

GSI - SEMINAR

Im Theorieseminarraum, SB3 Raum 3.170a

Darmstadt, Planckstraße 1

Donnerstag, den 30. Apr 2015, 15:00 Uhr

Dr. Alexander Löwer

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Max-Delbrueck-Center
and
TU Darmstadt

"Unleashing the guardian: dynamics and function of the tumor suppressor p53 in single cells"

DNA double strand breaks are among the most dangerous lesion for mammalian cells, as they lead to chromosomal aberrations and cellular transformation if left unrepaired. Upon damage induction, kinases of the PI3K-like kinase family relay the signal to the DNA damage response network, which arrests the cell cycle, activates repair or induces terminal cell fates such as senescence and apoptosis. A central hub in the DNA damage response is the tumor suppressor p53. We use a combination of time-lapse live-cell microscopy, quantitative single cell analysis and mathematical modeling to elucidate the dynamics of its response to genotoxic stress. Using this approach, we investigated the role of the kinases ATM, ATR and DNA-PK in activating p53. While cells can compensate the loss of ATM and ATR, we surprisingly observed that loss of DNA-PK activity led to a dramatic increase in the p53 response and, as a consequence, to premature induction of senescence. We show mechanistically that over-activation of p53 is caused by prolonged ATM activation due to unprocessed double-strand breaks. This reveals a novel regulatory interplay between DNA-PK and ATM, which may be exploitable for specifically targeting cancer cells during therapy.

Einladender: Prof. Dr. Gerhard Kraft

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