

Objectives of the project

Heart development has been studied extensively from the last couple of centuries, and cardiac diseases are one of the major challenges of the current era. Congenital heart disease is one of the most common type of birth defect, accounting for one-third of all major congenital anomalies. Worldwide, 1.35 million infants are born with congenital heart diseases each year. Among congenital heart disease, one of the major group of cardiac patients have disorders of the Cardiac Conduction System (CCS) and its associated tissues, causing life threatening severe arrhythmias (a problem with the heart rhythm; the heart may beat too slow, too fast, or irregularly). These conditions are particularly problematic because they often require corrective surgery to implant electrical pacemakers and lifelong medication, resulting in a significant degeneration in the quality of life.

To address this issue scientists have been working on different aspects of heart development using mouse and chicken embryos, to better understand heart development and diseases. Although heart development has been studied for more than a century, little is known about the development of its pacemaker cells. This is mainly due to the absence of a complete understanding of the genetic mechanism regulating its proper development. The recent invention of state-of-the-art instruments such as next generation sequencing technology opens the possibility to study pacemaker cells through a revolutionary approach of genomics, allowing a comprehensive assessment of all genetic factors involved in CCS development. A complete knowledge of the molecular mechanisms and key regulators involved in CCS development will be the first crucial step for our understanding of arrhythmia-related diseases like fibrillation (irregular heart beat), tachycardia (>100 beats/min), and bradycardia (<60 beats /min).

Description of the research

In this project, I would like to investigate the genetic mechanisms involved in the formation of these specialized cells of the heart. CCS cells are present in two different locations in the heart, which are known as the sinoatrial node (SAN) and atrioventricular node (AVN). These two components control the basal rate of cardiac rhythm generated in the heart. This conduction system spontaneously generates an electrical pulse and a well-coordinated network of cells transmitting the electrical signal to the contractile working myocardium (muscle of the heart). I will use zebrafish as an in vivo model system, mainly because the study of CCS cells is not so easy in other model organisms like mice and chicken, as the heart is a very vital organ for the survival of these organisms such that any mutations or defects due to experimental procedures cause very early lethality. On the other hand, zebrafish can survive for a few days even without a functional heart in the early embryonic stages. Another advantage is that zebrafish is a unique fish that shares thousands of developmental genes with humans and other mammals. So, it is an ideal model to study the role of different conserved genes in development and disease.

During this study, I will isolate these pacemaker cells, i.e. SAN and AVN, from the zebrafish heart, using state-of-the-art techniques and instruments. I will then use highly sophisticated genomic methods of ATAC-seq (a very reliable technique to study the interactions between DNA and proteins regulating the expression of genes) and RNA-seq (a technique which is widely used in molecular biology to check the expression levels of all genes in a given sample) to check which genes are being actively expressed in these cells at a particular stage of development. I will then validate a subset of these genes through RNA in situ hybridization to detect their expression patterns in targeted cardiac tissues and cells.

Reasons for choosing this research topic

Heart diseases are one of the major medical problems of the modern world. According to American Heart Association, cardiovascular diseases are the leading global cause of death, accounting for 17.3 million deaths per year, a number that is expected to grow to more than 23.6 million by 2030. As it is one of the major organs without which life is not possible, it has always fascinated me. In humans, heart rhythm starts in the womb around 6-8 weeks and it works non-stop till death. This interesting organ and my previous background of basic research and clinical diagnostic experience, compelled me to choose this topic. This basic research study will become the basis for future development of biological research and development of medical treatment for heart conditions.