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SFB 635
Posttranslational control of protein function

Seminars in Genetics and Molecular Cell Biology

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Molecular mechanisms of DNA recognition by the tumour suppressor p53

The tumour suppressor p53 is at the centre of a large transcriptional network. It is activated by cellular stress signals and mediates a cellular response through the transcription of various target genes. Such target genes are involved in apoptosis, senescence, and cell-cycle arrest, thus promoting tumour suppression. However, p53 target genes are also pivotal for several cell survival functions such as DNA repair, metabolism regulation, and embryo implantation. The functions of the p53 network are partially overlapped by the homologous proteins p63 and p73. The aim of this project was to understand the molecular mechanisms that provide p53 family members with transcriptional selectivity, using in vitro biophysical analysis. The p53 family members share a largely conserved target DNA sequence, which indicates that DNA-binding specificity of p53 is a necessary but not sufficient condition for target selectivity. I hypothesized that the cooperative binding of two transcription factors to DNA increases target specificity and can present evidence that the transcription factor KLF4 increases the DNA-binding affinity of p53 through the formation of a ternary complex on DNA. This effect strongly depended on the distance between the response elements of KLF4 and p53. Further, I identified the interaction sites on both proteins. The strength of this interaction was strongly affected by phosphorylation of p53 residues Ser46 and Thr55, which are associated with the transcription of cell-cycle arrest genes. Taken together, the cooperative binding of KLF4 and p53 to DNA exemplifies a novel regulatory mechanism that increases p53 target selectivity.

Wednesday, April 27, 2011 at 01.00 p. m.

Institute for Genetics,
Zülpicher Str. 47 a, Lecture hall, 4th floor

Host: Thomas Langer, Institute for Genetics,
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