Rencontre MOCA Lille, 19. Mai 2005, IBL

9:30 Jean-François Bodart (Lille)

Regulation of non-genomic functions of Mitogen Activated Protein Kinase (MAPK)

10:15 K. Sriram (Paris)

Modeling the dynamics of simply cyclical protein regulatory networks and its application to the budding yeast cell cycle

After 11:00: MOCA internal meeting

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Jean-François Bodart (USTL, Lille)

Regulation of non genomic functions of Mitogen Activated Protein Kinase (MAPK).

Underscoring the importance of MAPK (Mitogen Activated Protein Kinase) /Erk (Extracellular signal Regulated kinases) pathway in tumorigenesis, activated MAPK/Erk or elevated MAPK/Erk expression have been detected in a wide variety of human tumors and therefore, MAPK/Erk signalling has been identified as a potential target for anticancer strategies.

The *Xenopus* oocyte is cellular context which enable to study biochemical, morphological as well as ionic mechanisms involved in cell cycle progression. Using this meiotic model we analyzed the role of MAPK during cell reorganization at M-Phase. Using different approaches to inhibit the Mos – MEK – MAPK/Erk – Rsk pathway (morpholinos and phosphorothioate anti-Mos antisense, small molecule inhibitor U0126), we demonstrated that activation of MEK – MAPK/Erk cascade induced by insulin is strictly dependent upon oncoprotein Mos accumulation. Moreover, Ras dependent mechanisms triggered by insulin failed to fully phosphorylate and activate Raf in absence of MEK activity. Either in oocyte stimulated by progesterone or insulin, we observed that even if chromosomes condense, oocytes failed to establish a bipolar spindle at the plasma membrane : microtubule aster-like structures are observed in deep cytoplasm. Such structures do not enable oocytes to equally segregate their genomic content and suggest that cell cycle catastrophic events like unproper spindle morphogenesis could be driven by MAPK/Erk inhibition.

Spindle restoration experiment showed that (1) Mos – MEK – MAPK/Erk – Rsk pathway is required to establish a bipolar spindle of division and that (2) Mos and Rsk play essential roles in spindle morphogenesis : Spindle morphogenesis is restored if both Mos and Rsk are active and present. Moreover, Mos and Rsk appear to play complementary role in the formation of the spindle and the establishment of the bipolar axis. These results engage to consider the members of the MAPK / Erk pathway not only as modules of a cascade but also as part of a network where each module can play a particular role.

MODELLING THE DYNAMICS OF SIMPLE CYCLICAL PROTEIN REGULATORY NETWORKS AND ITS APPLICATION TO THE BUDDING YEAST CELL CYCLE

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ABSTRACT

In this talk, the dynamics of the cyclical organization of simple protein networks and its application to the budding yeast cell cycle will be discussed by taking simple nonlinear models. The protein network consists of two small cyclical loops, where each loop in the absence of interaction with the other exhibits different dynamical behavior. Bistability is exhibited by one loop in which the proteins are positively regulated by the preceding one and in turn regulates positively the subsequent one in a cyclic clockwise fashion. Limit cycle oscillations are exhibited by the second loop in which the proteins are negatively regulated by preceding one and in turn negatively regulates the subsequent one in a cyclic anticlockwise fashion. Coupling of both the cyclical loops by positive feedback loop displays complex behavior such as multi-stability, coexistence of limit cycle and multiple steady states. Also, the coupling brings in the notion of checkpoint in the model. The model exhibits domino-like behavior, where limit cycle oscillations takes place in a stepwise fashion. As an application, the events that govern the cell cycle of budding yeast is considered. In budding yeast, the feedback interactions among the important transcription factors, cyclins and their inhibitors in G1, S-G2 and M phases are taken for the construction of the biological circuit diagram. Surprisingly, the sequential activation of the transcription factors, cyclins and their inhibitors forms two independent cyclical loops, with transcription factors involved in the cyclic positive regulation in clockwise direction, while the cyclins and its inhibitors involved in the negative regulation in anticlockwise direction. The coupling of the transcription factors and the cyclin and its inhibitors by positive feedback loops generates rich bifurcation diagram that can be related to the different events in the G1, S-G2 and M phases of cell division cycle in terms of dynamical system theory. The different checkpoints in the cell cycle are accounted for by appropriately silencing the positive feedback loops that couple the transcription factors and the cyclin and their inhibitors.