Research reveals promising novel strategy to target cancer-causing protein

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A team of scientists, comprising researchers from the Institute of Molecular and Cell Biology (IMCB), a research institute under the Agency for Science, Technology and Research (A*STAR), Singapore, and the VIB Laboratory of Molecular Cancer Biology (VIB/KU Leuven), has revealed the mechanism by which tumor cells elevate levels of MDM4, a protein that is highly expressed in cancer cells but not in normal adult tissues. The team has also found that the mechanism can be interfered with antisense oligonucleotides (ASOs) to suppress cancer growth. The study which paves the way for the development of novel cancer therapeutics was published in the leading *Journal of Clinical Investigation* (JCI).

MDM4 in cancer cells inhibits p53 protein

P53 is a tumor suppressor which cancer cells need to inhibit in order to multiply. In the case of skin-related melanoma, it had been proposed that tumor cells accomplish the inhibition with an overexpression of MDM4.

The research team had previously proven MDM4's ability to bind directly to p53 and inhibit its tumor suppressor function in Metastatic Melanoma (MM), a rare but most aggressive type of skin cancer. While the study served as a useful proof-of-concept therapeutics, it was still unclear how the findings could be useful in a clinical setting. Finding small molecules that can interfere directly with MDM4 function has proven to be an enormous challenge and there is no clinically-compatible

alternative to selectively and efficiently disrupt the MDM4-p53 complexes. There is also an increasing body of evidence that MDM4 can facilitate tumor formation without necessarily binding to p53.

Prof Jean-Christophe Marine, who heads VIB and has been studying MDM4 for several years, said, "As an alternative to pharmacological inhibition of the MDM4-p53 protein interaction we reasoned that targeting MDM4 protein abundance—rather than its interaction with p53—may be easier to achieve pharmacologically. In addition, it may also have broader and more robust antitumor effects as this would inhibit both p53-dependent and independent oncogenic functions of MDM4."

Targeting MDM4 abundance with antisense oligonucleotides (ASOs)

Headed by Dr Ernesto Guccione, the laboratory in IMCB has been researching on the use of ASOs technology to interfere with pre-mRNA splicing and protein abundance. Leveraging IMCB's expertise in the field of ASOs and through a collaborative effort, the scientists found in the latest study that targeting MDM4 protein abundance using antisense oligonucleotides (ASOs) could impair tumour growth, reduce cell proliferation and increase cell death. This novel discovery suggests that MDM4 is indeed a promising clinically-compatible therapeutic target which can be suppressed with ASOs, and offers alternative therapeutic avenues not only for melanoma, but also for a wide range of other MDM4-expressing cancers such as breast cancer, ovarian cancer, B-cell lymphoma or retinoblastoma.

Dr Guccione, Senior Principal Investigator at IMCB and co-lead for the study, said, "This work is a good example of how ASOs can target proteins that are hard to inhibit by traditional approaches such as small molecule inhibitors, and it greatly expands our options for therapeutic

intervention."

Provided by VIB (the Flanders Institute for Biotechnology)

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