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Guest Editorial

Molecular Regulations of Left to Right asymmetries of organs in Vertebrate Embryogenesis

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Bilateral symmetry of body plans is observed in early embryogenesis most vertebrate of animals. The bilateral symmetry body plans are defined in three axes; these are anterior-posterior (A-P), dorsal-ventral (D-V) and left to right (L-R) axes. The A-P and D-V bilateral axes are perfect and showed mirror image of each other. However, most of animals are showed L-R asymmetries which can be defined in three categories. A. Fluctuating asymmetries; in which minimal deviation from L-R symmetry, caused by developmental noise (Developmental noise is phenomenon in the developmental biology; in which the phenotype differ among the different individuals moreover; both the genotypes and the environmental factors are similar in these individual). B. Anti-symmetric; in this category the structures are constantly asymmetrical nevertheless with asymmetrical direction and distributed randomly (for e.g. left handed or right handed). C. Directional asymmetries; this group characterized by constant asymmetries of structures or organs, however, the direction of asymmetries is similar in all persons. The directional asymmetries are more prevalent in bilateral animals. The examples of directional asymmetries are pavement of different internal organs in vertebrate. For instance, in human asymmetries are found in heart, stomach, liver, spleen, right and left lungs and right and left-brain hemispheres [1].

The L-R asymmetries of organs were first studied in 19th century [2] and in 1921; it was hypothesized that asymmetries of organism had an underlying mechanism [3]. However, in 1990 a research paper published by Brown and Wolpert [4] explaining there was an underlying molecular mechanism which was responsible for L-R asymmetries of organs. First research paper describing genetic control of L-R asymmetries was published in a year of 2016 in Journal of Cardiovascular Development and Disease [5].

Disturbance of L-R asymmetries is called as Heterotaxy Syndrome, which is a rare disorder; with the incidence of 1 - 1.5/10,000 live births [6,7]. The heterotaxy is defined as abnormal arrangement of thoraco-abdominal viscera due disturbance in the L-R asymmetries. Situs solitus is the normal positions of different thoraco-abdominal organs maintaining the normal L-R asymmetries. A congenital anomaly situs inversus in which the major organs are at inverted positioned or mirror image of normal positions of different organs. Breaking of asymmetries associated with a number of visceral and cardiac anomalies; these anomalies have impact on prenatal postal course and outcome [6-9].

Initial stages of development vertebrate there is symmetrical positioning of tissues and organs. Due to evolutionary conserved events; there are repeated breaking of symmetries of organs, which resulted in asymmetries [10,11]. The L-R asymmetries of organs produced and marinated by the cascade of genes; which are expressed in early development of tissues and organs. This cascade of genes is comprised of TGF-β family members Nodal and Lefty, transcriptional factor Pitx2 [12].

The serotonin or 5-hydroxytryptamine (5-HT) is a neurotransmitter; moreover, serotonin is played a crucial role in cell's signaling system and important molecules in embryonic development. The serotonin molecule is highly conserved evolutionary molecules in

different species from Drosophila to mammals [13]. The serotonin acts by means of signals which act on specific receptors responsible for vertebrate laterality; this was known since 19th century and it was confirmed by the different experiments in 1921 that, there was fundamental mechanism for producing asymmetries [14,15]. In process of gastrulation serotonin has been implicated as an important signaling molecule for the establishment of laterality of viscera, craniofacial development and cardiac morphogenesis [16-22].

Serotonin is involved in number of physiological phenomenon; for instance mood status and physiological disorders like depression. There are two hypotheses; 1st alteration of serotonin concentration in developing tissues or organs 2nd there may be altered response of targeted serotonin receptors. This provides etiological phenomenon for a physiological disorder the "depression". Additionally, there is a class of drugs are collectively classified as Selective Serotonin Re-uptake Inhibitors (SSRIs) was developed for mood elevation frequently prescribed in general population and also in pregnant women [23]. In past decade; there was rapid increased in diagnosis of depression in pregnant women and frequent used of SSRIs drugs. The data were collected from National Birth Defects Prevention Study in 1998 disclosed that used of antidepressant drugs (SSIRs) was 2.5% in different states of US. However, these number had been increased approximately 8.1% in 2005 [24]. Although, another study from Netherlands was conducted in similar period of times displayed raised of used SSIRs drugs from 1% to 3% [25]. Likewise, this finding was coincides with increased in development and distribution of new antidepressant drugs and prescribed by physicians in pregnant women in 2005 [26].

In process of cardiac development a series of key factors are involved; suggested involvement of 5-HT signaling pathway. 5-HT signaling pathway not only responsible for L-R axis development however, this pathway also required proper cardiac morphogenesis. For instance, at very early stage of patterning of cardiac progenitor cells, lengthening and looping of heart tube, development of outflow tract, morphogenesis cardiac chambers and septation heart. The Cardiac Progenitor Cells (CPCs) are developed from upper end of primitive streak and primitive node on day 16th after fertilization. CPCs are migrated bilaterally in cranial and ventral directions; cranial to buccopharyngeal membrane. CPCs are collected in splanchnic layer of lateral plate of mesoderm; patterning bilateral Primary Heart Fields (PHFs). In splanchnic layer of lateral plate of mesoderm the CPCs are proliferate, differentiated and formed longitudinal endothelial tubes in PHFs. PHFs are responsible for development of primitive left ventricle and atria. Two PHFs are move medially above the buccopharyngeal membrane and formed cardiac crescent; in which two longitudinal tubes fused to form single longitudinal heart tube. At this stage longitudinal heart tube consists of 3 layers; from in to outside are endocardium, cardiac jelly and myocardium [27,28].

At approximately the same time when there is a migration of CPCs and development of bilateral PHFs, likewise there is establishment of the asymmetries and laterality of embryo L-R axis [17,18]. Molecular signaling pathway is required for establishment L-R laterality. The molecular signaling pathway is propagated through an asymmetric cascade; which is targeting specific cell's populations arising from upper end of primitive streak and primitive node and also cell's populations in lateral plate of mesoderm. The specific molecular pathway is then direct sidedness for the morphogenesis of asymmetric organs. The cascade of molecular pathway for L-R laterality is including genes for instance nodal, sonic hedgehog and PITX2; PITX2 is considered to be as "mater" gene in specifying the laterality of organs. The investigations are suggested that ligand "serotonin" which occupied top position of this cascade and serotonin acting on upstream and expressed at earlier stages of embryonic development [17,18,29].

Disturbance in PITX2 signaling in frogs [29] and mice [30] results in situs inversus, heterotaxy, and dextrocardia and a number of cardiac defects like atrial septal defects, atrial isomerism, ventricular septal defects, double outlet right ventricle, transpositions of great vessels, double outlet right ventricle and common truncus arteriosus [31]. Moreover, the cardiac laterality, positioning and patterning of heart and cardiac septation are dependent on proper expression of PITX2 [32].

It is concluded that during the early embryogenesis pattering of different structures and organs is bilaterally symmetrical. However, approximately on day 16th after fertilization asymmetrical signaling pathway becomes operational and providing normal L-R asymmetries, which observed in different organs of body. Disturbance in signaling pathway or malfunctioning of ligand serotonin is disturbed the normal asymmetries of organs (situ solitaire).

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