ABSTRACTS

Abstracts for Plenary Lectures:

PL1.

THE NEW NICE GUIDELINES ON THE TREATMENT OF HYPERTENSION

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In 2011, American and British guidelines on the management of hypertension are scheduled to be updated. The British guidelines, developed by the National Institute for Clinical Excellence, have just been published in August 2011. There are several significant changes in these guidelines. Ambulatory blood pressure is named the new gold standard in the diagnosis of hypertension. It is valuable not only in people with white coat hypertension, but also in people whose ambulatory blood pressures are higher than blood pressure readings in the clinic. Home blood pressure monitoring is now recognised as being useful and informative. Largely as a result of the ASCOT study, calcium channel blockers (CCB) and blockers of the renin-angiotensin system have surpassed diuretics and beta-blockers as first line drugs. Patients 55 or younger should receive an ACE inhibitor, or an angiotensin receptor blocker if the former is not tolerated. Older patients are started on a CCB. A thiazide diuretic is used as the third drug, but interestingly, chorthalidone and indapamide are preferred as they showed favourable outcomes in large clinical trials. Treatment with these three drug classes should be sufficient in the majority of patients, but if triple therapy is insufficient, referral to a hypertension specialist is recommended. Alpha and beta blockers do not even make fourth place, which is taken up by spironolactone.

While the new UK guidelines are controversial, the changes are based on the best available current evidence. In Hong Kong, the prevalence of hypertension has been increasing among young and middle-aged men, and is approaching 50% among the elderly. Current efforts are channelled towards the detection and treatment of hypertension in middle and old age. The linear rise in the prevalence of hypertension with age means that measures to prevent hypertension, such as a healthy diet and regular physical activity, should start early in life.

PL2.

MITOCHONDRIAL SUPEROXIDE FLASHES IN PROGENITOR CELLS

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The mitochondrion is a prominent cellular organelle pivotal to bioenergetics, cell proliferation, cell survival, and cell death. As the primary source of reactive oxygen species (ROS), mitochondria constantly generate low level of ROS due to the slippage of the electron transport chain (ETC). By employing a newly developed mitochondrial matrix-targeted superoxide indicator, mt-cpYFP, we have recently shown that individual mitochondria undergo spontaneous bursts of superoxide generation, termed "superoxide flashes", in many types of cells under physiological conditions, in intact beating hearts, or even in skeletal muscles and sciatic nerves of living animals. Individual flashes are triggered by transient openings of the mitochondrial permeability transition pore (mPTP), and the bursting superoxide production depends also on the integrity of the ETC, suggesting that they are a highly regulated phenomenon. Evidence is further provided that such superoxide flash activity offers a measure of oxidative stress under pathophysiological conditions (e.g., during ischemia-reperfusion injury). In cancer cells (e.g., HeLa cells), it serves as an early mitochondrial signal for oxidative stress-related apoptosis. In transgenic mice, the superoxide flash activity in skeletal muscles surges in response to systemic glucose challenge or insulin stimulation, in an apparently frequency modulatory (FM) manner. This result uncovers a tight metabolism-mPTP-superoxide flash coupling as a housekeeping mechanism that connects distinct functions of the mitochondria. Moreover, most recent results suggest a novel role for mitochondrial superoxide flashes in regulating neural progenitor cell fate, and as a mediator of the negative impact of amyloid β-peptide (Aβ) on neurogenesis. Taken together, our studies suggest that (i) superoxide flashes represent a novel, mPTP-regulated mode of ROS production and signaling by the mitochondria; (ii) activities of superoxide flashes could serve as a valuable biomarker for oxidative stress-related diseases, and (iii) the discovery of superoxide flashes may shed new light on mPTP and ETC functions as well as their heretofore unappreciated coupling in health and disease.

ABSTRACTS

Abstracts for Plenary Lectures:

PL3.

GENE THERAPY FOR CONGESTIVE HEART FAILURE – INHIBITION OF PROTEIN PHOSPHATASE 1 AS A PROMISING THERAPEUTIC TARGET

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A defect in calcium cycling via reduced SERC2a activity is a primary pathogenic mechanism in heart failure (HF). Approaches to increasing SERCA2a involve modulating upstream proteins that impact its activity. A central protein in the regulation of SERCA2a is protein phosphatase 1 (PP1). The association between PP1 and calcium cycling involves several upstream and downstream events. In HF, PP1 activity is increased leading to the dephosphorylation of phospholamban (PLN) which in turn decreases SERCA2a activity. Inhibition of PP1 results in inhibition of phospholamban (PLN) which in turn increases SERCA and Ca^{2+} uptake and contractility. In addition, inhibition of PP1 has other effects relevant to HF including inhibition of apoptosis and inhibition of the activity of MAP kinases. Apoptosis represents a common pathway in ischemic and non-ischemic HF in which cells progress from injury to cell death. The MAP kinases play a major role in the remodeling processes (i.e. fibrosis and hypertrophy) that occurs in the more chronic stages of HF (either ischemic or non-ischemic). Thus, inhibition of PP1 in the failing heart results in increases in phospholamban phosphorylation, leading to improvement of SR Ca^{2+}-handling, contractility and reversal of adverse remodeling by directly decreasing fibrosis and cardiac hypertrophy. An upstream modulator of PP1's activity is protein phosphatase inhibitor-1, designated I-1, which is activated via phosphorylation by protein kinase A (PKA). As further evidence of I-1's role in HF, I-1 has been reported to be inactivated (via reduced PKA-phosphorylation) in human failing hearts (Carr et al. 2002). While I-1 protein levels were found to be similar in non-failing and failing hearts, the inactive (dephosphorylated) form of I-1 was the predominant form (~60%) in the failing hearts, consistent with increased PP1 activity and PLN inhibition of SERCA2a. Since I-1 is inactive in human failing hearts, interventions to increase its activity may be beneficial. Rodent studies have shown that constitutively activating inhibitor 1 (I-1c) of PP1 (AA 1-65 with T35D) within the failing rat heart improves not only contractility but also reverses adverse remodeling by directly decreasing fibrosis and cardiac hypertrophy (Pathak et al., 2005). New translational research data will be presented demonstrating that overexpression of I-1c by intracoronary in vivo gene transfer of adeno-associated viral vector type 9 encoding for I-1c preserves cardiac function and reduces scar size in a preclinical model of heart failure.

PL4.

MOLECULAR CHARACTERIZATION AND FUNCTIONAL PROPERTIES OF INDUCED PLURIPOTENT STEM CELLS-DERIVED CARDIOMYOCYTES FROM HEALTHY AND DISEASED INDIVIDUALS

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In view of the therapeutic potential of cardiomyocytes derived from human induced pluripotent stem cells (iPSC-CM), our overall goal is to investigate their molecular characteristics, functional properties related to the excitation-contraction coupling (e.g., $[Ca^{2+}]_i$ handling), pacemaker function and underlying ion currents, the effects of β-adrenergic stimulation, and responsiveness to common modifiers of cardiac function (e.g., I_f blocker). The iPSC clones we investigated were derived from human foreskin fibroblasts, dermal fibroblasts and hair keratinocytes. Reprogramming was accomplished by infecting the cells with retroviruses containing the four human genes: OCT4, Sox2, Klf4 and C-Myc. Our major findings show that iPSC-CM: (1) express cardiac specific RNA and proteins; (2) exhibit regular pacemaker activity; (3) exhibit key features of the excitation contraction coupling machinery; (3) respond to ryanodine and caffeine (albeit less than adult cardiomyocytes), and express the SR-Ca^{2+} handling proteins ryanodine receptor and calsequestrin. Hence, our work demonstrated that iPSC-CM exhibit features resembling the adult myocardium, and thus constitute a potential source for cardiac regeneration. Additionally, we investigated iPSC-CM generated from skin biopsies obtained from patients with the inherited arrhythmia Catecholaminergic Polymorphic Ventricular Tachycardia (CPVT). Our study focused on the autosomal recessive form of the disease caused by the missense mutation D307H in the cardiac calsequestrin gene, CASQ2. The major findings were that the CPVT cardiomyocytes demonstrated catecholamine-induced arrhythmogenesis, indicating that the CASQ2-mutated cardiomyocytes can be used to study the electrophysiological mechanisms underlying CPVT and for tailoring patient-specific anti-arrhythmic therapy.

ABSTRACTS

Abstracts for Plenary Lectures:

PL5.

THERAPEUTIC POTENTIAL OF PLURIPOTENT STEM CELL-DERIVED MESENCHYMAL STEM CELLS IN CARDIOVASCULAR REGENERATION

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Recent experimental and clinical studies suggest that transplantation of bone marrow derived mesenchymal stem cells (BM-MSCs) is an attractive therapeutic option for ischemic cardiovascular diseases. However, there are several potential limitations of using BM derived-MSCs (BM-MSCs). Firstly, BM-MSCs display a limited proliferative capacity and a large variability of cell quality derived from different donors. Secondly, during ex-vivo expansion before possible therapeutic use, these cells quickly loose differentiation potential and decrease ability to produce protective factors. Importantly, survival capacity and stem cell functions of BM-MSCs derived from aged or diseased donors are profoundly impaired, and thus limit their therapeutic efficacy. Human pluripotent stem cells (i.e.hESCs/iPSCs) may provide an alternative source of functional MSCs for tissue repairs. Here we will introduce the generation, characterization and application of human ESC and iPSC-derived MSCs for the treatment of cardiovascular diseases.