Mon. Nov 23, 2020

Track2

JSPCCS AHA Joint session

JSPCCS AHA Joint session (II-AHAJS)

座長:土井 庄三郎（国立病院機構 災害医療センター）
座長:Shelley Miyamoto（Pediatrics/Cardiology, University of Colorado Anschutz Medical Campus Children's Hospital Colorado）
8:10 AM - 9:40 AM Track2

[II-AHAJS-1] Challenging in diagnosis and management of mitochondrial cardiomyopathy
○武田 充人 （北海道大学大学院薬学研究院 小児科学教室）

[II-AHAJS-2] The challenge of developing mitochondrial nano medicine based on MITO-Porter Technology
○山田 勇磨 （北海道大学大学院 薬学研究院）

[II-AHAJS-3] Mitochondrial function and mitochondrial-targeted therapies in pediatric cardiomyopathy and heart failure
○Shelley D. Miyamoto （University of Colorado Anschutz Medical Campus and Children's Hospital Colorado）

[II-AHAJS-4] Mitochondrial transplantation for Cardioprotection
○James D. McCully （Boston Children's Hospital / Harvard Medical School）

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[II-AHAJS-1] Challenging in diagnosis and management of mitochondrial cardiomyopathy

○武田 充人 （北海道大学大学院薬学研究院 小児科学教室）

Mitochondrial cardiomyopathy (MCM) is defined as a disorder of oxidative phosphorylation in the myocardium due to genetic mutations. In clinical, it is usually recognized as a serious cardiac complication in mitochondrial diseases. Also, it could be a causative disorder of “ unknown” cardiomyopathy including lethal infantile cardiomyopathy. To date, we have provided an advanced diagnostic system using the trinity of biochemical, genetic, and pathological examinations using biopsied myocardium, cultured skin fibroblast, and blood samples. Most cases were diagnosed by respiratory chain enzymatic assay in biopsied myocardium, while oxygen consumption rate in cultured skin fibroblast has emerged as a substitute diagnostic tool. Recently, we have provided an immunohistopathologic study using paraffin-embedded samples of the myocardium. The management of MCM has been challenging. In common mitochondrial disease, the progression of cardiac complications has unique characteristics and attention should be paid to the type of cardiomyopathy, serial changes in the electrocardiogram, and cardiac function. In some lethal infantile MCM, a mitochondrial rescue regimen could be life-saving. Also, we would like to discuss the lethal arrhythmia in patients with suspected MCM.

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[II-AHAJS-2] The challenge of developing mitochondrial nano medicine based on MITO-Porter Technology

○山田 勇磨 （北海道大学大学院 薬学研究院）

In recent years, mitochondrial dysfunction has been implicated in a variety of diseases, including neurodegenerative diseases, diabetes, cancer and a variety of inherited mitochondrial diseases. This makes this organelle a promising therapeutic drug target, and mitochondrial therapy would be expected to be useful and productive for the treatment of the above diseases. To achieve such an innovative therapy, it will be necessary to deliver therapeutic agents to the interior of mitochondria in living cells. However, only a limited number of approaches are currently available for accomplishing this. We recently reported on the development of a MITO-Porter, a liposome-based carrier that can be used to introduce macromolecular cargos into mitochondria via membrane fusion (Y. Yamada et al, Biochim Biophys Acta 1778: 423-432 (2008), Y. Yamada et al, Adv. Drug. Deliv. Rev. (in press)). In this presentation, we discuss novel therapeutic strategies that involve the use of a mitochondrial drug delivery system (DDS) focusing on “ cell therapy via mitochondrial activation”. Concerning the topic of cell therapy, we report findings to show that Cardiac progenitor cells activated by a MITO-Porter system (MITO cell) enhance the survival of a cardiomyopathy mouse model via the mitochondrial activation of a damaged myocardium (J. Abe et al, J Control Release 269: 177-188 (2018)).

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[II-AHAJS-3] Mitochondrial function and mitochondrial-targeted therapies in pediatric cardiomyopathy and heart failure

○Shelley D. Miyamoto (University of Colorado Anschutz Medical Campus and Children's Hospital Colorado)

The most common indication for heart transplantation in children is heart failure as a consequence of dilated cardiomyopathy. Unfortunately, heart failure outcomes from children still lag behind that of adults, supporting ongoing pre-clinical and clinical research in this patient population. While mitochondrial dysfunction is known to contribute to heart failure in adults, less is known about the role of mitochondria in pediatric heart failure. Mitochondrial targeted therapies have also been shown to be beneficial in adult heart failure yet remain underexplored in children. The objectives of this talk will be: (1) review existing literature regarding the current state of the field regarding mitochondrial function in children suffering from heart failure with a focus on dilated cardiomyopathy, and (2) discuss mitochondria as a potential target of heart failure therapy in children. Focused study of the mechanisms involved in pediatric heart failure are critical in order to identify novel therapeutic targets.

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[II-AHAJS-4] Mitochondrial transplantation for Cardioprotection

○James D. McCully (Boston Children's Hospital / Harvard Medical School)

The importance of the mitochondrion in the maintenance and preservation of cellular homeostasis and function is well established and there is a sufficient body of evidence to show that mitochondrial injury or loss of function is deleterious. In our research, we have focused on the myocardium, a highly aerobic organ in which mitochondria comprise 30% of cellular volume. The mitochondria supply the energy requirements of the myocardium, derived through oxidative phosphorylation and is dependent upon oxygen delivery through the coronary circulation. Our studies and those of others have demonstrated that attenuation or cessation of oxygen delivery to the myocardium (ischemia) damages mitochondrial structure, volume, calcium accumulation, complex activity, oxygen consumption, high energy synthesis, and the mitochondrial-mediated intrinsic apoptotic pathway, and causes mtDNA deletion. These events occur during ischemia and extend into reperfusion to severely compromise post-ischemic functional recovery and cellular viability.
Instead of targeting a single step or one mediator of a complex, or the interconnected reactions of mitochondrial injury, we have pioneered a novel therapy based on mitochondrial transplantation. This approach uses replacement of native mitochondria with viable, respiration-competent mitochondria isolated from non-ischemic autologous tissue to overcome the many deleterious effects of ischemia/reperfusion injury on native mitochondria.
In this presentation we will provide evidence for the safety and efficacy of mitochondrial transplantation and show methods for the rescue of myocardial cellular viability and function.

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