Representative researcher : Masatsugu Hori (professor)
Pathological signal medicine (internal medicine 1), Signal Medicine, Department of Medical Research

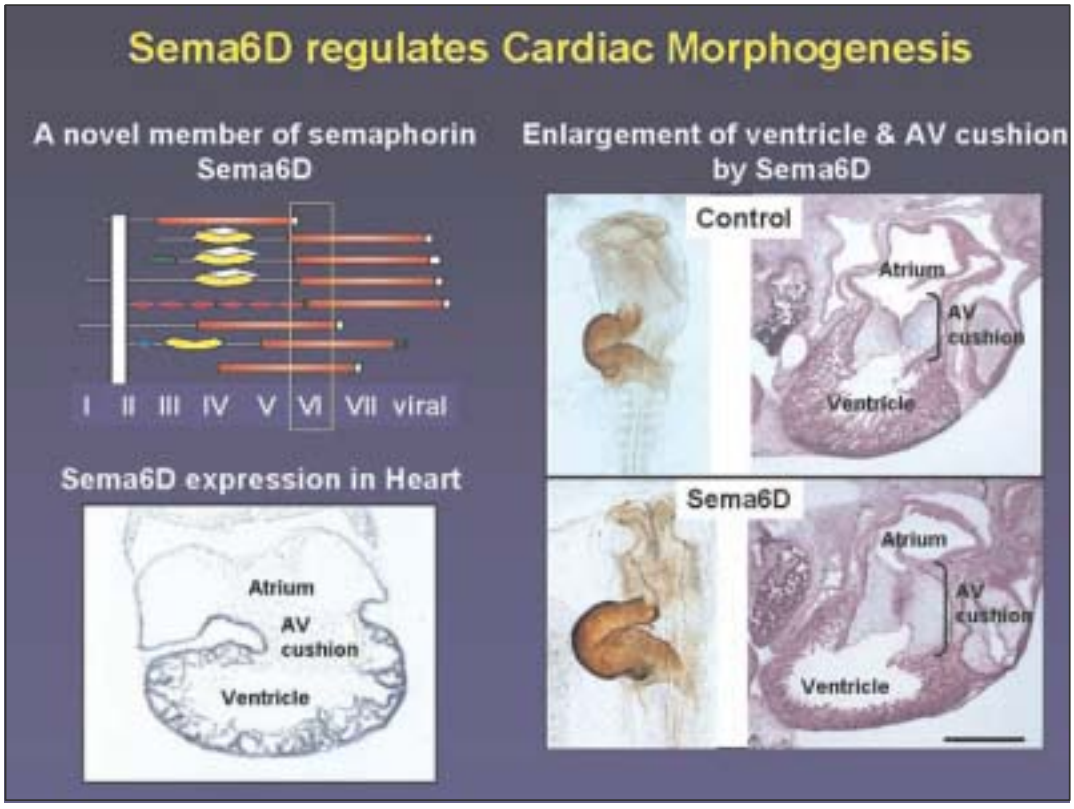
1

Development and morphogenesis of the heart

Cardiac muscle cells originate from the lateral region of the mesoderma through various differentiation and growth factors. Cardiac muscle cells located on the bilateral sides then move to the median and construct a tubular structure, and repeat several rotations and regional fusions, completing the mature heart consisting of 4 lumens and 4 valves.

At present, none of the factors involved in this series of morphogenesis have been understood. We have been performing functional analysis of various factors of development of the heart by defective and excessive expression using retrovirus by the RNAi method in chick fetuses, and found that a new type of Semaphorin molecule (Sema6D) known as nerve axon-inducing factor plays an important role in early morphogenesis of the heart.

We are now preparing Sema6D-defect mice for analysis of its role in mammals. In this COE, we will investigate congenital abnormality of the heart and mutation of Sema6D.



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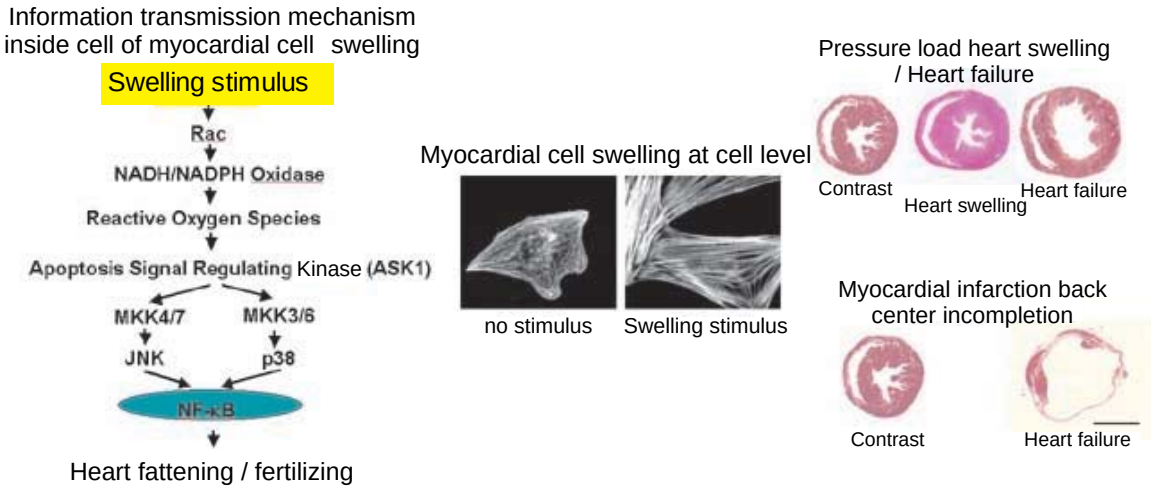
2 Molecular mechanism of hypertrophy and cell death of cardiac muscle cells

Cardiac muscle cell hypertrophy occurs to adapt to stress in all heart diseases such as myocardial infarction, cardiomyopathy, valvular disease, and hypertension, corresponding to the pressure and volume loads. However, when excess stress persists for a long time, cell death of cardiac muscle cells occurs, and the heart expands, resulting in heart failure.
In this study, we will clarify the molecular mechanism of hypertrophy and death of cardiac muscle cells, identify the target molecules for treatment of heart failure, and develop a novel therapy for heart failure.
We have recently clarified that MAP kinases, particularly apoptosis signal-regulating kinase (ASK1) related to apoptosis, play an important role in hypertrophy and cell death of cardiac muscle cells because they are resistant in mice with knockout-induced heart failure.
In this study, we will investigate whether ASK1 can be used as the target molecule in the treatment of heart failure by introducing a mutant gene that inhibits activity of the enzyme in the animal model of heart failure. In addition, we will identify substances involved in cell death of cardiac muscle cells present downstream of ASK1 using proteomics and genomics techniques, and cell-biologically investigate functions of the identified substances using genetically modified mice.

Based on the above, we will develop new drugs targeting molecules including ASK1 that are involved in cell death of cardiac muscle cells and play an important role in development of heart failure, aiming at clinical application.



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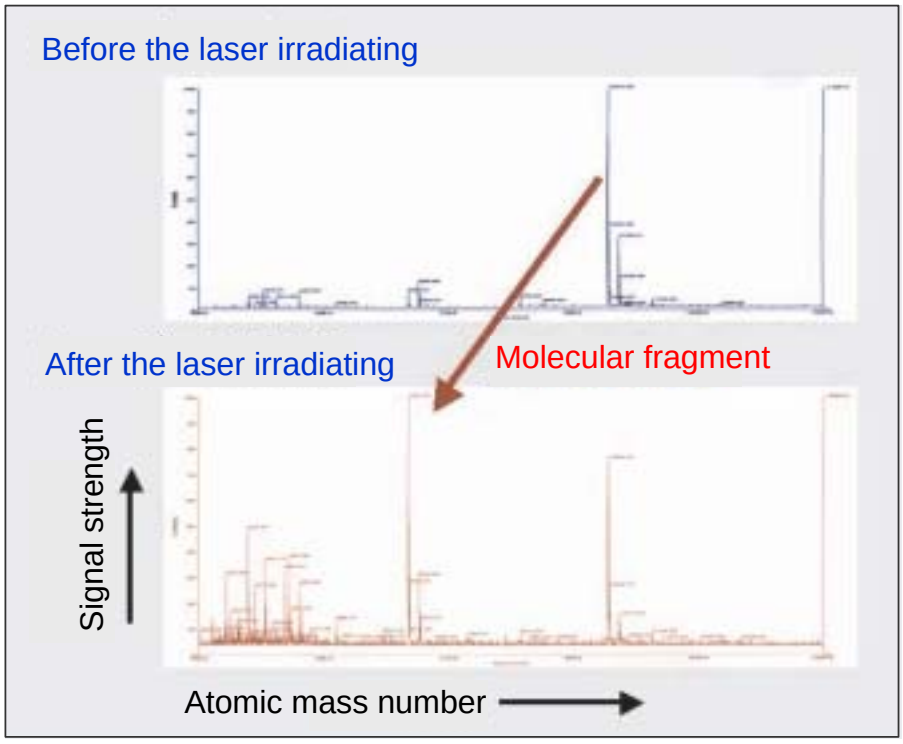
3

Control of the molecular system using photons

Short-wave ultraviolet and visual lights easily cause irreversible damage, as experienced in fluorescence microscopic observation, but when an infrared light with a small energy per photon is irradiated, the nonspecific effect is low, and damage can be reduced. We have selected an infrared light, which selectively resonates with specific chemical bonds in molecules and is selectively adsorbed, and succeeded in activation of target protein and peptide molecules alone and development of a structural control method such as degradation. In this COE, we will unify proteins and peptides, as drugs and regulatory factors, with delivery system in combination with pinpoint control of physiological activity under a laser spot, using laser irradiation as substitution for enzyme reaction, and introduction of substances into cells, to search for a method of controlling the microenvironment of cells and molecular systems, aiming at its use in the life sciences.



Other study contents of Hori laboratory

- Elucidation of the development mechanism of tissue damage and organ failure and establishment of a diagnostic and therapeutic strategy
- Elucidation of the molecular mechanism of ischemic responses in the heart and brain and study of the induction of an artificial ischemia-resistant response
- Large-scale study of the relationship between diabetes and arteriosclerosis
- Large-scale study and intervention study of the relationship between atrial fibrillation and arteriosclerosis
- Large-scale epidemiological survey and intervention study of myocardial infarction
- Analysis of genes related to diseases