WDR5 degradation

Characterization of small molecules for targeted degradation of WDR5 to interfere with oncogenic MLL activity in cancer

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Keywords			

Projektbeschreibung

Epigenetic processes regulate gene expression patterns during development and disease. Proteins involved in epigenetic gene regulation mostly exert their function in the context of multi-protein complexes, which can covalently modify chromatin. For instance, the MLL protein complex positively regulates gene expression by catalysing tri-methylation of the Lys-4 residue in histone H3 (H3K4me3) in the promoters of actively transcribed genes. The protein WDR5 is an important member of the core MLL protein complex, as it was shown to be critical for the catalytic activity of MLL.
Epigenetic pathways are often mutated or de-regulated in cancer. In particular, leukaemias were shown to require a functional wild-type or mutated MLL complex. Various cancers exhibit strong dependence on the protein WDR5, and forced down-regulation of WDR5 blocked tumour growth. To pharmacologically interfere with WDR5 function, we have recently characterized the first-in-class small molecule WDR5 antagonist. This chemical compound, termed OICR-9429, binds strongly to WDR5 and disrupts its interaction with MLL, thereby inactivating the MLL protein complex. OICR-9429 was shown to exhibit strong antiproliferative effects in leukaemia cells. Hence, we could provide a proof-of-concept for small molecule-mediated targeting of WDR5, which might represent an attractive therapeutic strategy to target leukaemia cells. However, the OICR-9429-targeted WDR5-MLL interaction most likely represents only one of several functions of the multi-functional protein WDR5, as other protein-protein interactions of WDR5 were also shown to be important. Thus, complete ablation of the WDR5 protein by pharmacological means might result in stronger anti-cancer activity than targeting exclusively the WDR5-MLL interaction.
Here we propose to modify OICR-9429 to completely ablate the WDR5 protein. It was recently shown that the E3 ubiquitin ligase Cereblon can be specifically recruited to any target protein by attaching a phthalimide moiety to an appropriate ligand. In collaboration with Drs. Georg Winter (CeMM Vienna) and Cheryl Arrowsmith (Structural Genomics Consortium, Toronto, Canada), we will synthesize several phthalimide-conjugated OICR-9429 variants. We will subject these WDR5 degrading compounds (termed dWDR5) to a detailed biophysical, biochemical and structural characterization. Cellular effects of most promising drug candidates will be tested in cell line- and mouse models of leukaemia. Finally, we will use our newly developed WDR5 degrader molecules to investigate novel biological functions of WDR5 in cancer.
In summary, the presented project will exploit the novel concept of targeted, small-moleculemediated degradation of WDR5 to selectively target the strong WDR5 dependence of cancer cells. Thus, results from this work might not only provide novel

insights into the function of WDR5 in cancer but might also validate the novel approach of targeted protein degradation in cancer treatment.

Projektpartner

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