Novel probe for metabolic diseases

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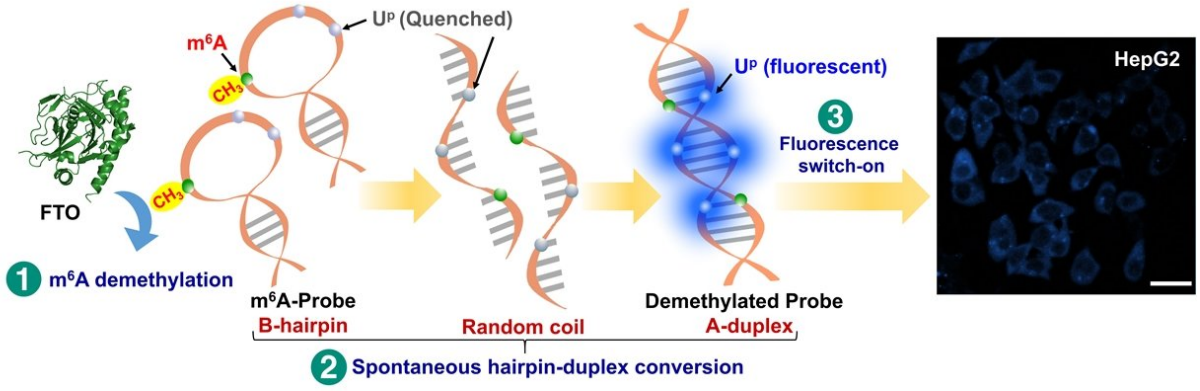

Figure shows the assay strategy for the detection of FTO levels in cells. Removal of the methyl group by FTO triggers a switch from a hairpin to a duplex structure, causing fluorescence. The image (right) shows the bright blue fluorescence of HepG2 cells after one hour of treatment with the probe. Credit: National University of Singapore

NUS pharmaceutical scientists have developed a simple, yet highly sensitive probe to detect the fat mass and obesity-associated protein (FTO) levels in cells. This can potentially help in the early detection and diagnosis of metabolic diseases such as diabetes.

Diabetes is becoming a serious health issue in Singapore. However, because it often begins with few noticeable symptoms, it is frequently left undiagnosed until it has progressed to later stages of the disease. By then, complications such as eye damage, kidney diseases and

cardiovascular diseases may have developed. There is therefore a need for better screening tools to allow for more efficient and earlier diagnosis of this disease.

Prof Esther Woon from the Department of Pharmacy, NUS and her team have developed a fluorescent probe that can directly detect FTO activity levels in living cells. The FTO protein is strongly associated with a range of metabolic disorders such as obesity and diabetes. The detection is achieved by using a dynamic ribonucleic acid (RNA) probe which, by design, has the capacity to assume different conformations according to its methylation status. When the probe is methylated, it preferentially adopts a hairpin structure. Removal of the methyl group by FTO causes the probe to switch to a duplex structure, with concomitant activation of bright blue fluorescence. Through the use of this probe, the research group was able to achieve highly sensitive detection of FTO levels in cells.

Prof Woon said, "We chose FTO as a biomarker because research has shown that it is strongly linked to diabetes in humans. There is extensive evidence that FTO levels are closely correlated with the onset and progression of the disease."

She added, "It is also increasingly clear that increased FTO expression is one of the earliest events in the development of diabetes. Thus, this new approach could potentially facilitate the functional and mechanistic studies in the development of a detection kit for early screening of diabetes."

More information: Adeline Cheong et al. A fluorescent methylation-switchable probe for highly sensitive analysis of FTO N6-methyladenosine demethylase activity in cells, *Chemical Science* (2018). DOI: 10.1039/c8sc02163e

Joel D. W. Toh et al. A strategy based on nucleotide specificity leads to a subfamily-selective and cell-active inhibitor of N6-methyladenosine demethylase FTO, *Chemical Science* (2014). DOI: 10.1039/c4sc02554g