University of Stuttgart

Stuttgart Research Center Systems Biology (SRCSB)

Systems Biology Seminar Talk

„The guardian on the move: dynamics and function of p53 in single living cells “

Prof. Dr. Alexander Löwer
Systems biology of the stress response, TU Darmstadt

Monday
December 5, 2022
2 p.m. – 3 p.m.

Lecture Hall 0.106
Allmandring 31
Stuttgart

Abstract:

The tumor suppressor p53 is a central hub in the signaling network mediating the mammalian DNA damage response. It converts incoming signals into alternate cell fate decisions by changing the expression of hundreds of target genes. Combining quantitative fluorescent time-lapse microscopy, computational data analysis and mathematical modeling revealed oscillation-like accumulation of p53 protein upon induction of DNA double strand breaks. During the response, the state of the broken chromatin changes, as a complex molecular machinery recognizes the lesions and initiates their repair. We were now interested in understanding if this change in the status of the genome would also be reflected in the molecular network regulating p53, leading to mechanistically different responses to acute and sustained damage. Using time-resolved single cell approaches, we confirm that the kinase ATM is crucial for activating p53 in response to new DNA damage detected by the cell. However, ATM is dispensable for sustaining pulsatile p53 accumulation upon persistent damage. Instead, ATM-initiated CHK2 activity keeps the p53 network operating. We provide molecular evidence that CHK2 modulates p53 levels by inducing degradation of the negative regulator MDMX thereby destabilizing MDM2. This moves the negative feedback between p53 and its ubiquitin ligase in a stable limit cycle, leading to sustained p53 oscillations, whose duration depends on the initial amount of activated Chk2. Interestingly, time-dependent differences in the p53 response are also reflected in the state of its posttranslational modifications and the activity of target gene promotors. Taken together, we provide evidence that differential regulation of p53 by upstream kinases allows cells to differentiate between acute and persisting DNA breaks.

CV:

April 2015 – present Professor, Technical University Darmstadt, Germany “Systems biology of the mammalian stress response”
May 2011 – Dezember 2015 Group Leader, Berlin Institute for Medical Systems Biology, Max Delbrueck Center Berlin-Buch
October 2005 – April 2011 Research Fellow, Department of Systems Biology, Harvard Medical School, Boston MA, USA “p53 dynamics and the control of cell fate”
June 2001 – June 2005 Dissertation in Molecular Cell Biology at the ZMBH, University of Heidelberg
October 1996 – May 2001 Undergraduate studies in Biology (Molecular Biology, Cell Biology, Biochemistry) at the University of Heidelberg

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