

From Bench to Bedside in Cardiovascular Research A Reflection on My Research Career

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The recent progress in cardiovascular research has been remarkable. This has undoubtedly been in great part due to advancements made in the field of molecular biology which have been applied to everyday cardiovascular research. In particular, the introduction of genetic engineering approaches has played a great part in the recent progress. Classically, cardiovascular research had been focused on the analysis of physiological and pharmacological mechanisms. In the past, approaches such as electrophysiology were used to elucidate for example the influx and efflux of ions from myocardial cells using the patch clamp method to present an explanation on the triggering of contractile mechanisms. However, without the molecular approaches of today, the molecular structure and functional regulation of ion channels and the muscle contractile apparatus itself would not have been clarified. This is but one introductory example of a cardiovascular phenomenon which has been better understood through recent research. It is indeed important to note that molecular and genetic approaches have played a critical and most important role in the advancement of cardiovascular research. Taking this opportunity, I would like to introduce our achievements and their clinical application in the past two decades.

Adaptive response of the heart to hemodynamic overload

The myocardium shows extraordinary plasticity at the biochemical and physiological levels, and the regulation of gene expression in the heart is also dynamic as cardiac myocytes have the ability to sense mechanical stress and convert it into intracellular biochemical signals.

When hemodynamic overload is a burden on the heart, protein synthesis is increased in the myocardium leading to cardiac hypertrophy to increase its contractility and maintain normal cardiac function. This adaptive response of the heart to hemodynamic overload is not only a quantitative reaction of increased contractile proteins, but also a qualitative reaction of isoformic transition of cardiac myosins. We originally found two types of cardiac myosin isozymes in the myocardium and

observed that during the development of cardiac hypertrophy, cardiac myosin isoforms were converted to a type with improved energy conversion efficiency for contraction as an adjustment for increased energy consumption. Subsequently, we established a unique biochemical diagnostic method of acute cardiac infarction using an immunoreactive assay of cardiac myosin light chain in serum.

Furthermore, we demonstrated hypertrophic mechanisms in response to mechanical stimuli in cardiac myocytes by using deformable culture dishes. Our views of signal transduction induced by mechanical stress are as follows: Mechanical stress leads to phosphorylation and activation of the serine/threonine kinase cascade in the order of PKC, Raf-1, MAP kinase kinase, and MAP kinase, subsequently leading to upregulation of gene expression and protein synthesis. This molecular process of cardiac hypertrophy is also modified by humoral factors such as the renin-angiotensin system.

Molecular mechanisms of the development of the cardiovascular system

Great progress has been made in the understanding of cellular development and differentiation of skeletal muscles such as the identification of MyoD, the master regulator of myocytes, which was just over 10 years ago. Thus similar advancements can be expected for the cardiovascular system as well. One notable advancement has been the identification of the first cardiac specific developmental factors such as the Csx homobox gene and GATA 4 cardiac specific transcription factor. We have also demonstrated that endothelin-1 is involved in the differentiation of vascular smooth muscle cells from neural crest cell lineages leading to the formation of the great vessels and cardiac outflow. By understanding the mechanisms involved in such cardiovascular processes, we will provide cardiovascular targets for specific therapeutic modalities. For example, identification of a MyoD-like molecule of cardiac muscles may provide a means for regeneration of cardiac muscles, and an understanding of the transcriptional factors involved in smooth muscle cell differentiation may lead to a target for anti-arteriosclerotic drugs.

Yoshio YAZAKI, MD

President 1998, The Japanese Society of Internal Medicine, President,
The Hospital, International Medical Center of Japan, 1-21-2, Toyama,
Shinjuku-ku, Tokyo 162-8655