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Research Highlight

ELABELA: a novel hormone in cardiac development acting as a new endogenous ligand for the APJ receptor

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Human *ELA* consists of three exons on chromosome 4, which generates a transcript (AK092578) that is annotated as a non-coding RNA. However, Chng *et al*. [1] has found that this gene contains a conserved open reading frame predicted to express a conserved vertebrate protein of 54 amino acids (aa) consisting of a secretory signal and a mature 32-aa peptide, which was called as ELABELA (ELA). The sequence of human mature ELA is Gln-Arg-Pro-Val-Asn-Leu-Thr-Met-Arg-Arg-Lys-Leu-Arg-Lys-His-Asn-Cys-Leu-Gln-Arg-Arg-Cys-Met-Pro-Leu-His-Ser-Arg-Val-Pro-Phe-Pro. Phylogenetic analysis revealed that the 32-aa mature peptide is evolutionarily highly conserved, with the last 13 residues being nearly invariant in all vertebrate species. ELA has also been previously reported to be highly expressed in undifferentiated human embryonic stem cells (hESCs) and be sharply down-regulated during differentiation [2]. Chng *et al*. [1] used an allelic series of zebrafish *ELA* mutants to show that *ELA* deficiency leads to severe defects in cardiac morphogenesis and often results in the complete absence of a heart. *ELA* mutant displayed specific defects in the mesendodermal lineage during gastrulation, as observed by the reduction of *gata5* and *sox17* expression. Taking together, these results suggested that ELA plays a role in the regulation of heart development. Whereas till now, no hormonal peptides has been reported to be involved in early development, particularly in the formation of the three embryonic germ layers. Chng *et al*. [1] first discovered an endogenous peptide hormone with potent embryonic signaling activity, which has great prospects in therapeutic applications such as heart repair and gene therapy in development.

During embryogenesis, six key signaling pathways (Wnt [3], Bmp/Nodal [4], FGF/IGF [5], Notch [6], Hedgehog [7], and Hippo [8]) have been reported to be crucial for embryonic patterning. Chng *et al*. [1] tried to explain ELA's functions in cardiac development by activating APJ receptor. Their reasons are as follows: i) ELA is concomitantly expressed with APJ (APLNR) before the onset of gastrulation. ii) The phenotypes of zebrafish ELA mutants stingingly resemble those of the APJ (APLNR) mutants specifically in cardiogenesis. iii) Extracellular ELA binds to APJ in a native cellular context. To our knowledge, APJ is a G protein-coupled receptor and its endogenous ligand is apelin. Apelin activates APJ receptor, and plays an important role in the physiological activities [9–11], especially in cardiovascular system [12]. However, a recent report has shown that APJ has some functions independent of apelin. Moreover, except apelin, APJ has also been activated by stretch in cardiac hypertrophy [13]. Researchers have tried to explore a second ligand for APJ. Chng *et al*. [1] stated that ELA, not apelin, is hence the long-sought-after alternative and earlier ligand for APJ, functioning in early cardiovascular development [1]. They demonstrated that the expression of ELA happens earlier than apelin and is concomitantly with APJ before the onset of gastrulation. Then, APJ depletion has different effects on cardiac morphogenesis compared with the depletion of apelin in zebrafish [14,15], frog embryos [15], and mice [16,17]. Whereas loss of ELA phenocopies the loss of APLNR (APJ gene). Based on these, they declared that ELA may be the second ligand for APJ in mediating endoderm differentiation and subsequent cardiogenesis. They first confirmed that a second ligand of APJ really exists *in vivo*, which forms another essential signaling axis in heart development. A further study supported this claim by reporting that a secreted peptide Toddler activates APJ signaling to promote the subsequent zebrafish gastrulation movements [18].

As we all know, apelin activated APJ signals through Gai by increasing the content of phosphorylated extracellular signal-regulated kinase (p-ERK). It was also reported that stretch may activate APJ receptor by recruiting β-arrestin. However, how ELA activates APJ *in vivo* is still unclear. ELA acts as an endogenous secreted peptide like apelin. It may have the same pathway as apelin in the activation of APJ. But more studies are needed. No matter what the signal will be, ELA's function in cardiac development suggested that the ELA/APJ axis appears to be exclusive for endoderm development. Therefore, it opens a new field for future research.

Figure 1. The multiple sequence alignment of apelin and ELA generated by ClustalW2

The established biological effects of apelin include major cardiovascular actions [19–23], neoangiogenesis [24], immunologic modulation [25], insulinemia control [26], as well as body fluid [27] and glucose homeostasis [28]. Chng *et al*. [1] showed that ELA has the same isoelectric points above 12 as apelin and both are the secretory proteins that are rich of basic residues. We used ClustalW2 to do Multiple Sequence Alignment and the results showed that the sequence similarity between apelin and ELA is 25%, suggesting that they might be homologous (**Fig. 1**). As a second ligand for APJ receptor, ELA shares some similar sequence with apelin. So it is interesting to explore whether ELA has the same functions as apelin. Furthermore, the imbalance of endogenous hormones is a main cause of certain diseases, such as insulin in diabetes mellitus [29], thyroid hormone in hypothyroidism [30] and sex steroid hormones in secondary sex characteristics [31]. Chng *et al*. [1] declared that ELA is a new endogenous hormones and its function will be widely discovered *in vivo*. ELA will become a hot topic in terms of how it works, what diseases it would be involved in, and how it maintains homeostasis *in vivo*.

Hormonal peptides are an important class of secreted signaling molecules and play key roles in adult physiology. Several human diseases are caused by some deficiencies of hormonal peptides, and hormonal replacement therapy has been an effective treatment method in clinic [32,33]. ELA acts as a new hormonal peptide and plays a key role in heart development. So ELA replacement therapy may also be an effective way to treat heart disease. For example, loss of cardiomyocytes often leads to heart failure, and apelin-13 has been shown to recruit stem cells and induce vascular progenitor cells to home into infarcted mouse hearts after myocardial damage by activating APJ receptor [34,35]. ELA activates APJ and has a function in hESC differentiation, so ELA supplement may be a new way to produce cardiomyocytes and an effective cure for heart failure.

Gene mutation is an important cause of disease and many diseases have been treated by gene therapy [36]. As ELA is essential for heart development, it would be desirable to detect cardiac anomalies before the disease development tendency by detecting this specific gene in embryo. It can also be used as an organ-specific therapy or molecularly targeted approach in heart disease. ELA's functions in early heart development suggested that gene therapy of ELA may be a way to increase the chances for a healthy pregnancy and a healthy baby.

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