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BISON GUEST LECTURE

PI(3,4,5)P3 and PI(3,4)P2 restrict Akt activity to cellular membranes

27/10/2016

University Campus Bohunice

Kamenice 5, Brno

Building **A11**, Room **205**

Dr. Thomas Leonard,

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START: 14.00

Protein kinase B/Akt regulates cellular metabolism, survival and proliferation in response to hormones and growth factors. Hyperactivation of Akt is frequently observed in cancer, while Akt inactivation is associated with severe diabetes. Here, we investigated the molecular and cellular mechanisms that maintain Akt activity proportional to the activating stimulus. We show that binding of the membrane lipids PI(3,4,5)P_3 and PI(3,4)P_2 to the PH domain of Akt is required for its allosteric activation while dissociation promotes rapid inactivation of Akt. We show that allosteric activation of Akt1 is achieved through enhanced substrate binding. Consistent with allosteric coupling between the PH and kinase domains, we demonstrate that in cells Akt dephosphorylation is rate-limited by dissociation from PI(3,4,5)P_3-containing membranes, dependent on the presence of Akt PH domain. We show that in live cells the Akt-substrate complex is associated with cellular membranes. Finally, we demonstrate that a somatic mutation in Akt1 associated with human cancer uncouples Akt1 activity from PI(3,4,5)P_3 and stabilizes hyperphosphorylated, active Akt1 in the cytosol of cells. Our results show that intramolecular allosteric and cellular mechanisms cooperate to enhance Akt signaling fidelity and the specificity of downstream substrate phosphorylation.

The lecture will be held within **NCBR seminar series**.

More information about the lecture HERE.

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