Etiology and Morphogenesis of Congenital Heart Disease

From Gene Function and Cellular Interaction to Morphology

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Preface

This book is based on the 7th Takao International Symposium on the Etiology and Morphogenesis of Congenital Heart Disease held in August 2013 in Tokyo, Japan. The Takao symposium was first held in 1978 by Dr. Atsuyoshi Takao. At that time, Dr. Takao wanted to organize an international conference to stimulate and integrate research on the morphogenesis of the heart because not many conferences were focused on this aspect in those days. Dr. Takao did not want to use his name in the title of the symposium and the conference was simply called "Symposium on the Etiology and Morphogenesis of Congenital Heart Disease." Since the first symposium, the Takao symposium has been held every 5 years, and proceedings were published after each symposium, in 1980, 1984, 1990, 1995, 2000, and 2005. This book, published in 2016, is the first one to be officially named the "Takao" book. I would like to note that the Takao symposium and its publications have been supported by the Akemi fund from The Sankei Newspaper since its inception. The Akemi fund is based on donations from many persons from all over Japan to save children with congenital heart disease.

For those who are not familiar with Dr. Takao, he was a professor and the chief of pediatric cardiology at The Heart Institute of Japan at Tokyo Women's Medical University from 1972 to 1990. He passed away on August 8, 2006, at the age of 81.

Dr. Takao was very interested in the research of cardiac morphogenesis. In the 1970s, research in his laboratory was aimed at inducing heart disease by centrifugation, radiation, and various drugs such as retinoic acid. Some of those studies found that maternal administration of retinoic acid caused heterotaxy syndrome and transposition of the great arteries in mice. Thymic abnormalities and interruption of the aortic arch (type B) were also noted. However, Dr. Takao began to see the limitations of the methodologies in experimental teratology in clarifying the mechanisms underlying heart malformation.

In 1965, DiGeorge reported on an infant with hypoparathyroidism and recurrent infections along with three necropsy cases with absent thymus and parathyroid glands. From the early 1980s, deletion of chromosome 22q11 was recognized as a cause of DiGeorge syndrome and microdeletion of this region was confirmed in 1991 and 1992.

Conotruncal anomaly face syndrome was first reported by Kinouchi and Takao in 1976. In the early 1970s, Dr. Takao began to recognize a characteristic facial appearance with a flat nasal bridge, small mouth, nasal voice, high arched palate, and ear lobe abnormalities, along with mental retardation among patients with conotruncal anomalies, mainly tetralogy of Fallot. He named this combination "conotruncal anomaly face syndrome." Soon, he recognized the importance of molecular biology in clarifying the etiology and mechanisms of this syndrome. In the early 1980s, the molecular biology laboratory was established in his department. Microdeletion of chromosome 22q11.2 was confirmed also in conotruncal anomaly face syndrome.

Although Dr. Takao realized the importance of molecular biology in the late 1970s, it was not until after he retired in 1990, that he began to study molecular biology techniques. In 1990, he set up the International Molecular Cellular Immunological Research Center. He worked as the director of the Institute until 2006. In 2003, investigators of the Institute, including Atsuyoshi Takao and Rumiko Matsuoka, published a paper suggesting that the *TBX1* mutation was responsible for conotruncal anomaly face syndrome.

It is amazing that so much progress has been accomplished since the first Takao symposium, with path-breaking changes occurring in fields ranging from experimental teratology to regenerative medicine. As we understand more about the detailed molecular mechanisms underlying cardiac malformation, we begin to see some hope of manipulating these mechanisms to treat congenital heart disease, as noted by Dr. Markwald in his chapter in this book. Recent progress in cardiac regenerative medicine by using progenitor cells is largely based on the knowledge obtained from research on the etiology and morphogenesis of congenital heart disease. Basic researchers and cardiologists who have been working in this field should be proud that they have contributed so significantly, in the past nearly 40 years, to this valuable progress.

I hope this book sheds light on the direction in which we should proceed in the research field in the next 5 years, to ultimately save the lives of those who suffer from congenital and acquired heart diseases.

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