Biology

Discovery of New Inducer for Myocardial Cell Differentiation

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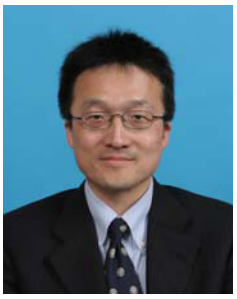

Background of Research

At present, heart transplants is the only medical measure for severe heart failure, but heart transplants has a number of problems including the absolute shortage of donors. One of the expected alternatives is regenerative therapy for failing heart. Especially, what has been gathering growing attention recently is a cell transplants therapy whereby such stem cells as embryo-derived stem cell (ES cell) or induced pluripotent stem cell (iPS cell) that can be differentiated into various types of cells are differentiated also into myocardial cells which in turn are transplanted to a functionally failing heart. There are, however, several issues to be solved for clinical application of the cell transplants therapy for regeneration of myocardia. Among other things, what poses the challenge is the fact that even when differentiating ES cells or iPS cells into myocardial cells in a standard method, a very low ratio of about 1% of such cells actually becomes myocardial cells. In case other cells or stem cells than myocardial cells are mixed in cell transplants, it can cause arrhythmic heartbeat or tumor. Having said that, it is necessary to develop a technology for differentiating stem cells into myocardial cells at a higher ratio in order to practically carry out the cell transplants therapy. Additional recent discoveries have revealed that several kinds of stem cells exist in the heart and in cases of heart failure such stem cells migrate to the damaged location and get differentiated to myocardial cells or vascular cells. This indicates that regeneration can take place albeit only slightly when the heart is damaged, that is even in the heart of mammals. Consequently, if this regenerative capacity can be improved, regeneration of the heart can be realized within the body without using the method of cell transplants. For this reason, identification of factors that strongly promote myocardial cells differentiation is important.

Achievements of Research

We surmised that for the development of a highly efficient method for inducing such myocardial differentiation it is important to find the secreted factor (myocardial differentiation inducer) that has a capability to differentiate stem cells to myocardial cells. Therefore, we have conducted a variety of experiments for discovering the myocardial differentiation inducer, and this time found out that a type of protein called IGFBP-4 is a strong myocardial differentiation inducer. When IGFBP-4 was actually added to ES cells, the myocardial differentiation efficiency was improved by more than 20 times. Furthermore, when suppressing the effect of IGFBP-4 conversely, the differentiation to myocardial cells does not take place, and even a regenerated heart in a frog was lost as a result. Namely, IGFBP-4 has been found out to be an extremely important factor that not only promotes myocardial differentiation but plays an indispensable role in forming a normal heart. IGFBP-4 is one of the IGF binding proteins, at least six kinds of which have been found, and as its names suggests it has been known to be bound to a hormone called IGF (insulin-like growth factor) and regulate its effect. However, the myocardial differentiation inducing effect of IGFBP-4 we discovered in this research has no relation to the effect as IGF. It was also made clear that IGFBP-4's function of regulating the effect of WNT factor largely responsible for carcinogenesis, arteriosclerosis or aging is vital for myocardial differentiation induction.

Prospect of Research

The discovery in this research has a large significance as a new inducer for myocardial differentiation has been identified to begin with. From now, IGFBP-4 will be added to ES cells or iPS cells to efficiently differentiate them to myocardial cells in order to observe the effect of transplants to the heart, and also IGFBP-4 will be administered to a failing heart with a view to examining whether the heart regeneration is promoted and the failure is improved in the body. If the above is verified by animal experiment, this therapy can be applied to the regenerative therapy for myocardial infarction or heart failure. Moreover, the obtained knowledge about IGFBP-4 being a regulating factor of WNT can be used not only to heart regenerative therapy but many other illnesses including cancer or other fields such as aging problems. We will continue our research on IGFBP-4 to find whether it is effective for therapies for cancer and aging.