Cancer biomarkers re-evaluated

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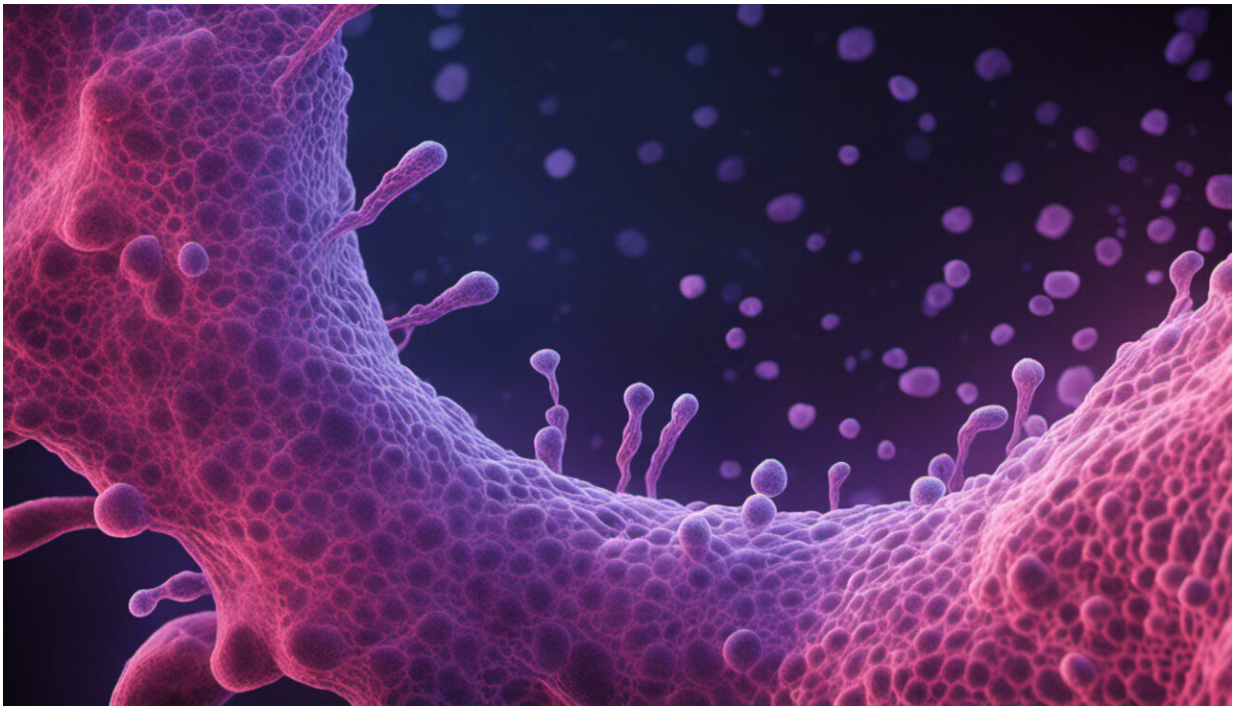

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(Medical Xpress) -- Researchers from ETH Zurich have developed a procedure to test the clinical benefits of cancer biomarkers. The method could radically shorten the path from the lab to their application.

Protein biomarkers, especially those that circulate in the blood plasma or urine and can therefore be obtained without any major intervention, are vital in personalised medicine. Biomarkers help in detecting diseases in

hospitals at an early stage, classifying them, selecting the suitable treatment and monitoring the treatment response.

Thanks to major advancements in proteomic and genomic research and modelling biological processes on the computer, researchers have discovered over a thousand potential protein biomarkers in recent years. Knowledge of the complete gene sequences of individual cancer patients is also on the rise, which will boost the number of possible biomarkers further.

Long list of candidates

However, the majority of the protein biomarkers proposed and recorded in the literature do not progress beyond the status “potential”. “The list of candidates for biomarkers has grown longer and longer, but the number approved for clinical use has stagnated,” sums up Ruth Hüttenhain, a postdoc from the group headed by professor of molecular systems biology Ruedi Aebersold. After all, in order to gauge whether biomarker candidates are clinically relevant in the first place, they have to be measured and validated in large cohorts of patient samples. The main reason why the development of new biomarkers for clinical use has not progressed is the lack of a verification procedure for most biomarker candidates.

Ruth Hüttenhain and Martin Soste, the first authors of a study that has just been published in Science Translational Medicine, have thus developed a strategy to measure potential biomarkers rapidly on a large scale and verify their clinical uses. The method is based on a targeted mass spectrometric, high-throughput technology, which can determine proteins that are present in biological samples at any particular point in time in a reliable and reproducible way. For this procedure, mass spectrometric coordinates, so-called assays, need to be developed beforehand for every protein.

Test process quickly narrows down list

In their study, the researchers developed assays for 1,157 potential biomarkers, the abundances of which change in different human cancer tissues and which are related to mutated genes that drive the development of cancer. The researchers ultimately tested their assays on blood and urine samples taken from cancer patients and healthy individuals. The scientists were able to detect over 180 different biomarkers in the blood plasma, the concentration of which reached the range of a billionth of a gram per millimetre of fluid. In the urine samples, the systems biologists found over 400 different biomarker proteins.

With the aid of the assays, the list of possible biomarkers can be narrowed down swiftly and efficiently. While these cannot be used directly in a cancer diagnosis, they bridge the gap between basic research and clinical applicability. “We hope that we are advancing studies on cancer biomarkers with our work and helping promising candidates to be used clinically,” says the postdoctoral student. To enable other researchers to benefit from the groundwork, the ETH-Zurich scientists have placed all the assays in a publicly accessible database that can be expanded rapidly and easily to include newly discovered biomarker candidates.

Case study on ovarian cancer confirms approach

A case study on the recognition of ovarian cancer confirms the ETH-Zurich researchers’ approach in that it verified potential biomarkers in blood plasma. To this end, the researchers not only measured the biomarker candidates described in the literature, but also new biomarkers that they predicted with computational models based on genomic data. “Using the blood plasma measurements, interestingly

some of the predicted biomarkers produced extremely promising results for the classification of ovarian cancer patients," stresses Ruth Hüttenhain. The results therefore underscored the great potential of the mass spectrometric method for validating new protein biomarkers. The study also describes an insightful link between cancer, genetic data and proteome measurements to determine the acute status of patients.

The ETH-Zurich researchers see a general strategy in their approach to link studies on gene and protein interactions more strongly. Due to the connection between the genes and gene products, the proteins, involved in tumour formation, the researchers can predict new, previously unknown biomarker candidates on the computer that can be tested with the aid of mass spectrometric assays in patient samples. "Our new method can be used to validate the proposed biomarker candidates in all patient samples," says Martin Soste. The strategy of developing highly specific verification procedures for disease-relevant proteins can also be applied to other diseases.

More information: Hüttenhain R, et al. Reproducible quantification of cancer-associated proteins in body fluids using targeted proteomics. *Sci. Transl. Med.* 4, 142ra94 (2012).

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