CENTRE FOR CANCER BIOMEDICINE

CCB welcomes you to our seminar by

Antoni Wiedlocha, Group leader, PhD, and Beata Nadratowska-Wesolowska, Postdoc, PhD

Thursday the 10th of May at 13:00 hrs

The Auditorium in the Research Building, the Norwegian Radium Hospital

Refreshments are served in the lobby after the seminar

At 13:00 hrs: Antoni Wiedlocha, Group leader, PhD – Department of Biochemistry, Institute for Cancer Research, The Norwegian Radium Hospital

Activation and Termination of Fibroblast Growth Factor Induced Cellular Signaling

Fibroblast growth factor 1 (FGF1) controls cellular activities through activation of specific cell-surface FGF receptors (FGFRs). Trans-phosphorylation of tyrosine residues in the kinase domain of FGFR leads to activation of intracellular signal cascades including mitogen-activated protein kinases (MAPKs). In addition to the kinase domain, FGFRs contain a serine rich C-terminal tail of unknown function. We unravel a novel downregulation mechanism of FGFR signaling based on direct phosphorylation of a specific serine residue (Ser777) in the C-terminal part of the receptor by the MAPKs ERK1/2. This serine phosphorylation significantly reduces the tyrosine phosphorylation in the kinase domain of the receptor. Prevention of FGFR1 Ser777 phosphorylation or S777A mutation results in enhanced receptor tyrosine phosphorylation, increased cell proliferation and cell migration, while a phosphomimetic mutation at Ser777 reduces FGFR1 signaling. Importantly, FGFR-independent activation of MAPKs also results in phosphorylation of Ser777 of FGFR1, thereby allowing cross-control of FGFR activity by other signaling receptors. Our data reveal a novel negative-feedback mechanism that controls FGF signaling and thereby protects the cell against excessive activation of FGFR.

At 13:30 hrs: Beata Nadratowska-Wesolowska, Post doc, PhD – Department of Biochemistry, Institute for Cancer Research, The Norwegian Radium Hospital

The ribosomal S6 kinase 2 (RSK2) binds and phosphorylates FGFR1

FGFR1 is one of four receptor tyrosine kinases that bind and are activated by members of the fibroblast growth factors family (FGFs). Phosphorylated tyrosine residues on the receptor function as docking sites for adaptor protein that activate multiple signal transduction pathways including Ras-MAPK, PI3K-AKT and PLCγ. By yeast two-hybrid screen we identify potential interaction partners with the FGFR1 cytoplasmic domain. RSK2 is one of the proteins we identified and this interaction was confirmed in the human osteosarcoma cell line stably expressing FGFR1 (U2OSR1). RSK2 belongs to the family of serine/threonine kinases that are activated through the mitogen activated protein kinase (MAPK) signal transduction pathway. RSKs are implicated in the regulation of transcription, protein synthesis, cell survival and cell proliferation.

We have shown that association between RSK2 and FGFR1 depends on RSK2 phosphorylation. Region of interaction FGFR1 with RSK2 is within the C-terminal tail of FGFR1 consisting of the 66 most C-terminal amino acids. Active RSK2 phosphorylates C-terminal tail of FGFR1 in in vitro kinase assay. Mass spectrometry analysis identified that RSK2 phosphorylates FGFR1 at Ser789. Depletion of RSK2 by siRNA or inhibition of RSK2 activity lead to prolongation of tyrosine transphosphorylation of FGFR1. FGF1 induced cell migration and shape changes are impaired in U2OSR1 S789D cells. These results support a novel regulatory mechanism whereby a MAPK cascade component directly interact with, and phosphorylates FGFR1, modulating the receptor signaling.