若手イニシアティブ主催セミナー

演題: Molecular Changes in the Human Heart

演者：Prof. Cristobal dos Remedios (University of Sydney)

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会場： 筑波大学 医学学系棟 4 階大会議室（ 4B482 ）

要旨： It is no secret that as humans age there is a decline in the functions of many organs. The heart is no exception. Animal studies of in the aging mouse heart (PLos Genet 3: e201-16) have provided insights into the kinds of molecular changes that might be expected in humans, but no one has examined the effects of aging on the human heart, mainly through lack of available tissue.

For nearly 20 years I have been collecting numerous samples from hearts from patients undergoing a heart transplant procedure that are therefore in terminal heart failure. During this period, we occasionally obtain hearts that are not failing and were not used in human heart transplantation for reasons such as lack of an available tissue compatible recipient. We also have tissue from other transplant centers including Harefield Hospital (London) and the Cleveland Clinic (USA). An unusual feature of these samples is that they are collected within minutes of the loss of coronary circulation.

We now have nearly 100 non-failing human hearts covering ages from 2 months to 78 years so we recently embarked on a transcriptomics study of these hearts using oligonucleotide gene arrays and qRT-PCR. Over 100 genes were identified covering a wide range of cellular functions. In this talk I will focus on genes involved in: (1) Ca release, transport and intracellular Ca movement; (2) ion channels; (3) mechanoreceptors and transcription factors; and (4) LIM domain proteins. Of these, one LIM domain protein in particular exhibited no change in expression until about 40 years of age. However, donors older than 40 exhibited a significant rise in expression of LIM kinase I (LIMK1), an enzyme that phosphorylates Ser-3 of cofilin. Cofilin is a small protein that regulates the conversion of polymeric (F-)actin into monomeric (G-)actin. Once phosphorylated, it cannot perform this function. Two related enzymes, Slingshot 1 and 2 can dephosphorylate phosphorylated cofilin, but expression levels of these enzymes did not appear to compensate for the changes in LIMK1. Thus, an increase in LIMK1 will maintain actin in its polymeric form and therefore perhaps be stiffer. We are currently doing experiments to determine if older hearts are indeed stiffer and if so, do they exhibit slower relaxation (diastole). These experiments are designed to help us understand the molecular changes that occur in the aging human heart. They are also used as age (and gender)-matched heart “controls” for samples from failing hearts.

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