Research group at the University of Freiburg publishes important study on post-translational modification in prostate cancer

Close relation to nanodiag BW

Post-translational modifications are chemical changes made by enzymes to synthesized proteins. They play an important role as molecular switches to control gene expression and cell growth, among other things, and are among the epigenetic regulatory mechanisms of the cell. A research group from the Department of Urology at the Freiburg University Medical Center, together with researchers from the fields of pharmacy and biochemistry, has now developed an active substance, called KMI169, which prevents a specific post-translational modification of this kind, the methylation of the histone protein H4 at the amino acid lysine in position 12, by inhibiting the enzyme KMT9 responsible for this. As the research group has previously shown, suppressing this methylation reaction inhibits the growth of various tumor cells, including prostate, lung and colon cancer cells.

The new study[1] is the first to present a small-molecule substance that can serve as a starting point for the development of drugs to treat these cancers by inhibiting the KMT9 enzyme. "We have long had our sights set on KMT9 as a potential target for prostate cancer. The development of the specific inhibitor is now a decisive step towards combating it much more effectively," explains study leader **Prof. Dr. Roland Schüle**, Scientific Director of the Department of Urology at the Freiburg University Medical Centre and member of the Cluster of Excellence CIBSS - Centre for Integrative Biological Signalling Studies and **Dr. Eric Metzger**, group leader in Schüle's department. Its potential use in therapy-resistant forms of cancer is particularly valuable. "In these cases, conventional anti-hormonal treatment often fails within a few months and the disease then progresses rapidly. The inhibitor we have developed offers us a highly innovative therapeutic approach here," says Schüle.

Prof. Jan C. Behrends, one of the spokespersons for nanodiag BW, emphasizes how important this study is for the nanodiag BW future cluster. "In nanodiag BW, together with the group at the University Hospital, we are developing an assay to be able to determine precisely this post-translational modification of H4 quickly, easily and quantitatively in future using nanopore technology. We already published the proof of principlein 2022.[2] The new results show us once again that we have set ourselves a worthwhile goal and have assembled groups in our consortium that are at the forefront of research in this area. Of the 21 authors of the study, five are already involved in nanodiag BW for the development of the nanopore assay, with which we can make an important contribution to establishing the new therapies."

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[1]Wang, S., S.O. Klein, S. Urban, M. Staudt, N.P.F. Barthes, D. Willmann, J. Bacher, M. Sum, H. Bauer, L. Peng, G.A. Rennar, C. Gratzke, K.M. Schüle, L. Zhang, O. Einsle, H. Greschik, C. MacLeod, C.G. Thomson, M. Jung, E. Metzger, and R. Schüle. 2024. Structure-guided design of a selective inhibitor of the methyltransferase KMT9 with cellular activity. Nat Comms. 15:43–12. doi:10.1038/s41467-023-44243-6

[2]Ensslen, T., K. Sarthak, A. Aksimentiev, and J.C. Behrends. 2022. Resolving Isomeric Posttranslational Modifications Using a Biological Nanopore as a Sensor of Molecular Shape. J. Am. Chem. Soc. 144:16060–16068. doi:10.1021/jacs.2c06211.