Department of Cellular and Molecular Pharmacology,
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GLOBAL COE SEMINAR

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演題 ： Mitochondrial Uncoupling Protein of Brown Fat: Electrophysiologist's Perspective

日時 ： 平成23年3月7日（月） 15:00～16:00

場所 ： 医学部教育研究棟13階　第5セミナー室

Uncoupling proteins (UCP1– UCP5) are integral transport proteins of the inner mitochondrial membrane (IMM) that increase its electrical conductance and thus dissipate the mitochondrial electrochemical proton gradient. UCPs uncouple mitochondrial respiration from ATP synthesis and make mitochondria to produce heat rather than ATP. UCPs contribute to thermogenesis and reduce fat depositions, but have also been implicated in attenuating reactive oxygen species production by mitochondria to protect the cell against oxidative damage and ageing. In spite of their physiological significance, the mechanism by which UCPs increase conductance of the IMM remain elusive due to the lack of direct methods to measure their activity. To resolve this problem, we applied the patch-clamp technique to the whole IMM of mitochondria from the brown adipose tissue to identify and characterize currents produced by the family's founding member, UCP1. In our experiments, both the cytoplasmic and matrix faces of the IMM were exposed to solutions that did not contain any ions normally permeable through ion channels or transporters, except for H^+ and OH^-. Under these conditions, we identified a current that demonstrated all signature properties of UCP1: it was strongly potentiated by micromolar concentrations of unsaturated fatty acids, inhibited by removing endogenous membrane fatty acids with bovine serum albumin, and blocked by micromolar concentrations of purine nucleotides. The current was absent in the IMM of COS-7 cells, in agreement with the fact that UCP1 is specifically expressed in the brown adipose tissue. Finally, the current disappeared in UCP1 knockout mice. In this presentation, I will discuss the dependence of UCP1 current on the membrane potential, matrix and cytosolic pH, as well as on the nature of the fatty compounds activating the current. The ultimate goal of this work is to elucidate the molecular mechanism employed by UCP1 and other UCPs to uncouple the mitochondrial oxidative phosphorylation in various tissues.

・Lishko PV, Botchkina IL, Kirichok Y. Progesterone activates the principal Ca^{2+} channel of human sperm. (2011) **Nature**, in press.
・Lishko PV and Kirichok Y. The role of Hv1 and CatSper channels in sperm activation. (2010) **J. Physiol.** 588: 4667-4672
・Lishko PV, Botchkina IL, Fedorenko A, Kirichok Y. Acid extrusion from human spermatozoa is mediated by flagellar voltage-gated proton channel. (2010) **Cell** 140; 327-337

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