavity for material transport but depended upon pumping movement based on a similar mechanism to the heart beat in higher organisms.

Although the level of atmospheric oxygen varied between 15-35% during the past 550 million years [8], for small sized animals, the development of the organ to transport oxygen throughout the animal by pumping movement may not have been a matter of high priority. Our current interpretation is therefore that pumping of the tissue that expresses *Nkx-2.5* orthologues might have played different roles such as the material transport in the gut. There is another example of pumping behavior in heart free invertebrates while involving an *Nkx-2.5* orthologue. In nematodes, *ceh-22* was originally identified as an *Nkx-2.5* orthologue that is expressed in the pharyngeal muscle cells [9]. The tissue that expresses *ceh-22* shows pumping movement constantly and this provides motive power to send ingested food throughout the digestive tract [10]. Possibly because of this function, the gut tissue of nematodes is not furnished with enteric nervous system (ENS) that plays the dominant role in sending bolus forward by peristaltic movement. These two examples, one in hydra and the other in nematodes suggest a possibility that pumping system that involved *Nkx-2.5* orthologues was a tool for transporting materials and fluids in the gut cavity in these organisms.

Although still unpublished and controversial, expression analysis of a candidate *Nkx-2.5* orthologue in *Nematostella vectensis* being undertaken by the group of Prof. Mark Martindale at Kewalo Marine Laboratory at University of Hawaii (information kindly provided by Prof. Martindale to the author) and a simple behavioral analysis by the author may provide a secondary breakthrough for the problem. In short, this case might be an example that the pumping movement that is genetically related to *Nkx-2.5* orthologue termed *AnthoNk-2* plays a role in the locomotory activity of the animal. Nematostella

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is a sediment dwelling sea anemone that belongs to class Anthozoa of Cnidaria. For the purpose of burrowing into the sediment solely by the body column itself, Nematostella shows a specific pumping movement termed burrowing peristalsis for digging into the sediment (Figure 2). This movement takes place apparently to supply high hydropressure into the body column tissue on the aboral side of the polyp in order to put aside sand or mud by force thereby digging a hole into the sediment. This pumping function is a typical example of "hydrostatic skeleton" where the hydropressure plays a role in hardening the tissue. Our proposal is that this peristaltic and pumping movement and the pumping movement that was seen in hydra are essentially the same phenomenon because of the following arguments. The first is the different tissue property in the epithelial cells. Epithelial cells of hydra are connected to each other by numerous gap junction communications and this property makes the contraction of the body column tissue synchronous like the synchronous contraction of mammalian heart. In sharp contrast, Nematostella epithelium has no intercellular gap junction communication. Most likely because of this tissue property, the contraction of epithelial tissue in the burrowing peristalsis takes place not in a synchronous manner in the tissue but locally in very narrow travelling bands (Figure 2). The second argument is about the area of tissue that shows the movement. The peristaltic wave is seen in a wide area of body column except the oral region. Then an interesting analysis preliminarily obtained by Martindale's laboratory is that a candidate of *Nkx-2.5* orthologue termed *AnthoNk-2* in Nematostella is expressed in an area of body column tissue that closely matches the area of tissue where the burrowing peristalsis takes place (Martindale, personal communication). If we assume that the burrowing peristalsis is a manifestation of *Nkx-2.5* orthologue related pumping movement in this organism, this could be an indication that the ancestral form of cardiac system was involved in supplying hydropressure for the locomotory activity hence was not related to transferring of material in the gut. Although there has been no genetic analysis, another sea anemone also shows wave like contraction. Sessile sea anemones stick, for example, to the surface of rocks in seawater. They move although rarely along the surface of the rocks by showing waves of contraction, however, this time in a quite different manner from Nematostella. For the locomotion along the surface of the substrate, the wave of contraction takes place in horizontal orientation (Figure 3), therefore, vertically to the burrowing peristalsis in Nematostella. Currently there is no direct proof that this activity is related to *Nkx-2.5* orthologue in the animal, however, the fact that wave of contraction takes place in the same region of the body column to Nematostella suggests a possibility that the wave of contraction in sessile sea anemone that contributes to the locomotion of the animal is also a manifestation of the involvement of *Nkx-2.5* orthologue in this animal. In sum, in anthozoans which is the most ancestral class of Cnidaria, the pumping movement related to *Nkx-2.5* orthologues seems to be used as a tool for locomotion.

The use of hydropressure produced by the heartbeat for the locomotory activity is in fact not restricted to Cnidarians but is seen also in Arthropods. Spiders have relatively big sized heart and the coelomic space in the legs is relatively thick in size. It is known that spiders have contraction muscle for the legs but has no extension muscle. To compensate for the absence of extension muscle, spiders' heart rate is elevated and sends blood into the coelom of the legs (not the vein of them because Arthropods have open circulatory system) to extend them by means of high hydropressure thereby contributing to locomotion of the animal [11]. In mammals, extension of sex organs e.g. penis and clitoris takes place with the help of increased supply of blood into the space of the organs termed Corpus Cavernosum, which functions not only to extend them but also to harden them.

Figure 1: Transfer of gastrovascular fluid in Hydra (Hydrozoa).

Figure 2: Movement in Nematostella which is possibly related to *Nkx-2.5*orthologue (Anthozoa).

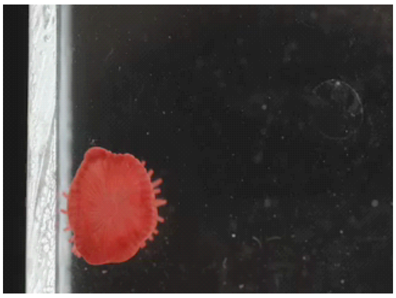

Figure 3: Movement in Actinaria which is possibly related to *Nkx-2.5*ortholog (Anthozoa).

From all the information available so far, a possible scenario for the evolution of cardiac system can be hypothesized. The pumping behavior accompanied by expression of *Nkx-2.5* is an ancient invention although its exact origin still remains unknown. The function of pumping changed during the course of evolution. In ancestral Cnidarians, the hydropressure supplied by the pumping was directly used for locomotory activity. In the descendant Cnidarian Hydra and in Nematoda, the pressure was used for circulatory and/or digestive

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purposes transporting fluid and food contents in the gut cavity. As the animal size grew bigger and the demand for active transport of oxygen, nutrients and waste materials increased, the pumping cardiac system and blood vascular system merged to construct cardiovascular system as the tool for the circulation of blood. The ancestral system survived and played roles in tissue or organ extension as is seen in Arthropods and sex organs in mammals.

The significance of the pumping tissue (engine) as the direct power source for locomotion is maximal in ancestral Cnidarians (conventional vehicles e.g. Chevy Corvette), intermediate in Arthropoda e.g. spiders (hybrid vehicles e.g. Toyota Prius), and minimal in mammals where the heart plays only indirect and subsidiary roles as to motive power transporting oxygen, nutrients etc. to muscular tissue (Chevy Volt). From the view of the scenario, research of cardiac system has dealt with only the most advanced type of cardiac system that appeared relatively recently and has ignored ancestral type of the system. It seems therefore worth investigating whether the pumping system that involves *Nkx-2.5* orthologues is present in more basal metazoan phyla than Cndaria, e.g. Ctenophora, Porifera and Placozoa and what kind of roles the orthologues play. Even more interesting could be how *Nkx-2.5* appeared in metazoan evolution.

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